

HyperChem[®] Computational Chemistry

**Part 1
Practical Guide**

**Part 2
Theory and Methods**

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Table of Contents

Preface	1
Who Should Read this Guide?	1
Annotated Bibliography	2

Part 1: Practical Guide

Chapter 1 Practical Guide Introduction	7
What is Computational Chemistry?	7
What is HyperChem?	8
Building and Displaying Molecules	8
Optimizing the Structures of Molecules	8
Investigating the Reactivity of Molecules	8
Generating and Viewing Orbitals and Electronic Plots	9
Evaluating Chemical Pathways and Mechanisms	9
Studying the Dynamic Behavior of Molecules	10
Chapter 2 HyperChem Calculations	11
Exploring Potential Energy Surfaces	11
Complexity of Potential Energy Surfaces	14
Types of Calculations	16
Single Point	16
Geometry Optimization	16
Transition State Search	17
Molecular Dynamics	18
Langevin Dynamics	18
Monte Carlo Simulations	19

Chapter 3 Calculation Methods 21

Molecular Mechanics	21
Bonds and Angles	23
Torsions	25
van der Waals Interactions and Hydrogen Bonding	26
Electrostatic Potential	27
United versus All Atom Force Fields	28
Cutoffs	29
Quantum Mechanics.	31
Background	32
Molecular Geometry	32
Calculating Electronic Potential Energy	32
Range of Quantum Mechanics Methods.	34
Exclusion Principle	34
Simplified Wave Functions	36
Hartree-Fock Wave Functions	37
Extending the Wave Function Calculation	37
Extending the Wave Function Calculation	37
Configuration Interaction	37
Møller-Plesset Perturbation Theory	40
Molecular Orbitals and Electronic Structure.	41
Orbital Occupancy.	41
Atomic Orbitals and Their Interactions	42
SCF Technique	43
Virtual Orbitals	44
RHF and UHF	44
Multiplicity Considerations	45
Bond Breaking	46
RHF Half-Electron Technique	46
SCF Convergence	47
Calculation Results	48
Quantitative Results	49

Chapter 4 Single Point Calculations 51

Dipole Moment	52
Total Electron Density	52
Total Spin Density	52
Electrostatic Potential	53
Examples of Single Point Calculations	53

Chapter 5	Geometry Optimizations and Transition State Searching	57
	Geometry Optimizations	57
	Steepest Descent	58
	Conjugate Gradient	59
	Block Diagonal	60
	Eigenvector Following	60
	Setting Convergence Criteria	60
	Examples of Geometry Optimizations	61
	Solvation and Periodic Boundary Conditions	62
	Transition State Searching	65
	Eigenvector Following	66
	Synchronous Transit	67
Chapter 6	Molecular Dynamics	69
	Integration Algorithm	70
	Length of Simulations	71
	Conservation of Energy	71
	Temperature Control	72
	Simulation Periods	73
	Initial Conditions and Heating	73
	Equilibration and Data Collection	74
	Tests for Equilibration	75
	Effect of Solvent on Equilibration.	75
	Collecting Data	75
	Cooling.	76
	Examples of Molecular Dynamics Simulations	76
	Strategies	77
	Constant Temperature versus Constant Energy	77
	Conformational Searching.	78
	Quenched Dynamics.	78
	Simulated Annealing.	79
	Randomization During Molecular Dynamics	79
	Sampling Frequency	80
	When is Conformational Space Adequately Sampled?	80
	Using Geometric Restraints	81
	Using Experimental Data as Restraints	82
	Crossing Energy Barriers	82
	Limiting Conformational Changes during High Temperature Simulations.	82
	Docking Molecules	83

Freezing Part of a System	83
Solvent Simulations	84
Choice of Dielectric Constant	84
Effects on Dynamic Motion.	85
Collecting Averages from Simulations	85
Evaluating Stability and Equilibration	86
Constant Energy Simulations	86
Constant Temperature Simulations	87
Conformational Searches	87
Setting Up a Molecular Dynamics Simulation	88
Heating Time	88
Simulation or Run Time	88
Cooling (Annealing) Time	89
Step Size	89
Temperature	90
Bond Breaking.	90

Chapter 7 Langevin Dynamics and Monte Carlo 91

Langevin Dynamics	91
Integration Algorithm	92
Setting Up a Langevin Dynamics Simulation	93
Heating Time, Run Time, and Cooling Time	93
Time Step.	93
Temperature.	94
Constant Temperature vs. Constant Energy	94
Friction coefficient.	94
Additional Procedures.	95
Monte Carlo Simulations	95
Introduction	95
Background and Method	96
Monte Carlo Trajectories and Simulation Parameters.	97
Initial Configurations	97
Temperature.	97
Step Size and Acceptance Ratio	98
Initial Phase and Equilibration	98
Equilibration and Statistical Averaging	98
Heating and Cooling	99

Chapter 8 Using Molecular Mechanics Methods 101

Availability of Parameters	101
--------------------------------------	-----

Force Field Features	101
MM+	101
Electrostatic Interactions	103
Accuracy of Force Fields	103
Previous Experiences	103
Choosing Force Field Options	103
Dielectric Function	103
1–4 Nonbonded Scale Factors	104
Nonbonded Cutoffs	104
Restrains	105
References.	106

Chapter 9 Using Quantum Mechanics Methods 107

Obtaining a Starting Structure	107
Calculating Part of a Molecular System	108
Setting Up Options	109
Selecting Options for the Ab Initio Method	109
Choosing a Basis Set	109
Add Extra Basis Function	111
Applying a Basis Set	111
Charge and Spin Multiplicity	111
Convergence Criteria	112
UHF versus RHF	112
Convergence Acceleration	112
Calculate Gradient	113
Calculate MP2 Correlation Energy	113
Two-Electron Repulsion Integrals	113
Two-electron Integral Cutoff	113
Two-electron Integral Buffer Size	114
Regular Two-Electron Integral Format	114
Raffenetti Two-Electron Integral Format	114
Direct SCF Calculation	115
Initial Guess of MO Coefficients	115
Number of d Orbitals	115
Ghost-Atoms	116
Configuration Interaction	117
Selecting Options for the Extended Hückel Method.	117
Charge and Spin Multiplicity	117
Hückel Constant	117
d Orbitals	118
Selecting Options for NDO Methods	118
Convergence Criteria	118

Charge, Spin, and Excited State	119
UHF versus RHF	119
Convergence Acceleration	119
Configuration Interaction	119
Log File for Results	120
Log File for Results	120
Types of Calculations	120
Single Point Calculations and CI	121
Optimization Methods	122
Transition State Search	122
Molecular Dynamics	123
Energy Conservation in Molecular Dynamics Calculations	123
Vibrations	124
Contour Plots and Orbitals	124
Vibrational Spectrum	124
Electronic Spectrum	125
Saving Information in a Log File	125
Extended Hückel Method	125
Limitations of Extended Hückel	126
NDO Methods	126
Defining Electron-Electron Interactions	126
Treatment of Electron-Electron Interactions	127
CNDO, INDO, MINDO/3, ZINDO/1, and ZINDO/S Methods	127
MNDO, AM1, and PM3 Methods	128
Practical Uses of NDO Methods	128
Parameterization	128
Results of Semi-Empirical Calculations	130
Energies of Molecules	130
Geometries of Molecules	132
Energies of Transition States	133
Molecular Orbital Energies and Ionization Potentials	134
Dipole Moments	134
Electrostatic Potential	135
Atomic Charges	137
Chemical Reactivity	138
Atomic Charges and Reactivity	140
Frontier Molecular Orbitals	141
Vibrational Analysis and Infrared Spectroscopy	143
Experimental Characteristic IR Fundamental Frequencies	144
UV-visible Spectra	147

Choosing a Semi-Empirical Method	148
Extended Hückel	148
CNDO	149
INDO	149
MINDO/3	149
MNDO	150
AM1	150
PM3	150
ZINDO/1	151
ZINDO/S	151
Further Reading	152

Part 2: Theory and Methods

Chapter 10 Theory and Methods Introduction 155

HyperChem Architecture	155
The Back Ends	156
HyperChem Philosophy	157
Background on Computational Chemistry	158
Potential Energy Surfaces	158
Single Point	160
Geometry Optimization	161
Molecular Dynamics	161
The Born-Oppenheimer Approximation	161
The Hamiltonian of a Collection of Nuclei and Electrons	162
The Electronic Hamiltonian	163
The Nuclear Hamiltonian	163
Molecular Mechanics versus Quantum Mechanics	164
Classical Mechanics on a Potential Energy Surface	165
Force-Energy Generators	166

Chapter 11 Molecular Mechanics 167

Background	168
Atom Types	169
Definition of Atom Type	169
The Typing Rules.	170

Redefining or Adding Types.	172
Force Fields.	173
Background.	174
Energetic Terms in the Potential	174
Bond Stretching	175
Bond Angle Bending	175
Dihedrals	175
Improper Dihedrals.	176
van der Waals	176
Electrostatic	179
Hydrogen Bonding	179
Effective Dielectric Constants	180
Cutoffs	181
Terms Involving Vicinal 1-4 Interactions	182
MM+	182
Units	183
Bond Stretching.	183
Bond Dipoles	184
Angle Bending	185
Bond Stretch and Angle Bending Cross Term	186
Out-of-Plane Bending	186
Dihedrals.	187
van der Waals	187
AMBER	188
Bond Stretching.	189
Angle Bending	189
Dihedrals.	189
Improper Dihedrals	190
van der Waals	190
Electrostatic	190
Hydrogen Bonding.	191
Lone Pairs	191
OPLS	191
van der Waals	192
Electrostatic	192
BIO+	193
Bond Stretching.	193
Angle Bending	194
Dihedrals.	194
Improper Dihedrals	194
van der Waals	195
Electrostatic	196
Hydrogen Bonding.	196

Parameter Sets	196
Text or DBF Form for Parameters.	197
Modifying Existing Parameter Sets	197
Creating New Parameter Sets	198
Compiling Parameters	199
Chem.ini or Registry Setup of Force Field Options	199
Periodic Boundary Conditions and Solvent	200
The Periodic Boundary Conditions	201
Equilibrated Water Box.	202
Details of Solvation Methodology	202
Restraints	203
Definition of a Restraint	203
Adding Restraints	203
The Default MM+ Force Field	204
The Wild Card Approach	205
The Default Force Field	206
Approximate Hybridization	207
Bond Stretching	209
Parameters for Butadiene and Related Molecules	210
Angle Bending.	211
Stretch-Bends	211
Out-Of-Plane Bends	211
Torsions.	211
Single Bonds	212
Double Bonds	212
Electrostatic	213
van der Waals	213

Chapter 12 Quantum Mechanics 215

Background	216
Approximate Solutions of the Schrödinger equation	217
Charge and Multiplicity	218
Independent Electron Methods	219
The Independent Electron Approximation	219
Molecular Orbitals	219
Orbital Energy Diagrams	220
The MO-LCAO Approximation	221
The Matrix equations for the Molecular Orbitals.	222
Solving for the Molecular Orbitals	223
Self-Consistent Field Methods	224
Hartree-Fock Method	224

The Roothaan equations	225
Spin Pairing	226
Pople-Nesbet Unrestricted equations	227
Convergence	229
Spin Pairing—Restricted or Unrestricted?	230
Electronic States	232
Post Self-Consistent Field Calculations	235
Configuration Interaction	235
MP2 Correlation Energy	236
The Neglect of Differential Overlap Approximation	238
Characterizations of the Wave function	240
Contour Plots	240
Total Electron Density	241
Spin Density	243
Orbital Plots	243
Electrostatic Potential	244
Mixed Quantum/Classical Model	246
Choosing the Classical–Quantum Boundary	246
Capping Atoms and their Parameters	248
Supported Methods	250
Ab Initio Method	251
Normalized Primitive Gaussian Functions	253
Contracted Gaussian Functions	254
Minimal Basis Sets: STO-3G	254
Split-Valence Basis Sets	257
Polarized Basis Sets	260
Two-Electron Integrals	262
Regular Integral Format	263
Raffenetti Integral Format	264
Two-Electron Integral Cutoff	265
Direct SCF Calculation	265
Initial Guess of MO Coefficients	266
Projected Hückel	266
Projected CNDO/INDO	266
Mixed Model	267
Ghost-Atoms	267
Extended Hückel Theory	268
Basic Method	268
Valence Atomic Orbitals	269
Hamiltonian Matrix Elements	270
Choosing a Hückel Constant	272
Mixed Model	272
CNDO	273

	The CNDO equations	273
	Expectation Values	276
	Mixed Model (CNDO and INDO)	276
INDO		277
	Exchange Phenomena	277
	Differences Between INDO and CNDO	278
	Spin Interactions in INDO	279
MINDO/3		280
	Two-Center Two-Electron Integrals	281
	One-Center One-Electron Integral $H_{\mu\mu}$	281
	Two-Center One-Electron Integral $H_{\mu\nu}$ (Resonance Integral)	282
	One-Center Two-Electron Integral	282
	Core-Core Repulsion Integrals	283
	Mixed Model	283
MNDO		284
	Two-Center Two-Electron Integrals	286
	One-Center One-Electron Integral $H_{\mu\mu}$	289
	Two-Center One-Electron Integral $H_{\mu\nu}$	290
	One-Center Two-Electron Integrals	290
	Core-Core Repulsion Integrals	291
	Mixed Model (MNDO, AM1, and PM3)	292
AM1 and PM3		292
ZINDO/1		294
	Overlap Weighting Factors	295
	Mixed Model	295
ZINDO/S		296
	Mixed Model	296

Chapter 13 Computational Options 299

Single Points on a Potential Energy Surface	299
Local Minima on a Potential Energy Surface	301
Unconstrained Geometry Optimization	302
Optimization Methods	303
Steepest Descent	303
Conjugate Gradient Methods	304
Fletcher-Reeves	305
Polak-Ribiere	306
Newton-Raphson Methods	306
Block Diagonal Newton-Raphson	306
Transition Structures on a Potential Energy Surface	307
Transition States Search Methods	308

Eigenvector Following Method	308
Synchronous Transit Method	309
Molecular Dynamics on a Potential Energy Surface	310
Temperature	310
Statistical Averaging	311
Background	311
Newton's Equations of Motion	311
Leap-frog Algorithm	311
Statistical Mechanical Averages	312
Random Velocities or Restart Velocities	312
The Basic Phases of a Trajectory	313
The Fundamental Time Step	314
Heating and Cooling	314
Equilibration at a Temperature T	316
Collecting Data	316
Free Dynamics or Constant Temperature Dynamics	317
Data, Averaging, Snapshot, and Screen Refresh Periods	318
The Data Collection Period	318
The Statistical Averaging Period	318
The Snapshot Collection Period	318
The Screen Refresh Period	319
Averaging Energetic and Structural Data	319
Averaging Energetic Values	320
Averaging Named Selections	321
Deviations from the Average	321
The CSV File	322
Plotting Instantaneous Values Along the Trajectory	323
Obtaining and Understanding MD Graphs	323
Placing Graphs into Other Documents	324
Collecting Trajectory for Subsequent Playback	324
Creating a Snapshot (SNP) file	325
Reading a (HIN, SNP) File for Playback.	326
Global Minima on a Potential Energy Surface	327
Simulated Annealing	327
Simple Reactions on a Potential Energy Surface	327
Trajectory Analysis.	328
Setting Initial Coordinates and Velocities	329
Temperature Considerations.	330
RHF/UHF Considerations.	330
UV Visible Spectroscopy	331
Vibrational Analysis and IR Spectroscopy	332
Vibrational Calculation	332
Normal Coordinate Analysis	333

Infrared Absorption 336

Index

341

Preface

HyperChem Computational Chemistry contains two parts. Part 1, the *Practical Guide*, contains an overview and introduction to the types of calculations that you can perform with HyperChem™. Part 2, *Theory and Methods*, provides detailed information on the specific implementation of calculations in HyperChem.

This *Practical Guide* first explores the discipline of computational chemistry and the nature of HyperChem calculations. Next, it examines the concept of a potential energy surface and three calculations of the potential energy surface: single point, geometry optimization, and molecular dynamics. These calculations provide the energies and energy derivatives you need to construct and examine potential energy surfaces. Finally, the *Practical Guide* illustrates strategies for specific calculations.

Theory and Methods includes the equations, analytical descriptions, and data you need to understand the calculations. It deals with the science behind HyperChem calculations. Information on parameters and settings lets you modify and customize calculations.

Who Should Read this Guide?

HyperChem Computational Chemistry is for both novice computational chemists and for scientists with advanced knowledge and experience.

Novice users can benefit from this book in several ways:

- It gives an overview of the computational chemistry methods that you'll find in HyperChem. The overview acquaints you with the program and the power of methods.
- It helps you choose computational techniques and protocols.

- It includes general references to aid you in more detailed study. Although these references are not comprehensive, some are key references. Other references provide examples of research problems using these computational methods.

Advanced users can also benefit from reading this guide. Many people use a limited number of algorithms and methods for chemical calculations. This book compares of the different methods in HyperChem and helps you determine the most appropriate method for your research problems. The book discusses strengths and weaknesses of the methods and algorithms.

Annotated Bibliography

Although you can investigate many research problems after reading the *HyperChem Reference Manual* and *HyperChem Computational Chemistry*, you may also need information from textbooks and current journals. The following list of selected texts can supply the background necessary for understanding the calculations in HyperChem.

Allen, M.P.; Tildesley, D.J. *Computer Simulation of Liquids*, Clarendon Press, Oxford, 1987.

An important though demanding book. Topics include statistical mechanics, Monte Carlo simulations, equilibrium and non-equilibrium molecular dynamics, analysis of calculational results, and applications of methods to problems in liquid dynamics. The authors also discuss and compare many algorithms used in force field simulations. Includes a microfiche containing dozens of Fortran-77 subroutines relevant to molecular dynamics and liquid simulations.

Berkert, U.; Allinger, N.L. *Molecular Mechanics*, American Chemical Society Monograph 177, Washington, D.C., 1982.

The classical introduction to molecular mechanics calculations. The authors describe common components of force fields, parameterization methods, and molecular mechanics computational methods. Discusses the application of molecular mechanics to molecules common in organic and biochemistry. Several chapters deal with thermodynamic and chemical reaction calculations.

Brooks III, C.L.; Karplus, M.; Pettitt, B.M. *Proteins: A Theoretical Perspective of Dynamics, Structure, and Thermodynamics*, in: *Advances in Chemical Physics*, Vol. 71. John Wiley and Sons, New York, 1988.

This text is similar to that of McCammon and Harvey (see below), but also provides a background for force field-based calculations and a more sophisticated discussion. Includes numerous examples of computing the structure, dynamics, and thermodynamics of proteins. The authors provide an interesting chapter on the complementary nature of molecular mechanics calculations and specific experimental techniques.

Clark, T. *A Handbook of Computational Chemistry*, John Wiley and Sons, New York, 1985.

A practical introduction to molecular mechanics and semi-empirical quantum mechanics calculations, with extensive examples from the MMP2 (not in HyperChem), MINDO/3, and MNDO methods. One of the more accessible books for new computational chemists.

Dewar, M.J.S. *The Molecular Orbital Theory of Organic Chemistry*. McGraw-Hill, New York, 1969.

Provides a survey of quantum mechanics, semi-empirical computational methods, and the application of molecular orbital theory to organic chemistry. The concepts explored in this book should be easy for most readers to understand.

Hehre, W.J.; Radom, L.; Schleyer, P.v.R.; Pople, J.A. *Ab Initio Molecular Orbital Theory*, John Wiley and Sons, New York, 1986

Covers theory and applications of *ab initio* quantum mechanics calculations. The discussions are useful for understanding the differences between *ab initio* and semi-empirical methods. Although both sections are valuable, the discussion of the applications of *ab initio* theory fills a void. It includes comparisons between experiment and many types and levels of calculation. The material is helpful in determining strategies for, and the validity of, *ab initio* calculations.

Lipkowitz, K.B.; Boyd, D.B., Eds., *Reviews in Computational Chemistry*, VCH Publishers, New York, 1990.

Contains nine reviews in computational chemistry by various experts. This book is particularly useful for beginning computational chemists. Six chapters address issues relevant to HyperChem, including semi-empirical quantum mechanics

methods, using the results of semi-empirical calculations to obtain molecular properties, and a brief review of empirical calculations (particularly molecular dynamics). The chapter by D. B. Boyd, "Aspects of Molecular Modeling," contains an excellent basic review of quantum mechanics calculations and summaries of the accuracy of these methods.

McCammon, J.A.; Harvey, S.C. *Dynamics of Proteins and Nucleic Acids*, Cambridge University Press, Cambridge, 1987.

Focuses on force field calculations for understanding the dynamic properties of proteins and nucleic acids. Provides a useful introduction to several computational techniques, including molecular mechanics minimization and molecular dynamics. Includes discussions of research involving structural changes and short time scale dynamics of these biomolecules, and the influence of solvent in these processes.

Szabo, A.; Ostlund, N.S. *Modern Quantum Chemistry*, McGraw-Hill, New York, 1989.

A textbook describing the theory associated with calculations of the electronic structure of molecular systems. While the book focuses on *ab initio* calculations, much of the information is also relevant to semi-empirical methods. The sections on the Hartree-Fock and Configuration Interactions methods, in particular, apply to HyperChem. The self-paced exercises are useful for the beginning computational chemist.

Pople, J.A.; Beveridge, D.L. *Approximate Molecular Orbital Theory* McGraw-Hill, New York, 1970.

Presents the basic theory of quantum mechanics, particularly, semi-empirical molecular orbital theory. The authors detail and justify the approximations inherent in the semi-empirical Hamiltonians. Includes useful discussions of the applications of these methods to specific research problems.

Stewart, J.J.P. MOPAC: A Semiempirical Molecular Orbital Program. *J. Computer-Aided Molecular Design* 4:1-105, 1990.

A valuable review of the MOPAC program and the semi-empirical methods MNDO, MINDO/3, AM1, and PM3. Of particular use are theoretical discussions of these semi-empirical methods and many tables validating the accuracy of the MOPAC program and its associated Hamiltonians.

HyperChem® Computational Chemistry

**Part 1
Practical Guide**

Chapter 1

Practical Guide Introduction

What is Computational Chemistry?

Computational chemistry is a new discipline. Its advent and popularity have paralleled improvements in computing power during the last several decades. As with other disciplines in chemistry, computational chemistry uses tools to understand chemical reactions and processes. Scientists use computer software to gain insight into chemical processes. Although computational chemists frequently develop and refine software tools, their primary interest is in applying software tools to enhance chemical knowledge.

The challenges for computational chemistry are to characterize and predict the structure and stability of chemical systems, to estimate energy differences between different states, and to explain reaction pathways and mechanisms at the atomic level. Meeting these challenges could eliminate time-consuming experiments.

Software tools for computational chemistry are often based on empirical information. To use these tools, you need to understand how the technique is implemented and the nature of the database used to parameterize the method.¹ You use this knowledge to determine the most appropriate tools for specific investigations and to define the limits of confidence in results.

To ensure that computational chemistry develops in an orderly way, researchers must provide certain information so that others can reproduce and analyze their results. Gund *et al.* proposed guidelines for reporting molecular modeling results.² You should consider these guidelines for your publications.

1. Dearing, A., Computer-aided Molecular Modelling: Research Study or Research Tool *J. Computer-Aided Molecular Design* 2:179–189, 1988.

2. Gund, P.; Barry, D.C.; Blaney, J.M.; Cohen, N.C. Guidelines for Publications in Molecular Modeling Related to Medicinal Chemistry *J. Med. Chem.* 31:2230–2234, 1988.

What is HyperChem?

HyperChem is a versatile molecular modeler and editor and a powerful computational package. It offers many types of molecular and quantum mechanics calculations.

Building and Displaying Molecules

Submitting a structure to a calculation can be expensive in terms of human time and effort. HyperChem lets you build and display molecules easily. Since HyperChem contains a graphical interface, you can monitor the construction of molecules.

Using the Drawing tool, you can draw a two-dimensional (2D) representation of a molecule, and then use the Model Builder to generate a three-dimensional (3D) structure. The Model Builder adds implicit hydrogens to the molecule at your request. You can also manipulate individual bonds, bond geometries, angles, torsions, and atomic charges during model building (using the Constrain commands on the Build menu) or after model building (using the Set commands on the Edit menu).

HyperChem contains a database of amino and nucleic acid residues so you can quickly build polymers containing these subunits. You can also read in structures in files from standard databases, such as the Brookhaven Protein Data Bank (see the *HyperChem Reference Manual*).

Optimizing the Structures of Molecules

To calculate the properties of a molecule, you need to generate a well-defined structure. A calculation often requires a structure that represents a minimum on a potential energy surface. HyperChem contains several geometry optimizers to do this. You can then calculate single point properties of a molecule or use the optimized structure as a starting point for subsequent calculations, such as molecular dynamics simulations.

Investigating the Reactivity of Molecules

You can use HyperChem to investigate the reactivity of molecules and their functional groups. One method is to use Frontier Molec-

ular Orbital Theory³. You can use molecular orbital energies, coefficients, and nodal properties from single point quantum mechanics calculations to investigate issues such as the relative reactivity of different molecular substituents, regioselectivity of reactions, and site-selectivity of nucleophiles and electrophiles.

Generating and Viewing Orbitals and Electronic Plots

HyperChem can plot orbital wave functions resulting from semi-empirical and *ab initio* quantum mechanical calculations. It is interesting to view both the nodal properties and the relative sizes of the wave functions. Orbital wave functions can provide chemical insights.

You can also plot the electrostatic potential, the total charge density, or the total spin density determined during a semi-empirical or *ab initio* calculation. This information is useful in determining reactivity and correlating calculational results with experimental data. These examples illustrate uses of these plots:

- If you calculate the electrostatic potential for cyclopropane, three minima occur in regions that bisect the carbon-carbon bonds. This result is consistent with protonation of cyclopropane occurring along the bond bisector.
- Spin densities help to predict the observed coupling constants in electron spin resonance (ESR) spectroscopy. From spin density plots you can predict a direct relationship between the spin density on a carbon atom and the coupling constant associated with an adjacent hydrogen.

Evaluating Chemical Pathways and Mechanisms

Calculating single point properties and energies provides information about chemical pathways and mechanisms.

Example: Researchers have used MNDO and AM1 semi-empirical methods to calculate possible reaction pathways for the interaction of glycine and cocaine.⁴ In choosing possible interaction sites,

3. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions* John Wiley & Sons, New York, 1976.

4. Wu, C.S.; Neely, W.C.; Worley, S.D. A Semiempirical Theoretical Study of the Molecular Interaction of Cocaine with the Biological Substrate Glycine. *J. Comput. Chem.* 12:862-867, 1991.

they first calculated atomic charges and HOMO-LUMO (highest occupied and lowest unoccupied molecular orbitals) electron densities for the two molecules. Using this information, they proposed two possible reaction pathways and computed the heats of formation for geometry-optimized structures.

Studying the Dynamic Behavior of Molecules

A molecular system at room temperature is accurately characterized by its motion. Molecular dynamics simulations calculate the future positions and velocities of atoms based upon their current values. You can obtain qualitative and quantitative data from HyperChem molecular dynamics simulations.

The greatest value of molecular dynamic simulations is that they complement and help to explain existing data for designing new experiments. The simulations are increasingly useful for structural refinement of models generated from NMR, distance geometry, and X-ray data.

The results are also important for investigating macromolecules, where concerted motions may occur during ligand binding, enzymatic activity, and molecular recognition. Using constant temperature molecular dynamics, you can investigate an enzyme that has a loop of residues flanking the active site. You can store snapshots of a molecular dynamic trajectory (the set of positions and velocities of atoms over time) and use them to detect possible conformational changes of the loop region that could change the interaction with the active site. You can further investigate conformational change during the course of the simulation by averaging and plotting the dihedral angle values associated with the loop.

Chapter 2

HyperChem Calculations

Exploring Potential Energy Surfaces

HyperChem calculations examine potential energy surfaces with single point calculations, optimizations, and molecular dynamic simulations. Energies and derivatives of energy, such as the forces on atoms, are necessary to “construct” a potential energy surface. This concept gives the molecular and quantum mechanics methods a unifying purpose: they generate the energies and energy derivatives necessary to produce and examine potential energy surfaces.

Both molecular and quantum mechanics methods rely on the Born-Oppenheimer approximation. In quantum mechanics, the Schrödinger equation (1) gives the wave functions and energies of a molecule.

$$H\Psi = E\Psi \quad (1)$$

where H is the molecular Hamiltonian, Ψ is the wave function, and E is the energy. The molecular Hamiltonian is composed of these operators: the kinetic energy of the nuclei (N) and electrons (E), nuclear-nuclear (NN) and electron-electron repulsion (EE), and the attraction between nuclei and electrons (NE) (equation 1).

$$H = (\text{kinetic energy})_N + (\text{kinetic energy})_E + (\text{repulsion})_{NN} \\ + (\text{repulsion})_{EE} + (\text{attraction})_{NE} \quad (2)$$

Nuclei have many times more mass than electrons. During a very small period of time when the movement of heavy nuclei is negligible, electrons are moving so fast that their distribution is smooth. This leads to the approximation that the electron distribution is dependent only on the fixed positions of nuclei and not on their velocities. This approximation allows two simplifications

of the molecular Hamiltonian. The nuclear kinetic energy term drops out (equation 3).

$$\begin{aligned} H = & (\text{kinetic energy})_E + (\text{repulsion})_{NN} + (\text{repulsion})_{EE} \\ & + (\text{attraction})_{NE} \end{aligned} \quad (3)$$

Since the nuclear-nuclear repulsion is constant for a fixed configuration of atoms, this term also drops out. The Hamiltonian is now purely electronic.

$$H_{\text{electronic}} = (\text{kinetic energy})_E + (\text{repulsion})_{EE} + (\text{attraction})_{NE} \quad (4)$$

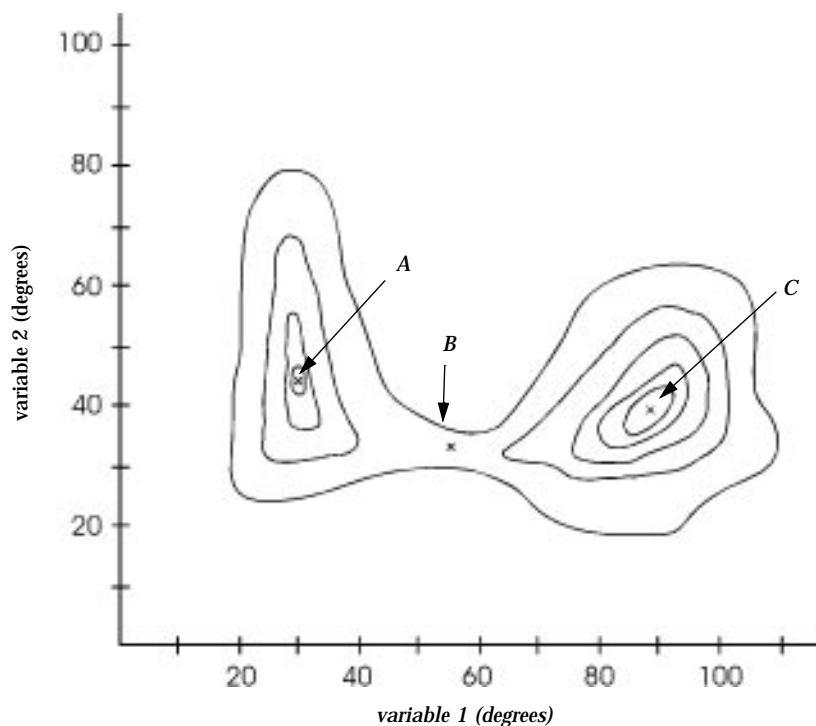
After solving the electronic Schrödinger equation (equation 4), to calculate a potential energy surface, you must add back nuclear-nuclear repulsions (equation 5).

$$\begin{aligned} H_{\text{electronic}} \Psi_{\text{electronic}} &= E_{\text{electronic}} \Psi_{\text{electronic}} \\ V_{\text{PES}} &= E_{\text{electronic}} + (\text{repulsion})_{NN} \end{aligned} \quad (5)$$

Generating the potential energy surface (PES) using this equation requires solutions for many configurations of nuclei. In molecular mechanics, the electronic energy is not evaluated explicitly. Instead, these methods solve the potential energy surface by using a force field equation (see “Molecular Mechanics” on page 21). The force field equation represents electronic energy implicitly through parameterization.

The dimensionality of a potential energy surface depends on the number of degrees of freedom in a molecule. If V_{PES} is a function of two variables, then a plot of the potential energy surface represents a 3D space.

Example: In this plot of a potential energy surface with two variables, points A and C are both minima.



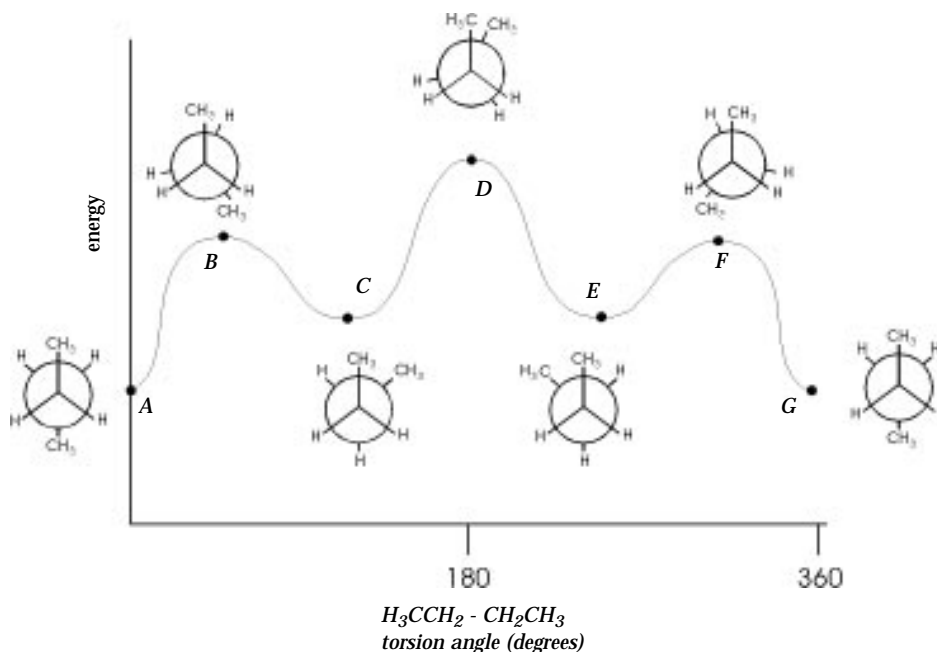
This means that the forces on the atoms are zero for the structures found at A and C. The structure at C is more stable than the structure at A. In fact, C is the *global* minimum for this example. Geometry optimizations seek minima such as A and C.

Point B is a maximum along the path from A to C (saddle point). The forces on the atoms are also zero for this structure. Point B represents a transition state for the transformation of A to C.

Convergence of a geometry optimization calculation does not necessarily mean that the calculation found a minimum on the potential energy surface. To categorize a point definitively on the potential energy surface, you must calculate the second derivatives of the potential energy with respect to atomic coordinates. You can then calculate vibrational frequencies from the second derivative matrix. A minimum configuration has six vibrational frequencies with a value of zero. For linear molecules the minimum is five with zero values. A transition state has one vibrational frequency, and this frequency is an imaginary number.

The path of minimum potential energy that connects reactants and products is known as the *reaction coordinate*.

Example: The reaction coordinate for rotation about the central carbon-carbon bond in *n*-butane has several stationary points. A, C, E, and G are minima and B, D, and F are maxima. Only the structures at the minima represent stable species and of these, the *anti* conformation is more stable than the *gauche*.



Complexity of Potential Energy Surfaces

Most potential energy surfaces are extremely complex. Elber and Karplus analyzed a 300 psec molecular dynamics trajectory of the protein myoglobin⁵. They estimate that 2000 thermally accessible minima exist near the native protein structure. The total number of conformations is even larger. Dill derived a formula to calculate the upper bound of thermally accessible conformations in a protein.⁶ Using this formula, a protein of 150 residues (the approx-

5. Elber, R.; Karplus, M. Multiple conformational states of proteins: a molecular dynamics analysis of myoglobin. *Science* 235:318-321, 1987.

6. Dill, K.A. Theory for the folding and stability of globular proteins. *Biochemistry* 24:1501-1509, 1985.

imate size of myoglobin) has an upper limit of 4×10^{34} conformations for the backbone atoms. Here are two of the consequences of this complexity:

- A single stable structure may not adequately represent the properties of a molecule. You should investigate a Boltzmann distribution of thermally accessible potential structures.
- For all but the smallest of molecules, a search for the global minimum may be impossible.

United atom force fields (see “United versus All Atom Force Fields” on page 28) are sometimes used for biomolecules to decrease the number of nonbonded interactions and the computation time. Another reason for using a simplified potential is to reduce the dimensionality of the potential energy surface. This, in turn, allows for more samples of the surface.

Example: Crippen and Snow reported their success in developing a simplified potential for protein folding⁷. In their model, single points represent amino acids. For the avian pancreatic polypeptide, the native structure is not at a potential minimum. However, a global search found that the most stable potential minimum had only a 1.8 Ångstrom root-mean-square deviation from the native structure.

Example: Solvation can have a profound effect on the potential energy profile for a reaction. Jorgensen’s research group provided important insights into the role of solvation⁸. Consider the nucleophilic addition of the hydroxide anion to formaldehyde:

Ab initio, gas phase calculations found two minima and one maximum for the reaction coordinate, leading to an exothermic formation of the tetrahedral complex. One minimum is an ion-dipole complex at a $\text{H}_2(\text{O})\text{C}-\text{OH}^-$ distance of 2.74 Ångstroms. The second is the tetrahedral complex at a $\text{H}_2(\text{O})\text{C}-\text{OH}^-$ distance of 1.47 Ångstroms. A potential-of-mean-force calculation was performed using a Monte Carlo simulation of the reactants in TIP4P water. The reaction coordinate showed no ion-dipole complex. In contrast to the gas phase study, the tetrahedral intermediate was

7. Crippen, G.M.; Snow, M.E. A 1.8Å resolution potential function for protein folding. *Biopolymers* 29:1479-1489, 1990.

8. Madura, J.D.; Jorgensen, W.L. *Ab initio* and Monte Carlo calculations for a nucleophilic addition reaction in the gas phase and in aqueous solution. *J. Am. Chem. Soc.* 108:2517-2527, 1986.

10–14 kcal/mol less stable than the reactants and there was a 24–28 kcal/mol activation barrier to the formation of the tetrahedral intermediate.

Types of Calculations

There are three types of calculations in HyperChem: single point, geometry optimization or minimization, and molecular dynamics.

Single Point

A single point calculation gives the static properties of a molecule. The properties include potential energy, derivatives of the potential energy, electrostatic potential, molecular orbital energies, and the coefficients of molecular orbitals for ground or excited states. The input molecular structure for a single point calculation usually reflects the coordinates of a stationary point on the potential energy surface, typically a minimum or transition state. Use a geometry optimization to prepare a molecule for a single point calculation.

One type of single point calculation, that of calculating vibrational properties, is distinguished as a *vibrations* calculation in HyperChem. A *vibrations* calculation predicts fundamental vibrational frequencies, infrared absorption intensities, and normal modes for a geometry optimized molecular structure.

You can use a single point calculation that determines energies for ground and excited states, using configuration interaction, to predict frequencies and intensities of an electronic ultraviolet-visible spectrum.

Geometry Optimization

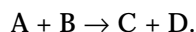
To carry out a geometry optimization (minimization), HyperChem starts with a set of Cartesian coordinates for a molecule and tries to find a new set of coordinates with a minimum potential energy. You should appreciate that the potential energy surface is very complex, even for a molecule containing only a few dihedral angles.

Since minimization calculations cannot cross or penetrate potential energy barriers, the molecular structure found during an opti-

mization may be a local and not a global minimum. The minimum represents the potential energy closest to the starting structure of a molecule. Researchers frequently use minimizations to generate a structure at a stationary point for a subsequent single point calculation or to remove excessive strain in a molecule, preparing it for a molecular dynamics simulation.

Transition State Search

As mentioned earlier, a potential energy surface may contain *saddle points*; that is, *stationary points* where there are one or more directions in which the energy is at a maximum. A saddle point with one negative eigenvalue corresponds to a *transition structure* for a chemical reaction of changing isomeric form. Transition structures also exist for reactions involving separated species, for example, in a bimolecular reaction



Activation energy, *i.e.*, the energy of the transition structure relative to reactants, can be observed experimentally. However, the only way that the geometries of transition structures can be evaluated is from theory. Theory also can give energetics and geometry parameters of short-lived reaction intermediates.

Transition state search algorithms rather climb up the potential energy surface, unlike geometry optimization routines where an energy minimum is searched for. The characterization of even a simple reaction potential surface may result in location of more than one transition structure, and is likely to require many more individual calculations than are necessary to obtain equilibrium geometries for either reactant or product.

Calculated transition structures may be very sensitive to the level of theory employed. Semi-empirical methods, since they are parametrized for energy minimum structures, may be less appropriate for transition state searching than *ab initio* methods are. Transition structures are normally characterized by weak “partial” bonds, that is, being broken or formed. In these cases UHF calculations are necessary, and sometimes even the inclusion of electron correlation effects.

Molecular Dynamics

A molecular dynamics simulation samples phase space (the region defined by atomic positions and velocities) by integrating numerically Newton's equations of motion. Unlike single point and geometry optimization calculations, molecular dynamics calculations account for thermal motion. Molecules may contain enough thermal energy to cross potential barriers. Molecular dynamics calculations provide information about possible conformations, thermodynamic properties, and dynamic behavior of molecules. (See also "Studying the Dynamic Behavior of Molecules" on page 10.)

Langevin Dynamics

Molecules in solution undergo collisions with other molecules and experience frictional forces as they move through the solvent. Using Langevin dynamics, you can model these effects and study the dynamical behavior of a molecular system in a liquid environment. These simulations can be much faster than molecular dynamics. Instead of explicitly including solvent molecules, the Langevin method models their effect through random forces applied to the molecule of interest to simulate collisions, and frictional forces are added to model the energy losses associated with these collisions.

Langevin dynamics simulations can be used to study the same kinds of problems as molecular dynamics: time dependent properties of solvated systems at non-zero temperatures. Because of the implicit treatment of the solvent, this method is particularly well-suited for studying large molecules in solution. It is possible to decouple the time scales of molecular motion and focus on just the slow modes associated with conformational changes, for example, or to follow the rapid bond stretching motions leading to chemical reaction, while incorporating the influence of molecular collisions. Langevin dynamics has been used to study solvent effects on the structural dynamics of the active site of the enzyme lysozyme, conformational equilibria and the dynamics of conformational transitions in liquid alkanes, and temperature effects on a system of interacting quantum harmonic oscillators.

Monte Carlo Simulations

The Monte Carlo method samples phase space by generating random configurations from a Boltzmann distribution at a given temperature. Averages computed from a properly equilibrated Monte Carlo simulation correspond to thermodynamic ensemble averages. Thus, the Monte Carlo method can be used to find average energies and equilibrium structural properties of complex interacting systems.

A sequence of successive configurations from a Monte Carlo simulation constitutes a trajectory in phase space; with HyperChem, this trajectory may be saved and played back in the same way as a dynamics trajectory. With appropriate choices of setup parameters, the Monte Carlo method may achieve equilibration more rapidly than molecular dynamics. For some systems, then, Monte Carlo provides a more direct route to equilibrium structural and thermodynamic properties. However, these calculations can be quite long, depending upon the system studied.

Monte Carlo simulations provide an alternate approach to the generation of stable conformations. As with HyperChem's other simulation methods, the effects of temperature changes and solvation are easily incorporated into the calculations.

Chapter 3

Calculation Methods

HyperChem uses two types of methods in calculations: molecular mechanics and quantum mechanics. The quantum mechanics methods implemented in HyperChem include semi-empirical quantum mechanics method and *ab initio* quantum mechanics method. The molecular mechanics and semi-empirical quantum mechanics methods have several advantages over *ab initio* methods. Most importantly, these methods are fast. While this may not be important for small molecules, it is certainly important for biomolecules. Another advantage is that for specific and well-parameterized molecular systems, these methods can calculate values that are closer to experiment than lower level *ab initio* techniques.

The accuracy of a molecular mechanics or semi-empirical quantum mechanics method depends on the database used to parameterize the method. This is true for the type of molecules and the physical and chemical data in the database. Frequently, these methods give the best results for a limited class of molecules or phenomena. A disadvantage of these methods is that you must have parameters available before running a calculation. Developing parameters is time-consuming.

The *ab initio* method may overcome this problem. However it is slower than any molecular mechanics and semi-empirical methods.

Molecular Mechanics

Molecular mechanical force fields use the equations of classical mechanics to describe the potential energy surfaces and physical properties of molecules. A molecule is described as a collection of atoms that interact with each other by simple analytical functions. This description is called a *force field*. One component of a force field is the energy arising from compression and stretching a bond.

This component is often approximated as a harmonic oscillator and can be calculated using Hooke's law.

$$V_{\text{spring}} = \frac{1}{2}K_r(r - r_0)^2 \quad (7)$$

The bonding between two atoms is analogous to a spring connecting two masses. Using this analogy, equation 7 gives the potential energy of the system of masses, V_{spring} , and the force constant of the spring, K_r . The equilibrium and displaced distances of the atoms in a bond are r_0 and r . Both K_r and r_0 are constants for a specific pair of atoms connected by a certain spring. K_r and r_0 are force field *parameters*.

The potential energy of a molecular system in a force field is the sum of individual components of the potential, such as bond, angle, and van der Waals potentials (equation 8). The energies of the individual bonding components (bonds, angles, and dihedrals) are functions of the deviation of a molecule from a hypothetical compound that has bonded interactions at minimum values.

$$E_{\text{Total}} = \text{term}_1 + \text{term}_2 + \dots + \text{term}_n \quad (8)$$

The absolute energy of a molecule in molecular mechanics has no intrinsic physical meaning; E_{Total} values are useful only for comparisons between molecules. Energies from single point calculations are related to the enthalpies of the molecules. However, they are not enthalpies because thermal motion and temperature-dependent contributions are absent from the energy terms (equation 8).

Unlike quantum mechanics, molecular mechanics does not treat electrons explicitly. Molecular mechanics calculations cannot describe bond formation, bond breaking, or systems in which electronic delocalization or molecular orbital interactions play a major role in determining geometry or properties.

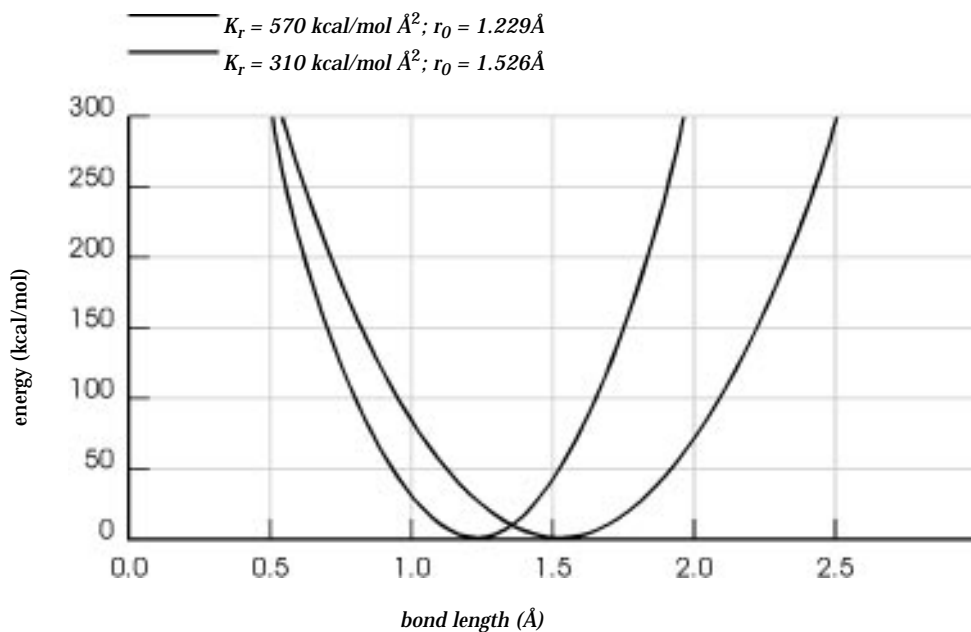
This discussion focuses on the individual components of a typical molecular mechanics force field. It illustrates the mathematical functions used, why those functions are chosen, and the circumstances under which the functions become poor approximations. Part 2 of this book, *Theory and Methods*, includes details on the implementation of the MM+, AMBER, BIO+, and OPLS force fields in HyperChem.

Bonds and Angles

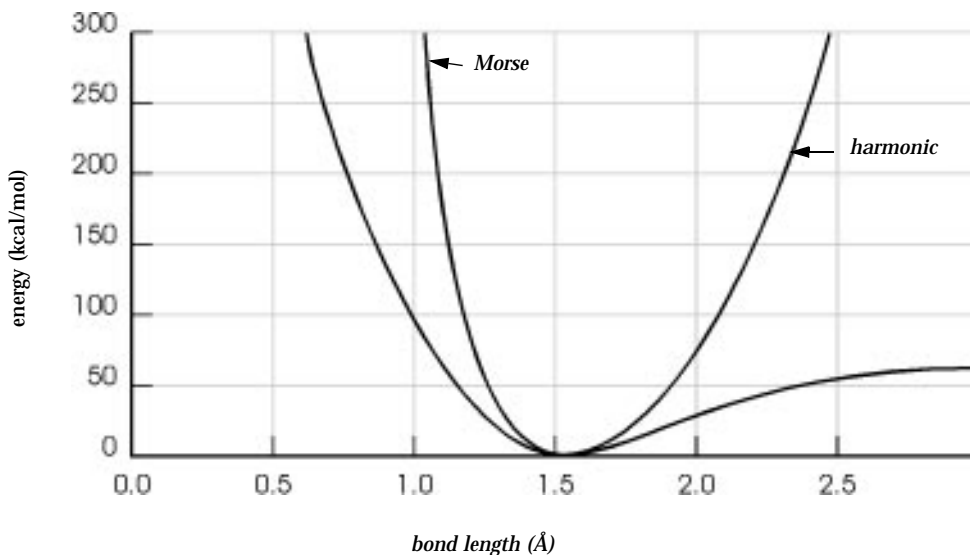
HyperChem uses harmonic functions to calculate potentials for bonds and bond angles (equation 9).

$$V_{\text{stretch}} = \sum_{\text{bond}} K_r (r - r_0)^2 \quad V_{\text{bend}} = \sum_{\text{angle}} K_\theta (\theta - \theta_0)^2 \quad (9)$$

Example: For the AMBER force field, a carbonyl C–O bond has an equilibrium bond length of 1.229 Å and a force constant of 570 kcal/mol Å². The potential for an aliphatic C–C bond has a minimum at 1.526 Å. The slope of the latter potential is less steep; a C–C bond has a force constant of 310 kcal/mol Å².



A Morse function best approximates a bond potential. One of the obvious differences between a Morse and harmonic potential is that only the Morse potential can describe a dissociating bond.



The Morse function rises more steeply than the harmonic potential at short bonding distances. This difference can be important especially during molecular dynamics simulations, where thermal energy takes a molecule away from a potential minimum.

In light of the differences between a Morse and a harmonic potential, why do force fields use the harmonic potential? First, the harmonic potential is faster to compute and easier to parameterize than the Morse function. The two functions are similar at the potential minimum, so they provide similar values for equilibrium structures. As computer resources expand and as simulations of thermal motion (See “Molecular Dynamics”, page 69) become more popular, the Morse function may be used more often.

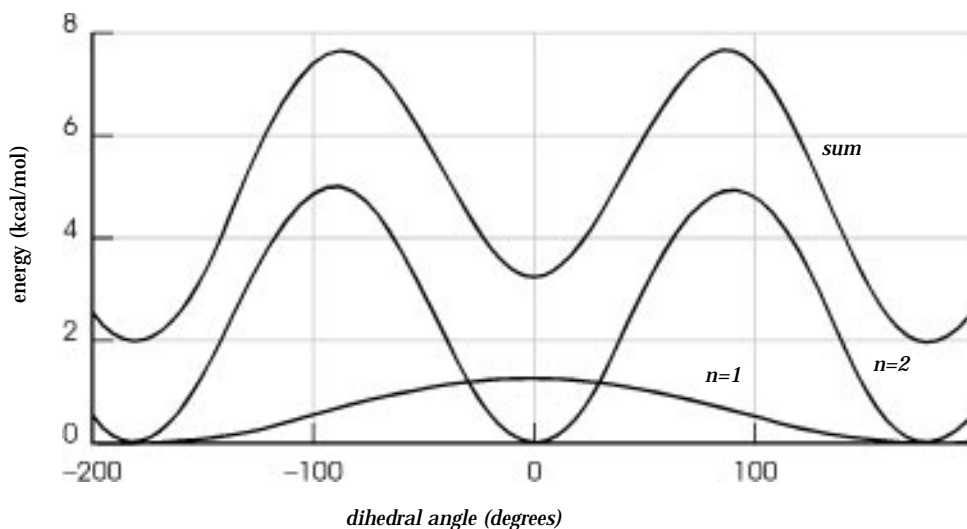
Torsions

In molecular mechanics, the dihedral potential function is often implemented as a truncated Fourier series. This periodic function (equation 10) is appropriate for the torsional potential.

$$V_{\text{dihedrals}} = \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \phi_0)] \quad (10)$$

In this representative dihedral potential, V_n is the dihedral force constant, n is the periodicity of the Fourier term, ϕ_0 is the phase angle, and ϕ is the dihedral angle.

Example: This example of an HN-C(O) amide torsion uses the AMBER force field. The Fourier component with a periodicity of one ($n = 1$) also has a phase shift of 0 degrees. This component shows a maximum at a dihedral angle of 0 degrees and minima at both -180 and 180 degrees. The potential uses another Fourier component with a periodicity of two ($n = 2$).



The relative sizes of the potential barriers indicate that the V_2 force constant is larger than the V_1 constant. The phase shift is 180 degrees for the Fourier component with a two-fold barrier. Minima occur at -180, 0, and 180 degrees and maxima at -90 and 90

degrees. Adding the two Fourier terms results in potential with minima at -180 , 0 , and 180 degrees and maxima at -90 and 90 degrees. (The “sum” potential is shifted by 2 kcal/mol to make this illustration legible.) Note that the addition of V_1 to V_2 shows that the *cis* conformation (dihedral_{h_{nc}o} = 0 degrees) is destabilized relative to the *trans* conformation (dihedral_{h_{nc}o} = 180 degrees).

van der Waals Interactions and Hydrogen Bonding

A 6–12 function (also known as a Lennard-Jones function) frequently simulates van der Waals interactions in force fields (equation 11).

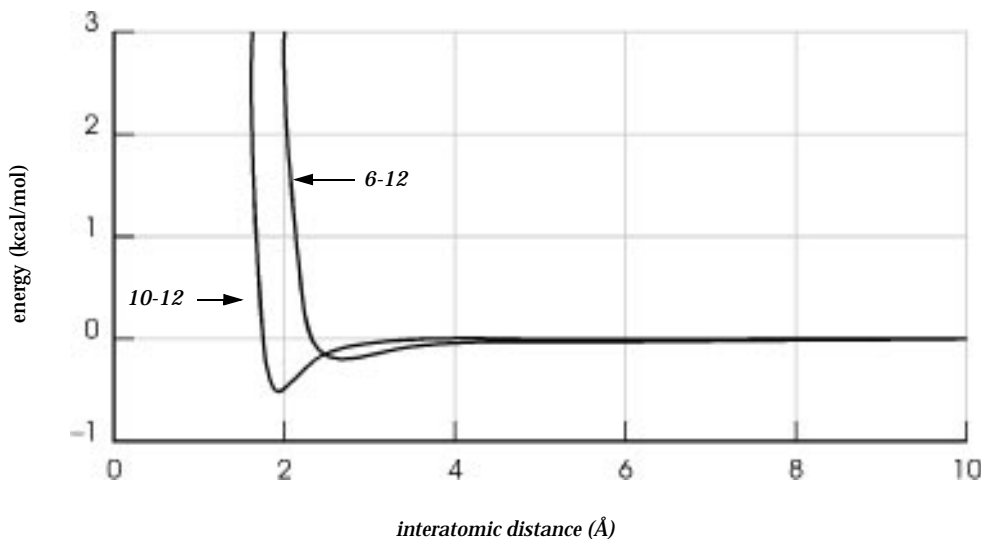
$$V_{\text{VDR}} = \sum_{i < j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} \right] \quad (11)$$

R_{ij} is the nonbonded distance between two atoms. A_{ij} , and B_{ij} are van der Waals parameters for the interacting pair of atoms. The R^{-6} term describes the attractive London dispersion interaction between two atoms, and the R^{-12} term describes the repulsive interaction caused by Pauli exclusion. The 6–12 function is not as appropriate physically as a 6-exponential function, but it is faster to compute.

The AMBER force field replaces the van der Waals by a 10–12 potential for pairs of atoms that can participate in hydrogen bonding (equation 12). The hydrogen bond potential does not contribute significantly to the hydrogen bonding attraction between two atoms; rather, it is implemented to fine-tune the distances between these atoms.

$$V_{\text{Hbonds}} = \sum_{\text{Hbonds}} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right] \quad (12)$$

Example: In this example, the van der Waals (6–12) and hydrogen bond (10–12) potentials are quickly damped.



The attraction for two neutral atoms separated by more than four Ångstroms is approximately zero. The depth of the potential wells is minimal. For the AMBER force field, hydrogen bonds have well depths of about 0.5 kcal/mol; the magnitude of individual van der Waals well depths is usually less.

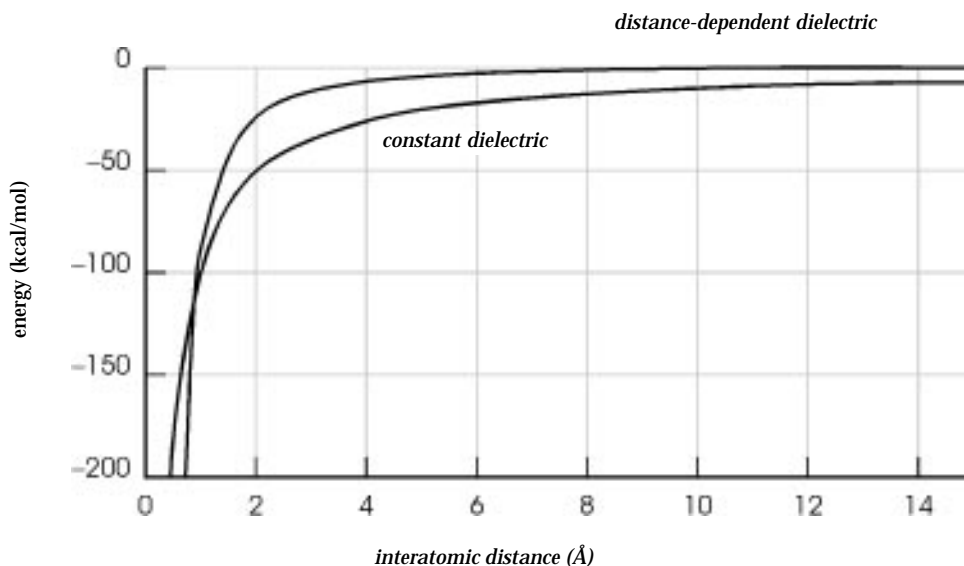
Electrostatic Potential

This is a typical function for electrostatic potential (equation 13).

$$V_{\text{EEL}} = \sum_{i < j} \frac{q_i q_j}{\epsilon R_{ij}} \quad (13)$$

In this model of electrostatic interactions, two atoms (*i* and *j*) have point charges q_i and q_j . The magnitude of the electrostatic energy (V_{EEL}) varies inversely with the distance between the atoms, R_{ij} . The effective dielectric constant is ϵ . For *in vacuo* simulations or simulations with explicit water molecules, the denominator equals ϵR_{ij} . In some force fields, a distance-dependent dielectric, where the denominator is $\epsilon R_{ij} \cdot R_{ij}$, represents solvent implicitly.

Example: For nonbonded interaction between two atoms having point charges of 0.616 and $-0.504 e$, a distance-dependent dielectric, compared to a constant dielectric, reduces long range electrostatic interactions. Unlike van der Waals and hydrogen bond potentials, the magnitude of electrostatic potential energy between two atoms is large and remains significant over long non-bonded distances.



United versus All Atom Force Fields

Because of the restricted availability of computational resources, some force fields use United Atom types. This type of force field represents implicitly all hydrogens associated with a methyl, methylene, or methine group. The van der Waals parameters for united atom carbons reflect the increased size because of the implicit (included) hydrogens.

United Atom force fields are used often for biological polymers. In these molecules, a reduced number of explicit hydrogens can have a notable effect on the speed of the calculation. Both the BIO+ and OPLS force fields are United Atom force fields. AMBER contains both a United and an All Atom force field.

Caution: If you are new to computational chemistry, do not use United Atoms for AMBER calculations. This HyperChem option is available for researchers who want to alter atom types and parameters for this force field.

Cutoffs

Force field calculations often truncate the nonbonded potential energy of a molecular system at some finite distance. Truncation (nonbonded cutoff) saves computing resources. Also, periodic boxes and boundary conditions require it. However, this approximation is too crude for some calculations. For example, a molecular dynamic simulation with an abruptly truncated potential produces anomalous and nonphysical behavior. One symptom is that the solute (for example, a protein) cools and the solvent (water) heats rapidly. The temperatures of system components then slowly converge until the system appears to be in equilibrium, but it is not.

A relatively simple method for alleviating some of the nonphysical behaviors caused by imposing a nonbonded cutoff is to use a potential switching function (equation 14).

$$\text{When } R_{ij} \leq R_{\text{on}}, \quad E'_{\text{EEL}} = E_{\text{EEL}} \geq 1$$

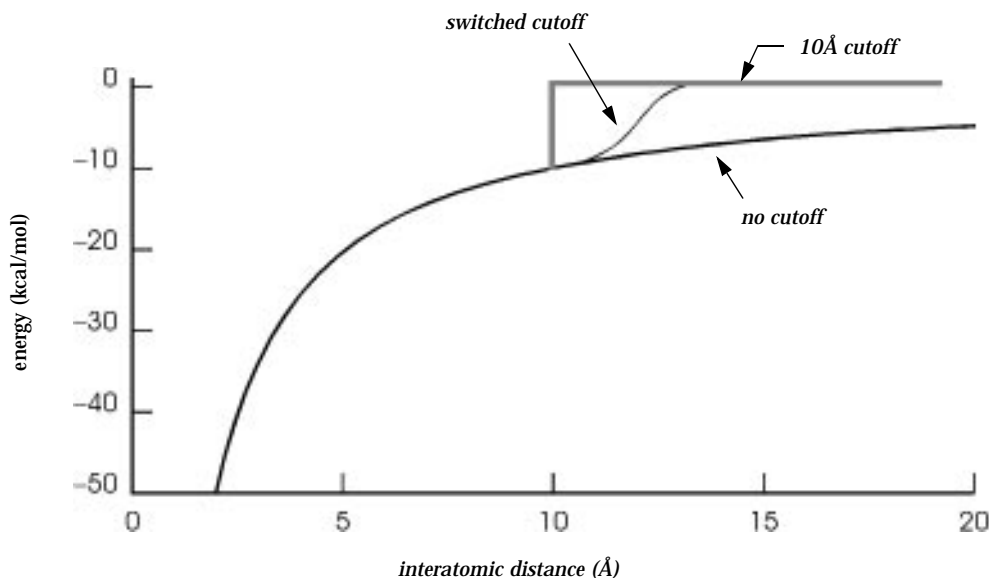
$$\text{When } R_{\text{on}} < R_{ij} \leq R_{\text{off}}$$

$$E'_{\text{EEL}} = E_{\text{EEL}} \bullet \frac{(R_{\text{off}} - R_{ij})^2 (R_{\text{off}} + 2R_{ij} - 3R_{\text{on}})}{(R_{\text{off}} - R_{\text{on}})^3} \quad (14)$$

$$\text{When } R_{ij} > R_{\text{off}}, \quad E'_{\text{EEL}} = E_{\text{EEL}} \geq 0$$

These functions allow the nonbonded potential energy to turn off smoothly and systematically, removing artifacts caused by a truncated potential. With an appropriate switching function, the potential function is unaffected except in the region of the switch.

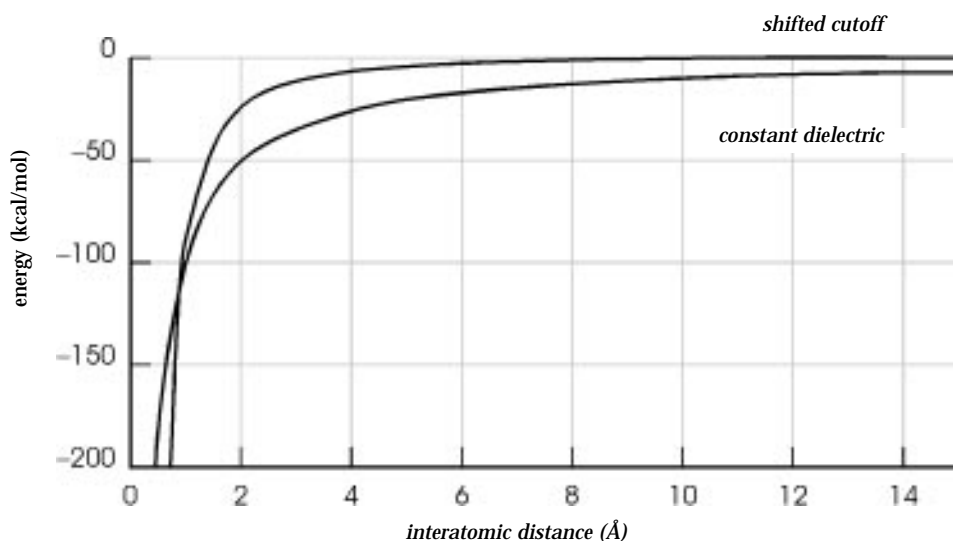
Example: For two atoms having point charges of 0.616 and $-0.504 e$ and a constant dielectric function, the energy curve shows a switching function turned on (R_{on}) at a nonbonded distance of 10 Å and off (R_{off}) at a distance of 14 Å. Compare the switched potential with the abruptly truncated potential.



HyperChem also provides a shifting potential for terminating nonbonded interactions (equation 15).

$$E'_{EEL} = E_{EEL} \cdot \left(1 - \frac{2R_{ij}^2}{R_{off}^2} + \frac{R_{ij}^4}{R_{off}^4} \right) \quad (15)$$

In an attempt to remedy truncation problems, a shifting potential multiplies the nonbonded electrostatic potential by a function that goes to zero. That is, the potential is shifted to zero at the cut-off R_{off} . Unlike the switching function, the shifted potential does not apply to van der Waals interactions.



Caution: Comparing the shifted constant dielectric to a constant dielectric function without a cutoff shows that the shifted dielectric, unlike a switching function, perturbs the entire electrostatic energy curve, not only the region near the cutoff.

Quantum Mechanics

This section provides an overview and review of quantum mechanics calculations. The information can help you use HyperChem to solve practical problems. For quantitative details of quantum mechanics calculations and how HyperChem implements them, see the second part of this book, *Theory and Methods*.

Ab initio quantum mechanics methods have evolved for many decades. The speed and accuracy of *ab initio* calculations have been greatly improved by developing new algorithms and introducing better basis functions.

Semi-empirical quantum mechanics methods have evolved over the last three decades. Using today's microcomputers, they can produce meaningful, often quantitative, results for large molecular systems. The roots of the methods lie in the theory of π electrons, now largely superseded by all-valence electron theories.

Background

Molecules consist of electrons and nuclei. Most applications of quantum chemistry separate the motion of the nuclei from the motion of electrons (the Born-Oppenheimer approximation). The approximation results in a model of nuclei moving on a potential energy surface, with electrons adjusting instantly to changes in nuclear positions. Nuclear motion is constrained by the interaction of nuclei and electrons. At any fixed positions of the nuclei, potential energy is the sum of repulsions among the positively charged nuclei and attractions arising from the electrons. Electrons are the “glue” holding nuclei together.

Molecular Geometry

The most important chemical structures are stable, equilibrium molecular geometries and transition states. Equilibrium geometry of a molecule (bond lengths and angles) describes the coordinates of a deep minimum on a potential energy surface (see page 11). A set of atoms may have a number of potential energy minima, each corresponding to a different isomer of the molecular system. Other, less-deep minima may correspond to intermediates in chemical reactions.

Saddle points serve as models for transition states of chemical reactions. The potential energy for saddle points is a maximum along one direction, called the reaction coordinate, and a minimum along all others. You can think of saddle points as mountain passes: they are the lowest barriers separating reactant and product potential energy valleys. For a discussion of the potential energy surface, see “Exploring Potential Energy Surfaces” on page 11.

Using the coordinates of special geometries, minima, and saddle points, together with the nearby values of potential energy, you can calculate spectroscopic properties and macroscopic thermodynamic and kinetic parameters, such as enthalpies, entropies, and thermal rate constants. HyperChem can provide the geometries and energy values for many of these calculations.

Calculating Electronic Potential Energy

How is electronic potential energy computed? Electrons, which are more than three orders of magnitude lighter than nuclei, are too small for classical mechanics calculations. Electronic energy must

be computed by solving the quantum mechanical Schrödinger equation. The lowest energy solution to this equation is called the ground-state wave function. Molecular orbital methods provide approximate solutions of the Schrödinger equation, the ground-state wave function, and certain low energy excited states.

Quantum mechanics methods have several attractive features:

- They require no information about the location or geometry of bonds in a molecular system.
- Parameters for elements (basis functions in *ab initio* methods usually derived from experimental data and empirical parameters in semi-empirical methods usually obtained from empirical data or *ab initio* calculations) are independent of the chemical environment. In contrast, parameters used in molecular mechanics methods often depend on the chemical environment.
- With simple precautions, quantum mechanics methods can describe bond breaking.
- HyperChem can perform quantum mechanics MO calculations on molecules containing 100 or more atoms. There is no restriction on the number of atoms, but larger structures may require excessive computing times and computer main memory.
- You can interpret results, including dipole moments and atomic charges, using the simple concepts and familiar vocabulary of the Linear Combination of Atomic Orbitals (LCAO)-molecular orbital (MO) theory.

Once HyperChem calculates potential energy, it can obtain all of the forces on the nuclei at negligible additional expense. This allows for rapid optimization of equilibrium and transition-state geometries and the possibility of computing force constants, vibrational modes, and molecular dynamics trajectories.

In addition to computing molecular geometries, energies, and forces, HyperChem computes and displays charge and spin density functions, atomic charges, dipole moments, and electrostatic potential. Individual molecular orbital contributions, important in visualizing and interpreting chemical results, are calculated and displayed graphically.

Range of Quantum Mechanics Methods

The quantum mechanics methods in HyperChem differ in how they approximate the Schrödinger equation and how they compute potential energy. The *ab initio* method expands molecular orbitals into a linear combination of atomic orbitals (LCAO) and does not introduce any further approximation.

The Extended Hückel method, for example, does not explicitly consider the effects of electron-electron repulsions but incorporates repulsions into a single-electron potential. This simplifies the solution of the Schrödinger equation and allows HyperChem to compute the potential energy as the sum of the energies for each electron.

Neglect of Differential Overlap (NDO) methods, such as CNDO and INDO, include electron repulsions, but the resulting equations are nonlinear. The energy calculation includes terms for pairs of electrons. These methods include nuclear repulsions, but only by reducing the charge on each nucleus by the number of core electrons shielding it. The other NDO methods, MINDO/3, MNDO, AM1, and PM3 replace nuclear repulsion terms in the potential energy by parameterized, core-repulsion terms. The terms compensate for considering only valence electrons in the electronic Schrödinger equation, and they incorporate effects of electron correlation (see “Configuration Interaction” on page 119). For more about these methods see “Using Quantum Mechanics Methods” on page 107 “Using Quantum Mechanics Methods” on page 107.

Exclusion Principle

Because of the quantum mechanical Uncertainty Principle, quantum mechanics methods treat electrons as indistinguishable particles. This leads to the Pauli Exclusion Principle, which states that the many-electron wave function—which depends on the coordinates of all the electrons—must change sign whenever two electrons interchange positions. That is, the wave function must be antisymmetric with respect to pair-wise permutations of the electron coordinates.

Example: If two functions are \sin and \cos and two variables are x and y , then $\sin(x)\cos(y)$ has the same sign if you interchange x and y to give $\sin(y)\cos(x)$. The antisymmetrized version,

$\sin(x)\cos(y) - \cos(x)\sin(y)$, does change sign. This is the determinant:

$$\begin{vmatrix} \sin(x) & \cos(x) \\ \sin(y) & \cos(y) \end{vmatrix}$$

Example: If $a(1)$ is a function of the coordinates of electron 1 and $b(2)$ is a function of the coordinates of electron 2, then the product function, $a(1)b(2)$, is not antisymmetric. The function $a(1)b(2) - b(1)a(2)$, an expansion of a 2×2 determinant, is antisymmetric.

The Exclusion Principle is fundamentally important in the theory of electronic structure; it leads to the picture of electrons occupying distinct molecular orbitals. Molecular orbitals have well-defined energies and their shapes determine the bonding pattern of molecules. Without the Exclusion Principle, all electrons could occupy the same orbital.

The Exclusion Principle also gives rise to the “exchange” phenomenon. This phenomenon is important in understanding the energy differences between electronic states of different spin symmetries; for example, singlet-triplet splittings and related properties. Exchange is also important in understanding the nature of the covalent bond. In the simplest description of bonds for the hydrogen molecule, almost all of the binding energy is due to exchange. (Binding energy is the energy of the two hydrogen atoms separated by infinity minus the energy of the stable hydrogen molecule at its equilibrium bond length.)

The Exclusion Principle is quantum mechanical in nature, and outside the realm of everyday, “classical” experience. Think of it as the inherent tendency of electrons to stay away from one another; to be mutually excluded. Exclusion is due to the antisymmetry of the wave function and not to electrostatic coulomb repulsion between two electrons. Exclusion exists even in the absence of electrostatic repulsions.

Consider what happens to the many-electron wave function when two electrons have identical coordinates. Since the electrons have the same coordinates, they are indistinguishable; the wave function should be the same if they trade positions. Yet the Exclusion Principle requires that the wave function change sign. Only a zero value for the wave function can satisfy these two conditions, identity of coordinates and an antisymmetric wave function. For the hydrogen molecule, the antisymmetric wave function is $a(1)b(1) -$

$b(1)a(1)$, which is zero. Since the wave function is a probability function, the probability of two electrons having the same coordinates is also zero. In this sense they are mutually excluded.

Simplified Wave Functions

The simplest many-electron wave function that satisfies the Exclusion Principle is a product of N different one-electron functions that have been antisymmetrized, or written as a determinant. Here, N is the number of electrons (or valence electrons) in the molecule. HyperChem uses this form of the wave function for most semi-empirical and *ab initio* calculations. Exceptions involve using the Configuration Interaction option (see page 119). HyperChem computes one-electron functions, termed molecular spin orbitals, by relatively simple integration and summation calculations. The many-electron wave function, which has $N!$ terms (the number of terms in the determinant), never needs to be evaluated.

N molecular spin orbitals must be different from one another in a way that satisfies the Exclusion Principle. Because the wave function is written as a determinant, interchanging two rows of the determinant corresponds to interchanging the coordinates of the two electrons. The determinant changes sign according to the antisymmetry requirement. It also changes sign when two columns are interchanged; this corresponds to interchanging two spin orbitals.

To avoid having the wave function zero everywhere (an unacceptable solution), the spin orbitals must be fundamentally different from one another. For example, they cannot be related by a constant factor. You can write each spin orbital as a product of a space function which depends only on the x , y , and z coordinates of the electron—and a spin function. The space function is usually called the molecular orbital. While an infinite number of space functions are possible, only two spin functions are possible: alpha and beta.

To use HyperChem for calculations, you specify the total molecular charge and spin multiplicity (see “Charge, Spin, and Excited State” on page 119). The calculation selects the appropriate many-electron wave function with the correct number of alpha or beta electrons. You don’t need to specify the spin function of each orbital.

Hartree-Fock Wave Functions

Quantum mechanics calculations use either of two forms of the wave function: Restricted Hartree-Fock (RHF) or Unrestricted Hartree-Fock (UHF). Use the RHF wave function for singlet electronic states, such as the ground states of stable organic molecules.

Spin orbitals are grouped in pairs for an RHF calculation. Each member of the pair differs in its spin function (one alpha and one beta), but both must share the same space function. For N electrons, $N/2$ different molecular orbitals (space functions) are doubly occupied, with one alpha (spin up) and one beta (spin down) electron forming a pair.

The UHF wave function is most often used for multiplicities greater than singlets. In this case, the space orbitals for alpha electrons need not be the same as for beta electrons. For open-shell systems, some of the spins are unpaired — alpha and beta electrons occupy different orbitals. This is because there are more alpha electrons than beta electrons, and they tend to repel each other more than they do beta electrons. This effect is known as exchange repulsion. It is a quantum mechanical effect with no classical analog and would persist even without electrostatic coulomb forces. Essentially, it is due to the requirement that the wave function must be antisymmetric (see “Exclusion Principle” on page 34). Exchange repulsion affects the choice of the semi-empirical method (see “Choosing a Semi-Empirical Method” on page 148).

The UHF wave function can also apply to singlet molecules. Usually, the results are the same as for the faster RHF method. That is, electrons prefer to pair, with an alpha electron sharing a molecular space orbital with a beta electron. Use the UHF method for singlet states only to avoid potential energy discontinuities when a covalent bond is broken and electrons can unpair (see “Bond Breaking” on page 46).

Extending the Wave Function Calculation

Extending the Wave Function Calculation

Configuration Interaction

You can extend the calculation of the Hartree-Fock semi-empirical wave function by choosing Configuration Interaction (CI) in the

Semi-empirical Options dialog box and you can also extend the calculation of the Hartree-Fock *ab initio* wave function by choosing CI in the Ab Initio Options dialog box. Use CI for these electron configurations:

- closed-shell singlet ground states (for both semi-empirical and *ab initio* methods)
- half-electron, excited singlet states (for semi-empirical methods only)
- half-electron, doublet and triplet open-shell ground states (for semi-empirical methods only)

Configuration Interaction (or electron correlation) adds to the single determinant of the Hartree-Fock wave function a linear combination of determinants that play the role of atomic orbitals. This is similar to constructing a molecular orbital as a linear combination of atomic orbitals. Like the LCAO approximation, CI calculations determine the weighting of each determinant to produce the lowest energy ground state (see “SCF Technique” on page 43).

CI calculations can be used to improve the quality of the wavefunction and state energies. Self-consistent field (SCF) level calculations are based on the one-electron model, wherein each electron moves in the *average* field created by the other $n-1$ electrons in the molecule. Actually, electrons interact instantaneously and therefore have a natural tendency to avoid each other beyond the requirements of the Exclusion Principle. This correlation results in a lower average interelectronic repulsion and thus a lower state energy. The difference between electronic energies calculated at the SCF level versus the exact nonrelativistic energies is the *correlation energy*.

There are two types of electron correlations: static and dynamic. Static correlation refers to a near degeneracy of a given state; a dynamic correlation refers to the instantaneous avoidance of electrons with each other.

CI calculations are perhaps the most widely used method of going computationally beyond an SCF description. An SCF computation yields a configuration describing the orbital occupancy of the electrons. Other configurations may be generated from this reference configuration by exciting electrons from the set of occupied orbitals to the set of virtual (*unoccupied*) orbitals. A CI calculation yields

a set of improved states, each of which is represented by a linear combination of these configurations.

There are two types of CI calculations implemented in HyperChem — singly excited CI and microstate CI. The singly excited CI which is available for both *ab initio* and semi-empirical calculations may be used to generate UV spectra and the microstate CI available only for the semi-empirical methods in HyperChem is used to improve the wave function and energies including the electronic correlation. Only single point calculations can be performed in HyperChem using CI.

You can use CI calculations to do the following:

- Calculate UV spectra
- Calculate the energy of excited states
- Study the making or breaking of bonds, and change of spin couplings (e.g. dissociation of H₂)
- Capture the effects of London dispersion forces
- Describe a nearly degenerate state
- Study singlet-triplet splittings more accurately

You can use CI to predict electronic spectra. Since the CI wave function provides ground state and excited state energies, you can obtain electronic absorption frequencies from the differences between the energy of the ground state and the excited states.

You can also use a RHF wave function with CI for calculations involving bond breaking, instead of using a UHF wave function (see also “Bond Breaking” on page 46).

The Microstate CI Method lowers the energy of the uncorrelated ground state as well as excited states. The Singly Excited CI Method is particularly appropriate for calculating UV visible spectra, and does not affect the energy of the ground state (Brillouin’s Theorem).

Be careful when you use the Orbital Criterion for symmetrical systems. To get correct results, you must include all or none of any set of degenerate orbitals in the CI, not just some of them. Carrying out an RHF calculation first and studying the Orbitals dialog box will help you to spot degenerate orbitals and avoid this pitfall.

In large systems there can be many orbitals in a small energy range, and the size of the CI matrix can be very sensitive to the value of the maximum excitation if you use Energy Criterion. Since calculation time depends heavily on the size of the CI matrix, you can end up with very long calculations, especially if you use the *ab initio* methods or the MNDO, AM1, or PM3 semi-empirical methods. This could exhaust the memory of your system. Again, inspecting the results of an RHF (no CI) calculation will help you avoid these pitfalls.

Using CI may not necessarily improve the calculation of ground state energies. Parameters for the MINDO/3, MNDO, AM1, and PM3 methods already include the effects of CI. CI calculations require more computing time.

Note: When you use CI, HyperChem does not calculate forces (gradient).

Møller-Plesset Perturbation Theory

Configuration interaction is a systematic procedure for going beyond the Hartree-Fock approximation. A different systematic approach for finding the correlation energy is perturbation theory (Rayleigh-Schrödinger many-body perturbation theory — RSPT). In this approach, the total Hamiltonian of the system is divided or partitioned into two parts: a zeroth-order part, H_0 (which has known eigenfunctions and eigenvalues), and a perturbation, V . The exact energy is then expressed as an infinite sum of contributions of increasing complexity. The expressions for these contributions contain the eigenvalues of H_0 and matrix elements of the perturbation between the eigenfunctions of H_0 . By introducing the ordering parameter λ , the total Hamiltonian can be written as⁹

$$H = H_0 + \lambda V$$

The exact eigenfunctions and eigenvalues can now be expanded in a Taylor series in λ .

$$\psi_\lambda = \psi^{(0)} + \lambda\psi^{(1)} + \lambda^2\psi^{(2)} + \dots$$

$$E_\lambda = E^{(0)} + \lambda E^{(1)} + \lambda^2 E^{(2)} + \dots$$

9. Szabo, A.; Ostlund, N. *Modern Quantum Chemistry*. Macmillan, New York, 1985

If H_0 is chosen wisely, then the perturbation is small and the perturbation expansion (i.e., the sum of the 1st, 2nd, ..., nth-order energies) converges quickly. To obtain a perturbation expansion for the correlation energy, the best way is to choose the Hartree-Fock Hamiltonian as the zeroth-order Hamiltonian. The application to N-electron molecular systems is sometimes called Møller-Plesset (MP) perturbation theory. These methods, which can be terminated at second (MP2), third (MP3), or fourth order (MP4), with these three being the most frequently used in different *ab initio* programs, calculate the correlation energy and rely on a good description of the virtual orbitals in the original SCF function. The calculated total correlation energy is therefore quite dependent on the quality of the basis set.

HyperChem supports MP2 (second order Møller-Plesset) correlation energy calculations using *ab initio* methods with any available basis set. In order to save main memory and disk space, the HyperChem MP2 electron correlation calculation normally uses a so called “frozen-core” approximation, i.e. the inner shell (core) orbitals are omitted. A setting in CHEM.INI allows excitations from the core orbitals to be included if necessary (melted core). Only the single point calculation is available for this option.

Molecular Orbitals and Electronic Structure

The molecular orbitals computed by HyperChem have several important properties. Each molecular orbital has a uniquely defined orbital energy. Interpretations of orbital energies give useful predictions. For example, the highest energy-occupied molecular orbital (HOMO) provides a remarkably accurate estimate of the first ionization potential (Koopmans’ theorem¹⁰). Orbital energies are also important in interpreting molecular geometry (Walsh’s rules) and chemical reactivity (Woodward-Hoffmann rules¹¹).

Orbital Occupancy

Because of the LCAO-MO approximation, *ab initio* and semi-empirical calculations produce occupied and unoccupied (virtual) orbitals. The Aufbau or “building up” principle determines the

10. Koopmans, T. On the Relation of Wave Functions and Eigenvalues to Individual Electrons of Atoms *Physica (Utrecht)* 1:104, 1933.

11. Woodward, R.B. and Hoffmann, R. *Conservation of Orbital Symmetry* Verlag Chemie, Weinheim, FRG, 1970.

occupancy of orbitals for the ground-state wave function. This first arranges the orbitals in order of increasing energy. Then it assigns electrons to orbitals beginning with the lowest energy. For example, in an RHF calculation for a molecule with ten electrons and twelve molecular orbitals, the five lowest energy orbitals receive two electrons each. The remaining seven virtual orbitals remain unoccupied and do not appear in the many-electron wave function. Some of these virtual orbitals are important in discussions of chemical reactivity and excited electronic states (see “Chemical Reactivity” on page 138).

In an Extended Hückel calculation, the Aufbau population of molecular orbitals is unambiguous. The calculation method is non-iterative and the total energy is proportional to the sum of the energies of occupied orbitals. The Aufbau guarantees the lowest energy wave function.

For NDO calculations (see “NDO Methods” on page 126), the Aufbau also produces the lowest energy wave function. However, in some cases, a calculation may converge to a result that is not the ground state (lowest energy), even though the Aufbau is satisfied (for example, RHF calculations on singlet biradicals or molecules with highly distorted bonds).

In extreme cases, a calculation may not converge on a lowest energy solution because of the iterative nature of the SCF procedure. The highest energy occupied (HOMO) and lowest energy unoccupied (virtual) orbitals (LUMO) may switch occupancies from one SCF cycle to the next when the two orbitals are close in energy (nearly degenerate). It is even possible, though unlikely, that the ground state would not satisfy the Aufbau—there is a virtual orbital with an orbital energy lower than an occupied orbital.

HOMO and LUMO, also known as Frontier orbitals, are important in interpreting results of a calculation (see “Frontier Molecular Orbitals” on page 141). You can use these molecular orbitals to compute the lowest excited electronic singlet state of molecules and the ground states of radicals.

Atomic Orbitals and Their Interactions

HyperChem uses the Linear Combination of Atomic Orbitals-Molecular Orbital (LCAO-MO) approximation for all of its *ab initio* semi-empirical methods. If ψ_i represents a molecular orbital and ϕ_μ

an atomic orbital, then the LCAO representation of the molecular orbital is

$$\psi_i = \sum_{\mu} C_{\mu_i} \phi_{\mu} \quad (16)$$

where C_{μ_i} is the coefficient or “weight” of the μ th atomic orbital in the i th molecular orbital.

This equation is important in interpreting the results of calculations. In *ab initio* and semi-empirical calculations, atomic orbitals are functions of the x, y, and z coordinates of the electron that closely resemble the valence orbitals of the isolated atoms.

These atomic orbitals, called Slater Type Orbitals (STOs), are a simplification of exact solutions of the Schrödinger equation for the hydrogen atom (or any one-electron atom, such as Li^{+2}). HyperChem uses Slater atomic orbitals to construct semi-empirical molecular orbitals. The complete set of Slater atomic orbitals is called the basis set. Core orbitals are assumed to be chemically inactive and are not treated explicitly. Core orbitals and the atomic nucleus form the atomic core.

Because the calculation of multi-center integrals that are inevitable for *ab initio* method is very difficult and time-consuming, HyperChem uses Gaussian Type Orbital (GTO) for *ab initio* methods. In truly reflecting a atomic orbital, STO may be better than GTO, so HyperChem uses several GTOs to construct a STO. The number of GTOs depends on the basis sets. For example, in the minimum STO-3G basis set HyperChem uses three GTOs to construct a STO.

SCF Technique

All molecular orbitals are combinations of the same set of atomic orbitals; they differ only by their LCAO expansion coefficients. HyperChem computes these coefficients, C_{μ_i} , and the molecular orbital energies by requiring that the ground-state electronic energy be at a minimum. That is, any change in the computed coefficients can only increase the energy.

The technique for this calculation involves two steps. The first step computes the Hamiltonian or energy matrix. The elements of this matrix are integrals involving the atomic orbitals and terms obtained from the Schrödinger equation. The most important con-

tributions to this matrix involve the overlap integrals, which are mainly responsible for the bonding between atoms.

The second step determines the LCAO coefficients by standard methods for matrix diagonalization. In an Extended Hückel calculation, this results in molecular orbital coefficients and orbital energies. *Ab initio* and NDO calculations repeat these two steps iteratively because, in addition to the integrals over atomic orbitals, the elements of the energy matrix depend upon the coefficients of the occupied orbitals. HyperChem ends the iterations when the coefficients or the computed energy no longer change; the solution is then “self-consistent.” The method is known as Self-Consistent Field (SCF) calculation.

Note: You should be aware that the length of semi-empirical calculations increases as the cube of the number of atomic orbitals, because this is the number of operations required for matrix diagonalization; and the length of *ab initio* calculations increases as the power of four of the number of atomic orbitals (basis functions), because of the calculation of two-electron repulsion integrals. A molecule with 60 atomic orbitals takes about eight times as long to compute as a molecule containing 30 atomic orbitals by using a semi-empirical method and sixteen times as long to compute by using the *ab initio* method.

Virtual Orbitals

Even with the minimal basis set of atomic orbitals used in most semi-empirical calculations, the number of molecular orbitals resulting from an SCF calculation exceeds the number of occupied molecular orbitals by a factor of about two. The number of virtual orbitals in an *ab initio* calculation depends on the basis set used in this calculation.

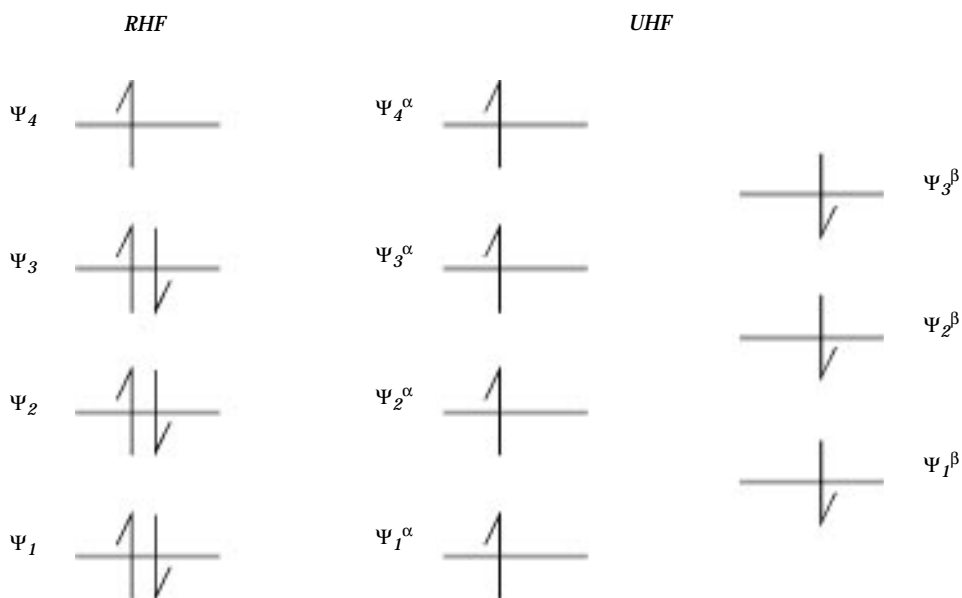
RHF and UHF

HyperChem quantum mechanics calculations must start with the number of electrons (N) and how many of them have alpha spins (the remaining electrons have beta spins). HyperChem obtains this information from the charge and spin multiplicity that you specify in the Semi-empirical Options dialog box or Ab Initio Options dialog box. N is then computed by counting the electrons (valence electrons in semi-empirical methods and all electrons in *ab initio* method) associated with each (assumed neutral) atom and

subtracting the charge. Multiplicity, which is related to the allowed values of the total spin angular momentum, is one for a singlet state, two for a doublet, three for a triplet, and four for a quartet.

Multiplicity Considerations

Most stable organic molecules have an even number of electrons and a singlet ground-state wave function. Half the electrons are alpha. For a radical with an odd number of electrons, the ground state is almost always a doublet with one more alpha than beta electron. For some highly symmetrical molecules, such as oxygen, the ground state is a triplet with two more alpha than beta electrons. Biradicals (metastable species formed, for example, by breaking a bond in a ring molecule) also frequently have triplet ground states.



If you specify a multiplicity of one (singlet), then you would most often choose the RHF method, unless the reactions result in bond breaking (see page 46). If the selected multiplicity is greater than one, then the system is open-shell and the usual choice is the UHF method, which uses different orbitals for electrons with different spins.

Bond Breaking

Applications of semi-empirical and *ab initio* methods frequently follow the course of chemical reactions that break and form covalent bonds. You must take care in choosing a method for these applications.

If a covalent bond is broken, as in the simple case of dissociation of the hydrogen molecule into atoms, then the RHF wave function without the Configuration Interaction option (see “Extending the Wave Function Calculation” on page 37) is inappropriate. This is because the doubly occupied RHF molecular orbital includes spurious terms that place both electrons on the same hydrogen atom, even when they are separated by an infinite distance.

An RHF wave function is also inappropriate for a reaction where reactants and products share different occupied orbitals, as in a Woodward-Hoffmann orbital symmetry forbidden thermal reaction. For example, in the absence of symmetry, the disrotatory ring opening of cyclobutene to butadiene must involve a change in the orbital occupancy between reactants and products. The lowest virtual orbital in reactants becomes the highest occupied in the product. This gives rise to an artificial and undesirable cusp in the potential energy surface along the reaction path, plus an unrealistically high activation energy. You can prevent this problem and the breaking of a covalent bond by using a UHF wave function for the singlet state. A minor disadvantage of the UHF method is that the space and spin symmetry of the molecular orbitals are broken. For example, the UHF wave function is a mixture of singlet and triplet states. To preserve spin symmetry, use RHF plus the Configuration Interaction option instead of UHF.

For Woodward-Hoffman allowed thermal reactions (such as the conrotatory ring opening of cyclobutane), orbital symmetry is conserved and there is no change in orbital occupancy. Even though bonds are made and broken, you can use the RHF wave function.

RHF Half-Electron Technique

With all semi-empirical methods, HyperChem can also perform pseudo-RHF calculations for open-shell systems. For a doublet state, all electrons except one are paired. The electron is formally divided into two “half electrons” with paired spins. Each half elec-

tron carries half the charge of a whole electron. The calculation produces a set of molecular orbitals appropriate for this pseudo-wave function. HyperChem then assigns the unpaired electron its proper spin (alpha), substitutes this electron in the orbital formerly occupied by the half electrons, and calculates energy and other properties.

You can think of the half-electron technique as a device to get reasonable orbitals to populate later with whole electrons.

The half-electron method can also apply to triplet states. For this calculation, HyperChem populates selected molecular orbitals with pairs of half electrons. The final energy is computed by assigning the proper spins.

You can study the lowest excited singlet state of a system with a closed-shell ground state. The difference in energy between this state and the singlet ground state is related to the lowest electronic absorption frequency. Here, the calculation is carried out for the half-electron triplet state. The final energy is computed using the appropriate singlet wave function (which involves two determinants) for this singly excited state.

An advantage of the half-electron technique is its simplicity. HyperChem can carry it out with only minor modifications of the usual calculation. A disadvantage is that forces may not be accurate because of the half electron approximation.

Although UHF is often a better theoretical treatment of open-shell systems than the RHF (half-electron) methods, it takes longer to compute. Separate matrices for electrons of each spin roughly double the length of the calculation.

SCF Convergence

Not all iterative semi-empirical or *ab initio* calculations converge for all cases. For SCF calculations of electronic structure, systems with a small energy gap between the highest occupied orbital and the lowest unoccupied orbital may not converge or may converge slowly. (They are generally poorly described by the Hartree-Fock method.)

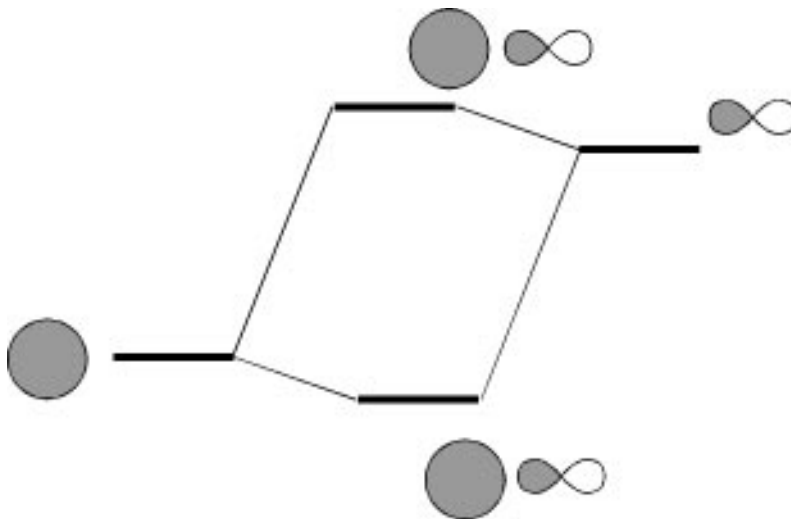
Some systems converge poorly, particularly those with multiple bonds or weak interactions between open-shell systems. HyperChem includes two convergence accelerators. One is the default convergence accelerator, effective in speeding up normally

convergent calculations. The other, called the Direct Inversion in the Iterative Subspace (DIIS) method, is available for all the SCF methods in HyperChem. You can turn on this accelerator in the Semi-empirical Options dialog box or in the Ab Initio Options dialog box. It uses more memory and computing time.

If you observe convergence problems, you might try a different semi-empirical method or first try optimizing the geometry using another method. Convergence problems occur more often away from optimized geometries than close to them. Often, a fast geometry optimization with a molecular mechanics calculation may solve convergence difficulties with a semi-empirical optimization.

Calculation Results

The results of calculations are often interpreted in terms of familiar orbital interaction diagrams. The simplest example is two one-electron atoms combining to form a molecule. This diagram shows a two-orbital interaction forming a bonding (lower energy) and antibonding (higher energy) combination.



Note: This simple orbital interaction picture is useful for interpreting results, but neglects many aspects of a calculation, such as electron-electron interactions. These diagrams are closely related to the results from Extended Hückel calculations.

A larger interaction energy (the off-diagonal element of an energy matrix, proportional to the overlap integral between two molecular orbitals) causes a larger energy separation between two atomic orbitals, and the lower orbital is doubly occupied according to the Aufbau principle (see “Orbital Occupancy” on page 41). The magnitude of this additional splitting is proportional to the magnitude of the overlap integral between the two atomic orbitals. The greater the splitting, the greater the strength of the covalent bond. The occupied molecular orbital results from the in-phase or positive combination of the two atomic orbitals. This is shown for an s-type orbital on the left atom and a sigma p-type on the right. The virtual orbital is the negative or out-of-phase combination. The occupied or “bonding” molecular orbital shows a buildup of electron density between the two atoms. The virtual orbital, on the other hand, has a node (a value of zero) between the atoms.

A simple example is the formation of the hydrogen molecule from two hydrogen atoms. Here the original atomic energy levels are degenerate (they have equal energy), but as the two atoms approach each other, they interact to form two nondegenerate molecular orbitals, the lowest of which is doubly occupied.

In the general heteronuclear case, individual atomic orbital and overlap energies determine the magnitude of energy difference between two molecular orbitals. Atomic orbital energies are the diagonal elements of the Hamiltonian matrix, and the interaction energy between atomic orbitals are the off diagonal elements.

HyperChem can display molecular orbitals and the electron density of each molecular orbital as contour plots, showing the nodal structure and electron distribution in the molecular orbitals.

Quantitative Results

HyperChem provides quantitative results for all calculations. The status line shows the binding energy and gradient (only binding energy if you use the Configuration Interaction option, see page 119). The log file for a calculation contains this information, plus more, including heats of formation (for all the SCF semiempirical methods in HyperChem), orbital coefficients, dipole moments, and atomic charges.

Chapter 4

Single Point Calculations

A single point calculation determines molecular properties, such as energy or spin density, of a defined molecular structure. Normally, these calculations are for stationary points on a potential energy surface. Occasionally, you may want to characterize the potential energy surface by calculating the energies of a grid of points on the surface. You can use those results to generate a contour plot of the surface.

With HyperChem, you can use either molecular or quantum mechanical methods for single point calculations. The calculation provides an energy and the gradient of that energy. The gradient is the root-mean-square of the derivative of the energy with respect to Cartesian coordinates. At a minimum the forces on atoms (the gradient) are zero. The size of the gradient can provide qualitative information to determine if a structure is close to a minimum.

In addition to total energy and gradient, HyperChem can use quantum mechanical methods to calculate several other properties. The properties include the dipole moment, total electron density, total spin density, electrostatic potential, heats of formation, orbital energy levels, vibrational normal modes and frequencies, infrared spectrum intensities, and ultraviolet-visible spectrum frequencies and intensities. The HyperChem log file includes energy, gradient, and dipole values, while HIN files store atomic charge values.

Dipole Moment

This describes the classical dipole moment:

$$\sum q_i \mathbf{r}_i$$

where q_i are point charges located at positions \mathbf{r}_i .

In the quantum mechanical description of dipole moment, the charge is a continuous distribution that is a function of \mathbf{r} , and the dipole moment is an average over the wave function of the dipole moment operator, μ :

$$\mu = \sum_i (-\mathbf{r}_i) + \sum_A Z_A \mathbf{R}_A \quad (17)$$

where Z_A is the charge of the nuclear core and \mathbf{R}_A is the distance between the origin and nucleus A. Note that the sign convention used in the quantum mechanical calculation of dipoles is opposite to that used in molecular mechanics dipole calculations; this reflects the differing sign conventions of physics and chemistry.

Total Electron Density

Electron density represents the probability of finding an electron at a point in space. It is calculated from the elements of the density matrix. The total electron density is the sum of the densities for alpha and beta electrons. In a closed-shell RHF calculation, electron densities are the same for alpha and beta electrons.

Total Spin Density

Total spin density reflects the excess probability of finding α versus β electrons in an open-shell system. For a system in which the α electron density is equal to the β electron density (for example, a closed-shell system), the spin density is zero.

Electrostatic Potential

The classical electrostatic potential for q_n point charges is the potential energy at a position \mathbf{R} (equation 18).

$$V = \sum \frac{q_i}{|\mathbf{R} - \mathbf{r}_i|} \quad (18)$$

For a molecule with a continuous electron charge distribution and nuclear point charges, the expression becomes:

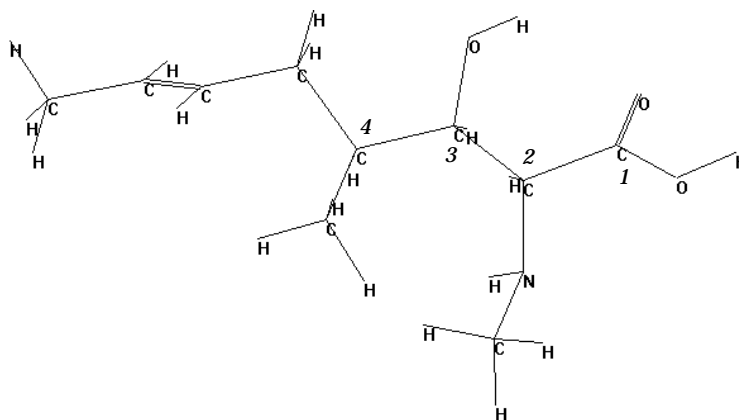
$$V = \sum \frac{Z_A}{|\mathbf{R} - \mathbf{R}_A|} - \int \frac{|\Psi|^2 d\tau}{|\mathbf{R} - \mathbf{r}|} \quad (19)$$

The potential indicates what a reactant 'sees' as it approaches a molecule. You can use a contour plot of electrostatic potential to visually determine possible trajectories for the approach of a reactant.

Examples of Single Point Calculations

Example: Suzuki et. al. used a reaction strategy to expand the C_{60} molecule, buckminsterfullerene, by adding divalent carbon equivalents.¹¹ Adding phenyl diazomethane to C_{60} , (I), followed by the loss of molecular nitrogen, results in a C_{61} compound.

11. Suzuki, T.; Li, Q.; Khemani, K.C.; Wudl, F.; Almarsson, Ö. Systematic Inflation of Buckminsterfullerene C_{60} : Synthesis of Diphenyl Fullerooids C_{61} to C_{66} *Science*, 254:1186-1188, 1991.



The researchers investigated three MeBmt analogs: the C-4 epimer ((4*s*)-MeBmt), the C-4 des methyl analog (MeBth), and the C-4 dimethyl (MeBm₂t) analog. The immunosuppressive activity of the analogs follows the order MeBmt > MeBm₂t > MeBth > (4*s*)-MeBmt.

Starting with the crystal and solution structures of cyclosporin A, Miller and Rich generated conformations of the parent structure and its analogs through a grid search of C₁-C₄ torsional angles. They minimized the conformations and calculated their potential energies, using the AMBER force field. They calculated a Boltzmann distribution for the conformations.

Miller and Rich assumed that cyclosporin A and its MeBmt analogs share a common bioactive conformation. Their molecular mechanics calculations found such a conformation. The Boltzmann population of the proposed bioactive conformation correlates with the immunosuppressive activities of the compounds.

Chapter 5

Geometry Optimizations and Transition State Searching

Geometry Optimizations

HyperChem can calculate geometry optimizations (minimizations) with either molecular or quantum mechanical methods. Geometry optimizations find the coordinates of a molecular structure that represent a potential energy minimum.

These are excellent references for optimization calculations:

- Fletcher, R. *Practical Methods of Optimization*, John Wiley & Sons, New York, 1980
- Gill, P.E.; Murray, W.; Wright, M.H. *Practical Optimization*, Academic Press, Inc., New York, 1981

For a potential energy V and Cartesian coordinates \mathbf{r}_i , the optimized coordinates satisfy this equation:

$$\frac{\partial V}{\partial \mathbf{r}_i} = 0 \quad (20)$$

You might perform a geometry optimization calculation with one of these goals in mind:

- Characterize a potential energy minimum. A geometry optimization results in a new structure at a minimum. You can examine atomic coordinates and energy of this structure.
- Obtain a new stable structure as a starting point for a single point, quantum mechanical calculation, which provides a large set of structural and electronic properties.

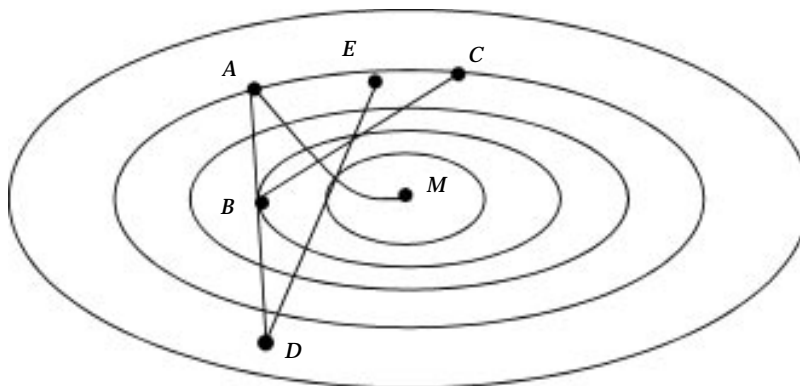
- Prepare a molecule for a molecular dynamics simulation. If the forces on atoms are too large, the integration algorithm may fail during a molecular dynamics calculation.

HyperChem supplies three types of optimizers or algorithms: steepest descent, conjugate gradient (Fletcher-Reeves and Polak-Ribiere), and block diagonal (Newton-Raphson).

Steepest Descent

The steepest descent method is a first order minimizer. It uses the first derivative of the potential energy with respect to the Cartesian coordinates. The method moves down the steepest slope of the interatomic forces on the potential energy surface. The descent is accomplished by adding an increment to the coordinates in the direction of the negative gradient of the potential energy, or the force.

Example: A potential energy surface has a minimum at M. If the minimization begins at point A and proceeds with infinitesimally small steps, the structure follows the overall path A-M during a steepest descent optimization. If the first step is larger, it might proceed along A-B, then the next step would proceed along B-C. A larger initial step might place the system at D. A second step could proceed along the path D-E, which diverges from the minimum.



The steepest descent method rapidly alleviates large forces on atoms. This is especially useful for eliminating the large non-bonded interactions often found in initial structures. Each step in

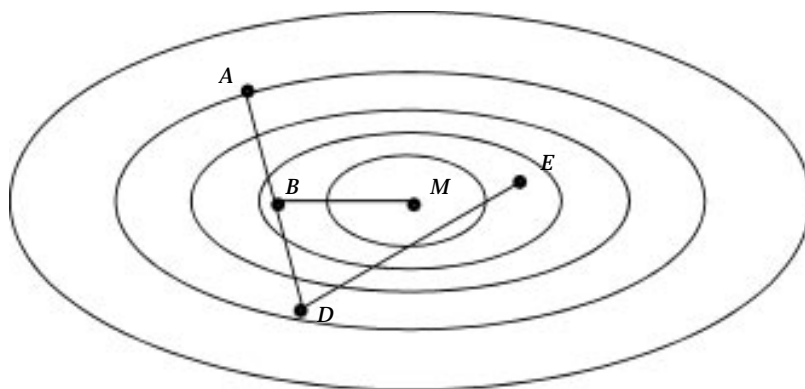
a steepest descent requires minimal computing time. Its disadvantage is that convergence toward a minimum is very slow.

Conjugate Gradient

A conjugate gradient method differs from the steepest descent technique by using both the current gradient and the previous search direction to drive the minimization. A conjugate gradient method is a first order minimizer.

The advantage of a conjugate gradient minimizer is that it uses the minimization history to calculate the search direction, and converges faster than the steepest descent technique. It also contains a scaling factor, b , for determining step size. This makes the step sizes optimal when compared to the steepest descent technique.

Example: Compare the steps of a conjugate gradient minimization with the steepest descent method. A molecular system can reach a potential minimum after the second step if the first step proceeds from A to B. If the first step is too large, placing the system at D, the second step still places the system near the minimum (E) because the optimizer remembers the penultimate step.



HyperChem provides two versions of the conjugate gradient method, Fletcher-Reeves and Polak-Ribiere. Polak-Ribiere is more refined and is the default choice in HyperChem.

Caution: Geometry optimizations of large molecules may take longer than you expect. The number of computing cycles required for a conjugate gradient calculation is approximately proportional

to the number of atoms (N), and the time per cycle is proportional to N^2 .

Block Diagonal

The Newton-Raphson block diagonal method is a second order optimizer. It calculates both the first and second derivatives of potential energy with respect to Cartesian coordinates. These derivatives provide information about both the slope and curvature of the potential energy surface. Unlike a full Newton-Raphson method, the block diagonal algorithm calculates the second derivative matrix for one atom at a time, avoiding the second derivatives with respect to two atoms.

This technique is available only for the MM+ force field. As is true for the conjugate gradient methods, you should *not* use this algorithm when the initial interatomic forces are very large (meaning, the molecular structure is far from a minimum).

Note: Because of its neglect of off-diagonal blocks, this optimizer can sometimes oscillate and fail to converge. In this case, use a conjugate gradient method.

Eigenvector Following

The Eigenvector Following method is in some ways similar to the Newton-Raphson method. Instead of explicitly calculating the second derivatives, it uses a diagonalized Hessian matrix to implicitly give the second derivatives of energy with respect to atomic displacements. The initial guess is computed empirically.

This method is available for all semi-empirical methods except Extended Hückel, and for *ab initio* calculations. This algorithm may be used if the structure is far from a minimum.

Setting Convergence Criteria

In setting up an optimization calculation, you can use two convergence criteria: the root-mean-square gradient and the number of optimization cycles.

You should terminate a geometry optimization based upon the root-mean-square gradient, because the number of cycles needed to minimize a molecule varies according to the initial forces on the

atoms and the type of optimizer used. There is no way of predicting how many cycles are needed for an adequate geometry optimization.

HyperChem automatically calculates a default number of cycles as 15 times the number of atoms. Use the cycle number as a termination condition when mixing optimization algorithms. Suppose you are preparing a protein for a molecular dynamics simulation. The initial structure of the protein comes from X-ray crystallography studies. A molecular mechanics force field or a quantum mechanics method would undoubtedly find some large forces associated with the protein. An efficient minimization scheme would first subject the protein to 500–1000 cycles of steepest descent minimization. Then it would minimize the structure using a conjugate gradient or Newton-Raphson optimizer, with the root-mean-square gradient as a termination condition.

Examples of Geometry Optimizations

Example: Saunders used conformational searching and molecular mechanics to investigate the structure of a fully reduced buckminsterfullerene, $C_{60}H_{60}$.¹³ By putting one of the hydrogens inside the reduced buckminsterfullerene he found that the molecule stabilized by 53 kcal/mol. After geometry optimization, the molecule with one hydrogen inside had three less eclipsed interactions and more favorable C-C-C angles than the isomer with all hydrogens outside. A search for other isomers, with different numbers of inside hydrogens, resulted in the finding that the most stable arrangement has ten hydrogens inside. This isomer, after minimization, had C_1 symmetry, with an energy 402 kcal/mol more stable than the all-outside isomer. Each of the six-membered rings had one inside hydrogen, and the closest H···H nonbonded distance for the inside hydrogens was greater than 3 Ångstroms.

Example: Jensen and Gordon calculated the potential energy surface of glycine using *ab initio* and semi-empirical methods.¹⁴ This study is of special interest to developers of molecular mechanics force fields. They frequently check their molecular mechanics methods by comparing their results with *ab initio* and semi-empirical calculations for small amino acids.

13. Saunders, M. Buckminsterfullerene: The inside story. *Science* 253:330-331, 1991

14. Jensen, J.H.; Gordon, M.S. The conformational potential energy surface of glycine: A theoretical study. *J. Am. Chem. Soc.* 113:7917-7924, 1991.

The researchers established that the potential energy surface is dependent on the basis set (the description of individual atomic orbitals). Using an *ab initio* method (6-31G*), they found eight C_s stationary points for the conformational potential energy surface, including four minima. They also found four minima of C_s symmetry. Both the AM1 and PM3 semi-empirical methods found three minima. Only one of these minima corresponded to the 6-31G* conformational potential energy surface.

Solvation and Periodic Boundary Conditions

Solvation can have a profound effect on the results of a chemical calculation. This is especially true when the solute and solvent are polar or when they can participate in hydrogen bonding. The solvent effect is expressed in several ways, including these:

- The solvent can strongly influence the energies of different solute conformations or configurations of atoms.
- The nature of solute-solute and solute-solvent interactions is dependent on the solvent environment. Solvent influences the hydrogen-bonding pattern, solute surface area, and hydrophilic and hydrophobic group exposures.

Be cautious when projecting the results of calculations in one solvent to those using a different environment.

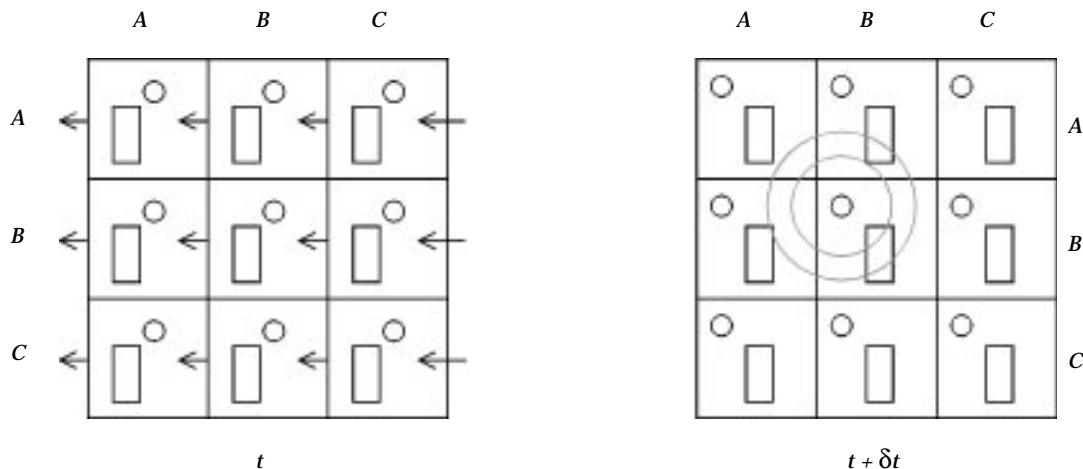
HyperChem uses the TIP3P water model for solvation.¹⁵ You can place the solute in a box of TIP3P water molecules and impose periodic boundary conditions. You may then turn off the boundary conditions for specific geometry optimization or molecular dynamics calculations. However, this produces undesirable edge effects at the solvent-vacuum interface.

Periodic boundary conditions place the molecular system in a box. Virtual identical images surround the initial box. The atoms farthest from the center of the original box no longer suffer from interactions with an edge, since the original box now meets an image of itself in all directions. HyperChem uses 26 virtual images. The solute in the original box interacts only with its nearest neighbor solute images.

15. Jorgensen, W.L.; Chandrasekhas, J.; Madura, J.D.; Impey, R.W.; Klein, M.L. Comparison of simple potential functions for simulation liquid water. *J. Chem. Phys.* 79:926-935, 1983.

Since the periodic images are exact copies of the original box, movements of atoms in the original box are duplicated in the images. When a particle leaves a box, its periodic image enters from the opposite box side and replaces it. This conserves the number of atoms in each box.

Choose the nonbonded cutoff carefully when using periodic boundary conditions. The cutoff must be small enough to prevent an atom from interacting simultaneously with another atom and with that atom's virtual image.



This example shows the round particle in cell {B,B} with two possible nonbonded cutoffs. With the outer cutoff, the round particle interacts with both the rectangle and its periodic image. By reducing the nonbonded cutoff to an appropriate radius (the inner circle), the round particle can interact with only one rectangle—in this case, the rectangle also in cell {B,B}.

For a rectangular box, the nonbonded cutoff should be less than one-half the smallest box dimension.



$$\text{cutoff} < 1/2b$$

Transition State Searching

HyperChem can calculate transition structures with either semi-empirical quantum mechanics methods or the *ab initio* quantum mechanics method. A transition state search finds the maximum energy along a reaction coordinate on a potential energy surface. It locates the first-order saddle point; that is, the structure with only one imaginary frequency, having one negative eigenvalue.

There are excellent references for transition state search calculations and methods:

1. Baker, J., "An Algorithm for the Location of Transition States," *J. Comp. Chem*, Vol. 7(4), 385-395 (1986)
2. Peng, C. and Schlegel, H.B., "Combining Synchronous Transit and Quasi-Newton Methods to Find Transition States", *Israel Journal of Chemistry*, Vol. 33, 449-454 (1993)

Computational strategies and many examples can also be found in: Hehre, W.J., Radom, L., Schleyer, P. von R., and Pople, J. A., *Ab Initio Molecular Orbital Theory*, John Wiley & Sons, New York, 1986.

To find a first order saddle point (*i.e.*, a transition structure), a maximum must be found in one (and *only* one) direction and minima in all other directions, with the Hessian (the matrix of second energy derivatives with respect to the geometrical parameters) being varied. So, a transition structure is characterized by the point where all the first derivatives of energy with respect to variation of geometrical parameters are zero (as for geometry optimization) and the second derivative matrix, the Hessian, has one and only one negative eigenvalue.

You might perform a transition geometry optimization calculation with one of these goals in mind:

1. Characterize a potential energy maximum along the reaction coordinate. Transition state searching results in a new structure. You can examine the atomic coordinates and energy of this structure.
2. Characterize a potential energy surface for a certain number of atoms, *i.e.*, detect all the local energy minima, the global minimum on the surface, and all the transition states between different minima.

3. Calculate activation energies for chemical processes and energy barriers for isomerization between different isomers of the same molecule.

HyperChem supplies two different types or algorithms for transition state search: eigenvector following and synchronous transit (linear and quadratic search).

Eigenvector Following

The eigenvector-following (or Hessian mode) method implemented in HyperChem is based on an efficient quasi-Newton like algorithm for locating transition states, which can locate transition states for alternative rearrangement/dissociation reactions, even when starting from the wrong region on the potential energy surface.

The algorithm consists of several steps. The first one involves making an initial guess at the position of the transition state. It will calculate the gradient vector \mathbf{g} and the Hessian matrix \mathbf{H} , at the initial point. The second step involve diagonalization of the Hessian and determination of local surface characteristics (number of negative eigenvalues). The next step depends on the structure of the Hessian. If the Hessian has the wrong number of negative eigenvalues, it will determine which Hessian mode has the greatest overlap with the eigenvector followed. If mode following has not been switched on, this algorithm will follow the lowest mode. The next step will determine SCF convergence. If the criteria are satisfied, it will stop at this point as the position of the transition state. If convergence criteria are not satisfied, it will calculate the energy and gradient vector at the new point, provided that maximum number of steps has not been exceeded.

If a transition state has not been reached after a certain number of steps, the user may need to upgrade the Hessian and repeat the calculation. It may be necessary if many calculation steps have been done, and the current geometry differs considerably from the starting point. The Hessian calculated at the starting point and updated at each new point may not be appropriate at the geometry reached by the search. This procedure can also help to get to a good starting point where the Hessian has a correct structure with only one negative eigenvalue.

HyperChem uses the eigenvector following method described in Baker, J, "An Algorithm for the Location of Transition States," *J. Comp. Chem*, Vol. 7(4), 385-395 (1986).

Synchronous Transit

The synchronous transit method is also combined with quasi-Newton methods¹⁶ to find transition states. Quasi-Newton methods are very robust and efficient in finding energy minima. Based solely on local information, there is no unique way of moving uphill from either reactants or products to reach a specific reaction state, since all directions away from a minimum go uphill. HyperChem has two synchronous transit methods implemented. The linear synchronous transit method (LST) searches for a maximum along a linear path between reactants and products. It may happen that this method will end up with a structure having two or more negative eigenvalues. The quadratic synchronous transit method (QST) is an improvement of the LST approach and searches for a maximum along a parabola connecting reactants and products, and for a minimum in all directions perpendicular to the parabola.

HyperChem offers a Reaction Map facility under the Setup menu. This is needed for the synchronous transit method to match reactants and products, and depending on λ (a parameter having values between 0 and 1, determining how far away from reactants structures a transition structure can be expected) will connect atoms in reactants and products and give an estimated or expected transition structure. This procedure can also be used if the eigenvector following method is later chosen for a transition state search method, *i.e.*, if you just want to get an estimate of the transition state geometry.

HyperChem uses the synchronous transit method described in Peng, C., and Schlegel, H.B., *Israel Journal of Chemistry*, **33**, 449-454 (1993).

16. Banerjee, A., Adams, N., Simons, J., and Shepard, R., *J. Phys. Chem.* **87**, 52(1985); Simons, J., Nichols, J., *Int. J. Quantum Chem.*, Quantum Chem. Symp. **24**, 263(1990)

Chapter 6

Molecular Dynamics

Molecular dynamics simulations calculate future positions and velocities of atoms, based on their current positions and velocities.¹⁶ A simulation first determines the force on each atom (\mathbf{F}_i) as a function of time, equal to the negative gradient of the potential energy (equation 21).

$$\mathbf{F}_i = -\frac{\partial V}{\partial \mathbf{r}_i} \quad (21)$$

where V = potential energy function and \mathbf{r}_i = position of atom i .

You can then determine the acceleration, \mathbf{a}_i , of each atom by dividing the force acting on it by the mass of the atom (equation 22).

$$\mathbf{a}_i = \frac{\mathbf{F}_i}{m_i} \quad (22)$$

The change in velocities, \mathbf{v}_i , is equal to the integral of acceleration over time. The change in the position, \mathbf{r}_i , is equal to the integral of velocity over time. Kinetic energy (K) is defined in terms of the velocities of the atoms (equation 23).

$$K = \frac{1}{2} \sum_{i=1}^N m_i \mathbf{v}_i^2 \quad (23)$$

The total energy of the system, called the Hamiltonian, is the sum of the kinetic and potential energies (equation 24).

16. See van Gunsteren, W.F.; Berendsen, H.J.C. Computer simulation of molecular dynamics – methodology, applications, and perspectives in chemistry *Angewandte Chemie, International Edition in English*, 29:992-1023, 1990, and Karplus, M.; Petsko, G.A. Molecular dynamics simulations in biology *Nature* 347:631-639, 1990.

$$H(\mathbf{r}, \mathbf{p}) = K(\mathbf{p}) + V(\mathbf{r}) \quad (24)$$

where \mathbf{r} = the set of Cartesian coordinates and \mathbf{p} = the momenta of the atoms.

Integration Algorithm

If the atomic positions at a particular time, t , are $\mathbf{r}_i(t)$, the velocities, $\mathbf{v}_i(t)$, are the first derivative of the positions with respect to time (equation 25).

$$\mathbf{v}_i(t) = \frac{d}{dt}\mathbf{r}_i(t) \quad (25)$$

HyperChem employs the leap frog algorithm to integrate the equations of motion. This algorithm updates the positions of atoms and the velocities for the next time step by this calculation (equation 26).

$$\mathbf{v}_i\left(t + \frac{1}{2}\Delta t\right) = \mathbf{v}_i\left(t - \frac{1}{2}\Delta t\right) + \Delta t\mathbf{a}_i(t) \quad (26)$$

In the first time step (Δt), the velocities advance from time $t=0$ to $(t + 1/2 \Delta t)$. In doing so, they “leap” over the positions at time t . The current velocities are then calculated using equation 27. This equation supplies only approximate velocities used to calculate energies at time t .

$$\mathbf{v}_i(t) = \frac{1}{2}\left[\mathbf{v}_i\left(t + \frac{1}{2}\Delta t\right) + \mathbf{v}_i\left(t - \frac{1}{2}\Delta t\right)\right] \quad (27)$$

The acceleration is determined and the cycle renewed. In the subsequent steps, the velocities advance from $t - 1/2 \Delta t$ to $t + 1/2 \Delta t$. The resulting set of positions and velocities is the molecular dynamics trajectory.

During a molecular dynamics simulation, HyperChem stores the current positions, $\mathbf{r}_i(t)$, and the mid-step velocities, $\mathbf{v}_i(t - 1/2 \Delta t)$. Since the algorithm provides mid-step velocities, but not velocities, $\mathbf{v}_i(t)$, for the positions at time t , HyperChem calculates approximate values of $E_{\text{TOT}}(t)$. This results in slightly larger fluctuations in $E_{\text{TOT}}(t)$ than an algorithm that calculates exact values of $\mathbf{v}_i(t)$.

Length of Simulations

HyperChem integrates the equations of motion using very small time steps (Δt). At each step, the algorithm evaluates energy and forces of the molecular system. Use a time step of about 0.5 to 1.0 femtoseconds (fs) for an All Atom system or 1 to 2 fs for a United Atom system. Small time steps allow the simulation to adequately integrate the highest frequency motions of the system, usually bond stretching vibrations on the order of several picoseconds. Adjust Δt for each molecular system to obtain energy conservation (see the next section).

One drawback to a molecular dynamics simulation is that the trajectory length calculated in a reasonable time is several orders of magnitude shorter than any chemical process and most physical processes, which occur in nanoseconds or longer. This allows you to study properties that change within shorter time periods (such as energy fluctuations and atomic positions), but not long-term processes like protein folding.

Conservation of Energy

Molecular dynamics calculations use equations 25–27. HyperChem integrates equations 26 and 27 to describe the motions of atoms. In the absence of temperature regulation, there are no external sources or depositories of energy. That is, no other energy terms exist in the Hamiltonian, and the total energy of the system is constant.

One way to test for success of a dynamics simulation and the length of the time step is to determine the change in kinetic and potential energy between time steps. In the microcanonical ensemble (constant number, volume, and energy), the change in kinetic energy should be of the opposite sign and exact magnitude as the change in potential energy. Though the total energy of the system should not change during the simulation, molecular dynamics simulations only approximate this condition. Energy conservation is difficult to achieve using computers with finite precision.

Because of limitations in computer power and time, it is frequently impractical to run a constant energy molecular dynamics simulation. Several approximations to the energy (usually to the potential energy) are possible, which require modifying the Hamilto-

nian. The most extreme approximation is to cut off intermolecular nonbonded interactions. Another common modification is temperature scaling: changing the atomic velocities to maintain a desired amount of kinetic energy.

Temperature Control

In a molecular dynamics calculation, you can add a term to adjust the velocities, keeping the molecular system near a desired temperature.¹⁷ During a constant temperature simulation, velocities are scaled at each time step. This couples the system to a simulated heat bath at T_0 , with a temperature relaxation time of τ . The velocities are scaled by a factor λ , where

$$\lambda = \left[1 + \frac{\Delta t}{\tau} \left(\frac{T_0}{T} - 1 \right) \right]^{1/2} \quad (28)$$

If the coupling parameter (the Bath relaxation constant in HyperChem), τ , is too “tight” (<0.1 ps), an isokinetic energy ensemble results rather than an isothermal (microcanonical) ensemble. The trajectory is then neither canonical or microcanonical. You cannot calculate true time-dependent properties or ensemble averages for this trajectory. You can use small values of τ for these simulations:

- To obtain a minimum energy structure at 0K.
- To reach equilibrium temperature quickly before starting the equilibration phase of a simulation (see “Equilibration and Data Collection” on page 74).

If the Bath relaxation constant, τ , is greater than 0.1 ps, you should be able to calculate dynamic properties, like time correlation functions and diffusion constants, from data in the SNP and/or CSV files (see “Collecting Averages from Simulations” on page 85).¹⁷

Note: This method of temperature regulation does not give all properties of the canonical ensemble. In particular, you cannot calculate C_V , heat capacity at constant volume.

17. Berendsen, H.J.C., Postma, J.P.M.; van Gunsteren, W.F.; DiNola, A.; Haak, J.R. Molecular Dynamics with coupling to an external bath *J. Chem. Phys.* 81:3684, 1984.

For a stable trajectory, use a Bath relaxation constant greater than 0.1 ps. A constant of 0.01 ps is too small and causes disturbances in a simulation.¹⁷

Simulation Periods

A molecular dynamics simulation can have three distinct time and temperature periods: heating, simulation (run), and cooling. If you want to measure equilibrium properties of a molecular system, you can divide the simulation period into two parts: equilibration and data collection.

Initial Conditions and Heating

A molecular dynamics simulation usually starts with a molecular structure refined by geometry optimization, but without atomic velocities. To completely describe the dynamics of a classical system containing N atoms, you must define $6N$ variables. These correspond to $3N$ geometric coordinates (x , y , and z) and $3N$ variables for the velocities of each atom in the x , y , and z directions.

To begin a molecular dynamics simulation from this static structure, HyperChem assigns velocity values that are realistic for the molecular system at a designated temperature.

Since HyperChem-constructed molecular systems are near 0 K (the atoms have zero velocity), a simulation usually begins by adjusting the system to a higher temperature during a heating step. Heating can take place in one step (from near 0 K to simulation temperature), but it is better to heat to the simulation temperature slowly, in small temperature increments. Slow heating allows the system to approach equilibrium during each heating step, so the system requires less time at the simulation temperature to reach equilibrium.

HyperChem can either use initial velocities generated in a previous simulation or assign a Gaussian distribution of initial velocities derived from a random number generator. Random numbers avoid introducing correlated motion at the beginning of a simulation.

HyperChem immediately scales (adjusts) the velocities of each atom so that the total kinetic energy is equal to $^{3}/_{2}kT$, where k is the Boltzmann constant and T is the specified starting tempera-

ture. Scaling creates a Gaussian distribution of velocities. After 100 to 300 steps of a simulation, this becomes a Boltzmann distribution.

Caution: For molecular dynamics simulations, use molecules that are optimized to an energy minimum or to a small gradient value. For room temperature simulations, the gradient should be ≤ 3 . At lower temperatures, the gradient should be smaller. This avoids artifacts caused by huge local forces in a high energy region. If a region of the molecule is highly strained, the molecular dynamics simulation tries to release the strain during the first few steps, leading to an explosion of the molecule or to structural distortion. Adequate geometry optimization is particularly important for molecular dynamics simulations of peptides or of large, flexible molecules.

Equilibration and Data Collection

In many molecular dynamics simulations, equilibration is a separate step that precedes data collection. Equilibration is generally necessary to avoid introducing artifacts during the heating step and to ensure that the trajectory is actually simulating equilibrium properties. The period required for equilibration depends on the property of interest and the molecular system. It may take about 100 ps for the system to approach equilibrium, but some properties are fairly stable after 10–20 ps.¹⁸ Suggested times range from 5 ps to nearly 100 ps for medium-sized proteins.

Equilibration corrects the velocities of atoms. Velocities resulting from heating do not simulate the type of motion found in a real molecular system. Instead, these velocities depend on a random distribution of values corresponding to a given temperature and on the forces in a partially minimized structure.

To generate characteristic velocities and bring a molecular system to equilibrium at the simulation temperature, atoms are allowed to interact with each other through the equations of motion. For isothermal simulations, a “temperature bath” scales velocities to drive the system towards the simulation temperature. Scaling occurs at each step of a simulation, according to equation 28.

18. Levitt, M.; Sharon, R. *Proc. Nat. Acad. Sci. (U.S.)* 85:7557–7561, 1989.

Tests for Equilibration

To determine when a molecular system reaches equilibrium, you can monitor fluctuations in temperature, kinetic energy, total energy, number of hydrogen bonds or nonbond contacts, or the number of times a particular configuration occurs. If you plot potential energy against time during a constant temperature run, then equilibration is close when average potential energy is constant. Other properties of the molecular system may also become constant unless a major conformational change occurs.

Effect of Solvent on Equilibration

In systems with solvent molecules, many properties may still show fluctuations even after equilibration periods lasting several tens of picoseconds.

Molecular dynamics simulations of proteins often begin with a known structure (such as an X-ray diffraction structure) that you want to maintain during equilibration. Since the solvent may contain high energy hot spots, equilibration of the protein and solvent at the same time can change the protein conformation. To avoid this, select only the water molecules and run a molecular dynamics equilibration. This relaxes the water while fixing the protein structure. Then deselect the water and equilibrate the whole system.

Caution: During a simulation, solvent temperature may increase while the solute cools. This is particularly true of small solvent molecules, such as water, that can acquire high translational and rotational energies. In contrast, a macromolecule, such as a peptide, retains most of its kinetic energy in vibrational modes. This problem remains unsolved, and this note of caution is provided to advise you to give special care to simulations using solvent.

Collecting Data

After initial heating and equilibration, the trajectory may be stable for thousands of time points. During this phase of a simulation, you can collect data. Snapshots and CSV files (see “Collecting Averages from Simulations” on page 85) store conformational and numeric data that you can later use in thermodynamic calculations.

In general, the longer the simulation, the more reliable the calculated properties. You can also average the data from several simulations.

Generating several different trajectories for the same molecular system can lead to more accurate and more reliable simulations of real physical systems and their properties. To increase the sampling of conformational states, you can run several medium-length simulations from the same molecular geometry but with different initial velocities or velocity vectors. You can change the distribution of velocities—but not their initial directions—by changing the number and size of heating steps. To change the directions of the initial velocities, you can rotate the molecular system in the Molecular Coordinate System, changing atomic coordinates.

Cooling

Cooling a molecular system after heating or equilibration can serve these functions:

- Reduce stress on molecules caused by a simulation at elevated temperatures. The cooling process, called simulated annealing, takes new, high energy conformational states toward stable conformations.
- Overcome potential energy barriers and force a molecule into a lower energy conformation than the one you might obtain using geometry optimization alone.

Examples of Molecular Dynamics Simulations

Example: Brady investigated classical dynamics of α -d-glucose in water.¹⁹ In this simulation, 207 water molecules surrounded one α -d-glucose. The system was in a cubic box with periodic boundary conditions. During the simulation, several hydroxyl group transitions occurred. These transitions are normally unlikely with an *in vacuo* simulation.

You can detect hydroxyl group transitions by plotting dihedral angles versus time over the course of the simulation. This is the “distance history.” Brady investigated the distance history of water

19. Brady, J.W. Molecular dynamics simulations of α -d-glucose in aqueous solution. *J. Am. Chem. Soc.* 111:5155–5165, 1989.

near the hydroxyl groups and found that the water structure for some conformations of the C-2 hydroxyl were different than for the anomeric hydroxyl group. He suggested that this difference might be related to the free energy differences between the α - and β -anomers.

Example: Paulsen and Ornstein investigated the molecular dynamics of a 414-amino acid protein, cytochrome p-450_{cam}.²⁰ The 175-psec simulation, with 40 psec used to equilibrate the protein, was carried out at constant temperature. The simulation was performed *in vacuo*, although 204 crystallographic waters were included in the structure. The trajectory analysis included the calculation of root-mean-square deviations and fluctuations, dihedral angle changes, and a hydrogen bond analysis. The authors analyzed the dynamic motion near the protein binding site with respect to a ‘gate-opening’ mechanism for substrate binding. In this example, the simulation does not model the motions of the protein.

Strategies

Molecular dynamics simulations can overcome energy barriers and provide information about the time-dependent motion of molecular systems. You can use various strategies to set up and run a molecular dynamics simulation, depending on your objective. This section defines many of these strategies and discusses specific considerations in setting up a simulation.

Constant Temperature versus Constant Energy

If there is no external temperature control (using a simulated constant temperature bath), molecular dynamics simulations are constant energy.

For a constant temperature simulation, a molecular system is coupled to a heat bath via a Bath relaxation constant (see “Temperature Control” on page 72). When setting this constant, remember that a small number results in tight coupling and holds the temperature closer to the chosen temperature. A larger number corresponds to weaker coupling, allowing more fluctuation in temper-

20. Paulsen, M.D.; Ornstein, R.L. A 175-psec molecular dynamics simulation of camphor-bound cytochrome p-450_{cam} *Proteins* 11:184–204, 1991.

ature and possibly an unstable trajectory. However, weak coupling leads to a more natural trajectory.

Most molecular dynamics simulations, and particularly those for proteins, use constant temperature conditions.

Conformational Searching

Molecular dynamics simulations are efficient for searching the conformational space of medium-sized molecules and peptides. Different protocols can increase the efficiency of the search and reduce the computer time needed to sample adequately the available conformations.

Quenched Dynamics

Quenched dynamics is a combination of high temperature molecular dynamics and energy minimization. This process determines the energy distribution of conformational families produced during molecular dynamics trajectories. To provide a better estimate of conformations, you should combine quenched dynamics with simulated annealing.

For a conformation in a relatively deep local minimum, a room temperature molecular dynamics simulation may not overcome the barrier and search other regions of conformational space in reasonable computing time. To overcome barriers, many conformational searches use elevated temperatures (600–1200 K) at constant energy. To search conformational space adequately, run simulations of 0.5–1.0 ps each at high temperature and save the molecular structures after each simulation. Alternatively, take a snapshot of a simulation at about one picosecond intervals to store the structure. Run a geometry optimization on each structure and compare structures to determine unique low-energy conformations.

Note: A molecular dynamics simulation cannot overcome constraints imposed by covalent bonds, such as disulfide bonds and rings. Check that such constraints are acceptable. Search other possible structures in separate simulations.

High temperature simulations require special consideration in choosing the sampling interval (see “Step size” on page 89).

The potential energy functions used in molecular mechanics calculations often cannot simulate the behavior of molecules at high temperature. This is true for United Atom representations of alpha carbons in amino acids; high temperatures can cause a change in chirality. In some cases, you can use restraints to control the behavior of molecules at high temperature (see “Using Geometric Restraints” on page 81).

Researchers report that high temperature molecular dynamics searches of many different starting conformations are much more efficient than using one starting structure and longer simulations.

Simulated Annealing

Quenched dynamics can trap structures in local minima. To prevent this problem, you can cool the system slowly to room temperature or some appropriate lower temperature. Then run room temperature molecular dynamics simulations to search for conformations that have lower energies, closer to the starting structure. Cooling a structure slowly is called simulated annealing.

Randomization During Molecular Dynamics

A problem in searching conformational space using molecular dynamics simulations is repeating a trajectory that generates the same structures. To reduce this possibility, you can randomize the velocities of the atoms.

To increase the possibly of finding new conformers, try one of these techniques:

- Run a molecular dynamics simulation, then rotate the molecular system in the Molecular Coordinate System. This changes the coordinates of all atoms, but not the velocity vectors present at the end of the last molecular dynamics simulation.
- Run a molecular dynamics simulation. Start another simulation with the same molecular system and with Restart off in the Molecular Dynamics dialog box. HyperChem assigns a new set of velocities at random.

Sampling Frequency

One of the most important considerations in using molecular dynamics for a conformational search is determining the sampling interval. HyperChem lets you sample the simulation in two ways:

- Snapshots at regular time intervals that store atomic coordinates and velocities. You can play back these snapshots to inspect the simulated structures or to average values. You specify a Snapshot period in the Molecular Dynamics Snapshots dialog box.
- Averages or plotted values at regular time intervals. You specify an Average/Graph period in the Molecular Dynamics Averages dialog box.

If the sampling interval is too short, the total number of structures that belong to unique structural families is small compared to the total number available. If the sampling interval is too large, the total number of available structures is small, and you can miss unique conformations.

High temperature molecular dynamics simulations add another consideration to setting the length of the sampling interval. Low potential energy regions in a molecule can develop high kinetic energies and velocities. If you are sampling a molecular dynamics simulation, you have a higher probability of observing the slow-moving conformations that have higher potential energy. Longer sampling periods accentuate this effect.

You must consider these factors when deciding on sampling interval. There is no ideal interval for all molecules; however, intervals of 0.5–1.0 ps are often used.

When is Conformational Space Adequately Sampled?

One of the most important questions for a conformational search strategy is, “When have I found all of the energetically interesting conformers?” This is an area of active research and the ideal answer seems to be, “When you find all of the local minima.” However, this answer is not always reasonable, because medium to large molecules have a large number of minima (see “Complexity of Potential Energy Surfaces” on page 14).

Sometimes you need only a quick survey of the available low energy structures near a known or suspected minimum. When you

need a broader search, you can assess the completeness of a search by observing the amount of variation between families of unique structures. To obtain this information you can monitor torsion angles, nonbonded distances, or other properties. You can also make a histogram of the number of times a search found each conformation. If each structure occurs many times, you can be confident that the search was adequate for that region of the potential energy surface. If each conformation occurs only one or a few times, the search may not have covered all possible structures and more simulations are probably necessary.

Using Geometric Restraints

You can include geometric restraints—for interatomic distances, bond angles, and torsion angles—in any molecular dynamics calculation or geometry optimization. Here are some applications of restraints:

- Include experimental data in a geometry optimization or molecular dynamics search.
- Force a geometric parameter to cross a barrier during a geometry optimization or molecular dynamics simulation.
- Reduce the possibility of undesired conformational changes during a molecular dynamics simulation.
- Dock two different molecules by restraining intermolecular (interatomic) distances.

Restraints add potential terms to a force field calculation, favoring the value that you specify in a restraint. The larger the value of the harmonic force constant, the more tightly the calculation restrains the value.

For all restraints, HyperChem uses named selections that contain two, three, or four atoms each. You use Name Selection on the Select menu to assign names to groups of selected atoms. Then you can apply named selections as restraints for a calculation in the Restraint Forces dialog box from Restraints on the Setup menu.

Caution: Restraints may significantly affect the property you are observing. When using restraints, check their effects on measured values.

Using Experimental Data as Restraints

You can often use experimental data, such as Nuclear Overhauser Effect (NOE) signals from 2D NMR studies, as restraints. NOE signals give distances between pairs of hydrogens in a molecule. Use these distances to limit distances during a molecular mechanics geometry optimization or molecular dynamics calculation. Information on dihedral angles, deduced from NMR, can also limit a conformational search.

When using NOE signals as restraints, choose the distance between the nonbonded atoms. A typical distance is about 4 to 5 Ångstroms. A typical force constant is 0.5 to 5.0 kcal/Å², depending on the flexibility of the rest of the molecule and the strength of the NOE signal.

You usually remove restraints during the final phases of molecular dynamics simulations and geometry optimizations.

Crossing Energy Barriers

Restraints can force molecules to cross energy barriers within reasonable calculation times. For example, you can flip a torsion angle using very high restraint values. This restraint still allows bond angles and distances for the atoms that define the dihedral angle to relax during a calculation. You can use this procedure with either geometry optimization or molecular dynamics.

Limiting Conformational Changes during High Temperature Simulations

High temperature searches of conformational space (see “Quenched Dynamics” on page 78), can produce unwanted conformational changes, such as *cis-trans* peptide flips, ring inversions, and other changes that you cannot reverse easily by geometry optimization. You can use restraints to prevent these changes.

Docking Molecules

Restraints can facilitate docking a substrate molecule to a binding site. Restraints can also facilitate the interaction of two molecules in solution. In both cases, it is unlikely that two different neutral molecules would come into van der Waals contact with each other without the use of restraints.

Example: If a drug molecule interacts with a receptor molecule through hydrogen bonds, then you might restrain the distance between the donor and acceptor atoms involved in the hydrogen bonds. During a molecular dynamics simulation, these atoms would stay near an ideal value, while the rest of the molecular system fully relaxes.

Example: You could explore the possible geometries of two molecules interacting in solution and guess at initial transition structures. For example, if molecule A undergoes nucleophilic attack on molecule B, you could impose a distance restraint between the two atoms that would form a bond, allowing the rest of the system to relax. Simulations such as these can help to explain stereochemistry or reaction kinetics and can serve as starting points for quantum mechanics calculations and optimizations.

Freezing Part of a System

You can completely freeze part of a molecule while allowing the remaining atoms to move in the field of the frozen atoms. This option is useful, for example, in a conformational search of part of a molecule.

To limit a molecular mechanics calculation to part of a molecule, select the atoms of interest. Only the selected atoms can move, but the other (frozen) atoms influence the calculation.

To limit a semi-empirical calculation to part of a molecule, select the atoms of interest. Then choose Extend to sp3 on the Select menu to terminate correctly the selected group of atoms. Only the selected atoms move, but the frozen atoms influence the calculation. This is now possible with all the semi-empirical methods in HyperChem.

To limit an *ab initio* calculation to part of a molecular system, select the molecules of interest. Only the selected molecules move, but the frozen molecules influence the calculation. The *ab initio*

method implemented in HyperChem does not support any boundary atoms between the selected and unselected regions. In other words, the *ab initio* method does not accept partially selected molecule.

Example: You can use this technique to dock a flexible drug molecule (selected) to a rigid receptor site. You can then use restraints to search the conformations available to the drug (see “Using Geometric Restraints” on page 81) and to simulate the interactions of the drug with the macromolecule (see “Docking Molecules” on page 83).

Example: Molecular dynamics simulations of selected portions of proteins can demonstrate the motion of an amino acid sequence while fixing the terminal residues. These simulations can probe the motion of an alpha helix, keeping the ends restrained, as occurs naturally in transmembrane proteins. You can also investigate the conformations of loops with fixed endpoints.

Solvent Simulations

Often you need to add solvent molecules to a solute before running a molecular dynamics simulation (see also “Solvation and Periodic Boundary Conditions” on page 62). In HyperChem, choose Periodic Box on the Setup menu to enclose a solute in a periodic box filled appropriately with TIP3P models of water molecules.

Choice of Dielectric Constant

Before running a molecular dynamics simulation with solvent and a molecular mechanics method, choose the appropriate dielectric constant. You specify the type and value of the dielectric constant in the Force Field Options dialog box. The dielectric constant defines the screening effect of solvent molecules on nonbonded (electrostatic) interactions.

Use a constant dielectric of 1.0 with TIP3P water molecules in a periodic box. Because of the parameterization of TIP3P molecules, using a distance-dependent dielectric or a value other than 1.0 gives unnatural results.

A distance-dependent dielectric constant is commonly used to mimic the effect of solvent in molecular mechanics calculations, in the absence of explicit water molecules.

Effects on Dynamic Motion

Including solvent in a molecular dynamics simulation creates a frictional force that damps some motion of the solute. This affects in particular the motions of exposed side chain in proteins.

Caution: Solvation in simulations can significantly increase computation time so that the simulation may be impractical.

Collecting Averages from Simulations

Molecular dynamics calculations can automatically average and save these values:

- Kinetic energy (EKIN)
- Potential energy (EPOT)
- Total energy (ETOT)
- Temperature (TEMP)
- Any length, bond angle, or torsion defined in a named selection (see the *HyperChem Reference Manual*)
- The RMS deviation (D_x) of any of the preceding values²¹

The calculation of average energies and their deviations from the mean are useful in several aspects of molecular dynamics simulations, such as these:

- Evaluating the stability of a simulation and the extent of equilibration.
- Identifying possibly interesting low energy conformations.

21. $D_x = \sqrt{\langle x^2 \rangle - \langle x \rangle^2}$, where x_i = value of EKIN, ETOT, EPOT, TEMP, or another value,

$$\langle x^2 \rangle = \left(\frac{1}{n} \sum_{i=1}^n x_i^2 \right), \text{ and } \langle x \rangle^2 = \left(\frac{1}{n} \sum_{i=1}^n x_i \right)^2.$$

You choose the values to average in the Molecular Dynamics Averages dialog box. As you run a molecular dynamics simulation, HyperChem stores data in a CSV file. This file has the same name as the HIN file containing the molecular system, plus the extension `.csv`. If the molecular system is not yet stored in a HIN file, HyperChem uses the filename `chem.csv`.

For more information about the contents of CSV files, see appendix A, “HyperChem Files”, in the *HyperChem Reference Manual*.

Evaluating Stability and Equilibration

Successful molecular dynamics simulations should have a fairly stable trajectory. Instability and lack of equilibration can result from a large time step, treatment of long-range cutoffs, or unrealistic coupling to a temperature bath.

Constant Energy Simulations

You can check the success of a simulation by studying averages of the energy terms and their deviations. Since energy is conserved in a constant energy simulation, you can monitor the equilibration by dividing the deviation of the total energy (D ETOT) by the average total energy (ETOT). The data to calculate these averages is in the CSV file. This is a convenient way to obtain the averages for a molecular dynamics run:

4. Before starting a molecular dynamics simulation, L-click on Averages in the Molecular Dynamics Options dialog box.
5. Choose D ETOT and Add to average this value. Repeat this process for ETOT. L-click OK.
6. Set options for the simulation and L-click Proceed.
7. After a molecular dynamics simulation or the playback of a simulation, L-click on Averages in the Molecular Dynamics Options dialog box.
8. L-click on D ETOT. The average appears below, after Value. Write down this number. Repeat for ETOT. This average replaces the previous average.
9. Calculate the ratio.

For simulations of liquids, the generally accepted upper limit for the ratio is 0.0001. For proteins and macromolecules, this number

can be larger, about 0.001. However, constant energy simulations of proteins are uncommon.

You can also use deviation of the total energy (D ETOT) divided by the deviation of the kinetic energy (D EKIN) to assist in evaluating the quality of a simulation. Acceptable ratios are less than 0.05.

Constant Temperature Simulations

To some extent you can monitor constant temperature simulations by the temperature (TEMP) and its deviation (D TEMP) or by kinetic energy (EKIN) and its deviation (D EKIN). Plot these values using the HyperChem Molecular Averages dialog box.

Large deviations in temperature and kinetic energy indicate there is a problem with the simulation or improper equilibration. Large fluctuations often accompany conformational or other geometry changes that induce rapid changes in the potential energy. It is useful to monitor both the kinetic and the potential energies as a function of time.

Conformational Searches

A molecular dynamics simulation used for a conformational search can provide a quick assessment of low energy conformers suitable for further analysis. Plot the average potential energy of the molecule at each geometry. This plot may also suggest conformational changes in a molecule.

Evaluating average distances, angles, and torsion angles, plus their deviations, can facilitate understanding of detailed molecular properties and functional characteristics.

Example: The distance between two ends of a large, flexible molecule can provide information about its structural properties or its interaction with solvent. Analysis of an angle can reveal a hinged motion in a macromolecule.

Example: You can monitor improper torsion angles to determine which side of a substrate molecule faces the active site of a protein. Select three atoms on the substrate molecule and a fourth in the active site. These atoms define an improper torsion angle. Save this selection as a named selection. Then observe a plot of this improper torsion angle (in the Molecular Dynamics Results dialog

box) to follow the motion of the substrate as it interacts with the macromolecule.

Setting Up a Molecular Dynamics Simulation

Heating Time

The choice of heating time depends on the purpose of the molecular dynamics simulation. If the simulation is for conformational searches, the heating step is not critical for a successful calculation. The heating step may be rapid to induce large structural changes that provide access to more of the conformational space.

Heating and equilibration are critical (see page 73 and page 74) for investigating equilibrium properties of a molecular system. Several strategies are available to heat and equilibrate molecules.

For simulations of biological molecules, many researchers advocate slow heating. This allows the molecule to heat while keeping the structure close to the starting conformation. These simulations often investigate the potential energy surface near an important local minimum, such as a crystal structure. The heat time might be in the range of 510 ps, with a temperature step of 6 K, until the system reaches a simulation temperature of 300 K. The heating rate (30 K/ps) should allow a molecule to equilibrate during each temperature step.

For constant energy simulations without temperature regulation, use heating steps of about 0.5 ps and a heating time of 20–30 ps. In general, short heating times and large temperature steps perturb the initial system more than longer heating times and small temperature steps.

Simulation or Run Time

The simulation or run time includes time for the system to equilibrate at the simulation temperature plus the time for data collection, while the trajectory evolves. Simulation times depend on the time scale of the property you are investigating.

Example: For a medium-sized molecule in the gas phase, with vibrations larger than 50 cm^{-1} , a trajectory of only 10 ps should be adequate to explore motions due to vibrations.

Example: For protein molecules with motions occurring at a frequency of about 1 cm^{-1} , the vibrational period is about 30 ps. Clearly, simulations of hundreds of picoseconds are necessary to probe adequately the motions of this system.

Cooling (Annealing) Time

Use the cooling time for simulated annealing (see “Cooling” on page 76). For simulated annealing following high temperature molecular dynamics (for example, 600 K), cool the system slowly to 300 K or lower. The result is a single molecular structure. To save computing time and obtain more annealed structures, start each new high temperature simulation from the coordinates and velocities of the previous high temperature simulation.

Step Size

Step size is critical in all simulations. This is the increment for integrating the equations of motion. It ultimately determines the accuracy of the numerical integration. For molecules with high frequency motion, such as bond vibrations that involve hydrogens, use a small step size.

Temperature also determines step size. An acceptable time step for room temperature simulations is about 0.5–1 fs for All Atom systems or for simulations that do not constrain hydrogen atoms. For United Atom systems or systems containing only heavy atoms, you can use steps of 1–2 fs.

In general, smaller time steps generally lead to more accurate trajectories, but they can increase computing time significantly. Since each integration step requires about the same computing time, decreasing the time step from 1.0 fs to 0.1 fs may require an order of magnitude more time. You must balance accuracy with available computing resources.

Higher temperatures correspond to increased velocities and greater distances traveled by atoms between time steps. Generally, the length of a time step should allow only a small energy change. However, high temperature simulations can cause large energy changes between time steps, resulting in inaccurate integrations and unstable molecular dynamics trajectories. If a high temperature conformational search uses a large time step ($> 1 \text{ fs}$), a molec-

ular structure can explode. These simulations sometimes require time steps as small as 0.1 fs.

Temperature

The temperature of a simulation depends on your objectives. You might use high temperatures to search for additional conformations of a molecule (see “Quenched Dynamics” on page 78). Room temperature simulations generally provide dynamic properties of molecules such as proteins, peptides, and small drug molecules. Low temperatures (<250 K) often promote a molecule to a lower energy conformation than you could obtain by geometry optimization alone.

Bond Breaking

Quantum mechanical calculation of molecular dynamics trajectories can simulate bond breaking and formation. Although you do not see the appearance or disappearance of bonds, you can plot the distance between two bonded atoms. A distance exceeding a theoretical bond length suggests bond breaking.

Chapter 7

Langevin Dynamics and Monte Carlo

Langevin Dynamics

The molecular dynamics method is useful for calculating the time-dependent properties of an isolated molecule. However, more often, one is interested in the properties of a molecule that is interacting with other molecules. With HyperChem, you can add solvent molecules to the simulation explicitly, but the addition of many solvent molecules will make the simulation much slower. A faster solution is to simulate the motion of the molecule of interest using Langevin dynamics.

Langevin dynamics simulates the effect of molecular collisions and the resulting dissipation of energy that occur in real solvents, without explicitly including solvent molecules. This is accomplished by adding a random force (to model the effect of collisions) and a frictional force (to model dissipative losses) to each atom at each time step. Mathematically, this is expressed by the Langevin equation of motion (compare to Equation (22) in the previous chapter):

$$\mathbf{a}_i = \frac{\mathbf{F}_i}{m_i} - \gamma \mathbf{v}_i + \frac{\mathbf{R}_i}{m_i}.$$

Here, γ is the friction coefficient of the solvent, in units of ps^{-1} , and \mathbf{R}_i is the random force imparted to the solute atoms by the solvent. The friction coefficient is related to the diffusion constant D of the solvent by Einstein's relation: $\gamma = k_B T / mD$. The random force is calculated as a random number, taken from a Gaussian distribu-

tion, with an average value of zero and no correlation with the atom's velocity.

Integration Algorithm

To integrate the Langevin equation, HyperChem uses the method of: M.P. Allen and D.J. Tildesley, *Computer Simulation of Liquids*, Clarendon Press, Oxford, 1987; Ch.9, page 261:

$$\mathbf{r}(t+\Delta t) = \mathbf{r}(t) + c_1\Delta t\mathbf{v}(t) + c_2\Delta t^2\mathbf{F}(t)/m + \Delta\mathbf{r}^G$$

$$\mathbf{v}(t+\Delta t) = c_0\mathbf{v}(t) + c_1\Delta t\mathbf{F}(t)/m + \Delta\mathbf{v}^G$$

where:

$$c_0 = e^{-t}$$

$$c_1 = (1 - c_0)/(\gamma \Delta t)$$

$$c_2 = (1 - c_1)/(\gamma \Delta t)$$

and $\Delta\mathbf{r}^G$ and $\Delta\mathbf{v}^G$ are random numbers chosen from a Gaussian distribution, with:

$$\langle \Delta\mathbf{r}^G \rangle = 0$$

$$\langle \Delta\mathbf{v}^G \rangle = 0$$

and standard deviations:

$$\sigma_r^2 = \Delta t^2(k_B T/m)(\gamma \Delta t)^{-1}(2 - (\gamma \Delta t)^{-1}(3 - 4 e^{-\gamma \Delta t} + e^{-2\gamma \Delta t}))$$

$$\sigma_v^2 = (k_B T/m)(1 - e^{-2\gamma \Delta t})$$

σ_r and σ_v are correlated, with correlation coefficient c_{rv} , defined through the relation:

$$c_{rv}\sigma_r\sigma_v = \Delta t(k_B T/m)(\gamma \Delta t)^{-1}(1 - e^{-2\gamma \Delta t})$$

Assuming that the interatomic force term $\mathbf{F}(t)$ varies linearly with time, the equations above can be rewritten in a form which produces more accurate simulations:

$$\mathbf{r}(t+\Delta t) = \mathbf{r}(t) + c_1\Delta t\mathbf{v}(t) + c_2\Delta t^2\mathbf{F}(t)/m + \Delta\mathbf{r}^G$$

$$\mathbf{v}(t+\Delta t) = c_0\mathbf{v}(t) + (c_1 - c_2)\Delta t\mathbf{F}(t)/m + c_2\Delta t\mathbf{F}(t+\Delta t)/m + \Delta\mathbf{v}^G$$

As γ approaches zero, this method reduces to the velocity Verlet algorithm:

$$\mathbf{r}(t+\Delta t) = \mathbf{r}(t) + \Delta t\mathbf{v}(t) + \frac{1}{2}\Delta t^2\mathbf{F}(t)/m$$

$$\mathbf{v}(t+\Delta t) = \mathbf{v}(t) + \frac{1}{2}\Delta t[\mathbf{F}(t) + \mathbf{F}(t+\Delta t)]/m$$

Setting Up a Langevin Dynamics Simulation

In general, Langevin dynamics simulations run much the same as molecular dynamics simulations. There are differences due to the presence of additional forces. Most of the earlier discussions (see pages 69–90 and p. 310–327 of this manual) on simulation parameters and strategies for molecular dynamics also apply to Langevin dynamics; exceptions and additional considerations are noted below.

Heating Time, Run Time, and Cooling Time

Most of the considerations described previously regarding the heat, run, and cool phases of a molecular dynamics simulation apply also to simulations that employ Langevin dynamics (see “Setting Up a Molecular Dynamics Simulation” on page 88). As with molecular dynamics, the time needed for these phases depends upon the purpose of the simulation and on the intrinsic dynamics of the system being studied as well. Gradual heating is needed for investigations of equilibrium properties. Conformational searches, on the other hand, are often successful with larger temperature steps and may be carried out with a very short heat period.

Time Step

When the friction coefficient is set to zero, HyperChem performs regular molecular dynamics, and one should use a time step that is appropriate for a molecular dynamics run. With larger values of the friction coefficient, larger time steps can be used. This is because the solution to the Langevin equation in effect separates the motions of the atoms into two time scales: the short-time (fast) motions, like bond stretches, which are approximated, and long-time (slow) motions, such as torsional motions, which are accurately evaluated. As one increases the friction coefficient, the short-time motions become more approximate, and thus it is less important to have a small timestep.

Temperature

Temperature is handled the same way in Langevin dynamics as it is in molecular dynamics. High temperature runs may be used to overcome potential energy barriers. Cooling a system to a low temperature in steps may result in a different stable conformation than would be found by direct geometry optimization.

Constant Temperature vs. Constant Energy

As with molecular dynamics, Langevin dynamics simulations may be run at constant temperature, using the heat bath described under “Temperature Control” on page 72 to regulate the temperature. In the absence of coupling to a heat bath, the simulations are conducted at constant energy. For a constant temperature simulation, the bath relaxation constant determines the strength of the coupling to the bath. A small bath relaxation constant results in tight coupling and holds the temperature closer to the chosen temperature. A larger number corresponds to weaker coupling, allowing more fluctuations in temperature (and possibly an unstable trajectory).

Friction coefficient

The friction coefficient determines the strength of the viscous drag felt by atoms as they move through the medium; its magnitude is related to the diffusion coefficient, D , through the relation $\gamma = k_B T / mD$. Because the value of γ is related to the rate of decay of velocity correlations in the medium, its numerical value determines the relative importance of the systematic dynamic and stochastic elements of the Langevin equation. At low values of the friction coefficient, the dynamical aspects dominate and Newtonian mechanics is recovered as $\gamma \rightarrow 0$. At high values of γ , the random collisions dominate and the motion is diffusion-like.

Example: Conformations of molecules like n-decane can be globally characterized by the end-to-end distance, R . In a comparison of single-molecule Brownian (Langevin) dynamics to molecular dynamics, the average end-to-end distance for n-decane from a 600 ps single-molecule Langevin dynamics run was almost identical to results from 19 ps of a 27-molecule molecular dynamics run. Both simulations were at 481K; the time step and friction coefficient for the Langevin simulation were 0.001 ps and 3.759 ps^{-1} , respectively.¹⁶

Example: The dynamical effects of solvent on supercoiled DNA have been explored extensively by Langevin dynamics simulations. In one study, the effects of solvent damping and the random forces due to molecular collisions on the dynamics of DNA supercoiling were examined by systematically varying the viscosity (friction coefficient, γ) over ten orders of magnitude. Three distinct physical regimes of DNA behavior were identified, from the low- γ region where DNA motions are mostly harmonic, to the high friction limit where the dynamics are dominated by random forces and the global modes are effectively frozen by overdamping. Analogous studies of the dynamics of the damped harmonic oscillator exhibit similar behavior.¹⁷

Additional Procedures

Refer to the following sections of this manual for related material: “Strategies” on page 77; “Using Geometric Restraints” on page 81; “Collecting Averages from Simulations” on page 85; “Molecular Dynamics on a Potential Energy Surface” on page 310.

Monte Carlo Simulations

Introduction

Monte Carlo simulations are commonly used to compute the average thermodynamic properties of a molecule or a system of molecules, and have been employed extensively in the study of the structure and equilibrium properties of liquids and solutions.¹⁸ Monte Carlo methods have also been used to conduct conformational searches under non-equilibrium conditions.

Monte Carlo calculations are somewhat similar to the molecular (or Langevin) dynamics calculations discussed earlier. All function by repeated application of a computational algorithm that generates a new configuration from the current configuration. The

16. W.f. van Gunsteren, H.J.C. Berendsen and J.A.C. Rullmann. “Stochastic dynamics for molecules with constraints. Brownian dynamics of n-alkanes.” *Molecular Physics*, 1981, Vol. 44, No.1, 69-95.

17. G. Ramachandran and T. Schlick. “Solvent effects on supercoiled DNA dynamics explored by Langevin dynamics simulations.”, *Phys.Rev. E*, Vol. 51, No. 6, p.6188 (1995).

18. Allen, M. P., and Tildesley, D.J., *Computer Simulation of Liquids*, Oxford University Press, New York (1987).

sequence of configurations of the molecular system constitutes a trajectory, and after an initial equilibration phase, system properties may be sampled and averaged for the duration of the run to obtain ensemble averages. Dynamics simulations use an equation of motion as the basis for generating new configurations, which constitute the dynamical trajectory of the system. Monte Carlo simulations employ a statistical sampling technique to generate configurations that represent a trajectory in phase space.

Thus, unlike molecular dynamics or Langevin dynamics, which calculate ensemble averages by calculating averages over time, Monte Carlo calculations evaluate ensemble averages directly by sampling configurations from the statistical ensemble.

If run long enough, Monte Carlo and molecular dynamics should give the same average results for the same system (provided that the system is ergodic). However, only molecular dynamics can calculate time-dependent properties of a system, such as rotational frequencies or transition rates. On the other hand, Monte Carlo is generally better at sampling the allowed states of a system, and thus often can calculate the average properties more quickly and accurately.

Background and Method

In order to compute average properties from a microscopic description of a real system, one must evaluate integrals over phase space. For an N -particle system in an ensemble with distribution function $\mathbf{P}(r^N)$, the experimental value of a property $A(r^N)$ may be calculated from

$$\langle A(r^N) \rangle = \int A(r^N) P(r^N) d r^N.$$

The problem with direct evaluation of this multi-dimensional integral (apart from the huge number of phase space points to be sampled) is that most of the configurations sampled contribute nothing to the integral, having energy that is so high that the probability of their occurrence is vanishingly small. The trick, then, is to generate trajectories that sample commonly occurring configurations more than rare ones.

Thermodynamically, the probability of finding a system in a state whose energy is ΔE above the ground state is proportional to $\exp(-\Delta E/kT)$. HyperChem uses the Metropolis method,¹⁹ which chooses random configurations with this probability, to concen-

trate sampling of configurations in regions of space that make important contributions to the calculation of thermodynamic averages.

In the Metropolis method, a randomly selected atom attempts to move by a random distance in a random direction. The energy change associated with this move is calculated. If the energy change is negative, then the move is accepted, and the energy of the system is added to the currently running average. If the energy change is positive, then the move is accepted with probability $\exp(-\Delta E/kT)$. So, the larger the positive change in energy, the less likely it is that the move will be accepted. If a move is rejected, then the energy of the old configuration is again added to the average.

In HyperChem, the atoms are not chosen randomly, but instead, each atom is moved once per Monte Carlo step.

Monte Carlo Trajectories and Simulation Parameters

Initial Configurations

A good starting configuration for a Monte Carlo simulation is one that can relax quickly to a structure that is representative of the system to be studied. It is not necessary to begin with an energy-minimized structure (as with molecular dynamics); in fact, a random configuration could be used, at least in principle. However, in order to minimize computational time it is best to begin with a physically reasonable choice. Many simulations of the liquid state have used a crystal lattice as a reproducible and well-defined starting point. With adequate sampling, results of a simulation will be independent of the starting configuration; in fact, dependence of the results on the starting configuration can be monitored as one index of the reliability of the simulation.

Temperature

The effect of temperature in Monte Carlo simulations is primarily to modulate the strength of intermolecular interactions, since temperature enters the simulation only through the Boltzmann factor $\exp(-\Delta E/kT)$, where ΔE represents a difference in potential

19. Metropolis, N., Rosenbluth, A.W., Rosenbluth, M.N., Teller, A.H. and Teller, E., Equation of state calculations by fast computing machines, *J. Chem. Phys.* **21**, 1087-92 (1953).

energy. Thus, at higher temperatures, configurations of higher energy become more probable and contribute more to computed averages. The simulation temperature also determines the average kinetic energy, which contributes a fixed amount to the configurationally averaged potential energy to give the average total energy.

Step Size and Acceptance Ratio

The step size, Δr , is the maximum allowed atomic displacement used in the generation of trial configurations. The default value of r in HyperChem is 0.05 Ångstroms. For most organic molecules, this will result in an acceptance ratio of about 0.5, which means that about 50% of all moves are accepted.

Increasing the size of the trial displacements may lead to more complete searching of configuration space, but the acceptance ratio will, in general, decrease. Smaller displacements generally lead to higher acceptance ratios but result in more limited sampling. There has been little research to date on what the optimum value of the acceptance ratio should be. Most researchers tend to try for an average value around 0.5; smaller values may be appropriate when longer runs are acceptable and more extensive sampling is necessary.

Initial Phase and Equilibration

The first phase of a run will, in general, be used to allow the system to move away from high-energy and thus statistically insignificant configurations. During this period, the potential energy may either increase or decrease, depending on the starting point; its instantaneous value should be monitored. The number of steps required before equilibration has been achieved and equilibrium averages can be accumulated is strongly dependent on the system, the starting point, the step size, and the temperature of the simulation. Typical values for Lennard-Jones liquids are 500-1000 steps.

Equilibration and Statistical Averaging

A thermodynamically stable system conserves energy. Thus, by monitoring the potential energy one can confirm that a stable (and productive) phase of the simulation has begun. Absence of systematic drift in computed averages is often used as a check on the stability of a Monte Carlo trajectory. Fluctuations in the energy

should be computed and used to quantitatively assess the reliability of the run; from statistical mechanics, one expects the mean-squared fluctuations in the energy for the canonical ensemble to be simply related to the constant-volume heat capacity: $\langle(\delta E)^2\rangle = k_B T^2 C_V$. For a simulation of finite duration this equality will not be strictly obeyed, but it is useful as a limiting value.

Averaging and storage of data for a Monte Carlo run are carried out in much the same way as for molecular dynamics (see p. 318-324).

Heating and Cooling

The use of heating and cooling phases are optional and not often used in Monte Carlo simulations. However, they may be useful for some applications.

Chapter 8

Using Molecular Mechanics Methods

HyperChem offers four molecular mechanics force fields: MM+, AMBER, BIO+, and OPLS (see “References” on page 106). To run a molecular mechanics calculation, you must first choose a force field. The following sections discuss considerations in choosing a force field.

Availability of Parameters

Force fields give the best results for molecules similar to those used to develop its parameters. Choose a force field developed for a range of molecules similar to your molecular system.

Force Field Features

The force field equations for MM+, AMBER, BIO+, and OPLS are similar in the types of terms they contain: bond, angle, dihedral, van der Waals, and electrostatic. There are some differences in the forms of the equations that can affect your choice of force field.

Note: The BIO+ force field is an implementation of the CHARMM (Chemistry at HARvard Macromolecular Mechanics) force field developed in the group of Martin Karplus at Harvard University. Like AMBER and OPLS, it is primarily designed to explore macromolecules.

MM+

MM+ is unique among the force fields in the way it treats bonds and angles. Both the bond and angle terms can contain higher

order terms than the standard quadratic. These bond and angle potentials express a harmonic motion better than a harmonic potential.

MM+ also contains a stretch-bend cross term, called a Urey-Bradley term. The other force fields in HyperChem normally evaluate non-bonded interactions for atoms separated by three or more bonds (1–4 and larger interactions). A Urey-Bradley term includes 1–3 interactions, which are critical for accurately simulating molecules. For example, the bond angles for heavy atoms in cyclobutane are compressed, compared to the natural bond angle for C sp^3 orbitals, and the carbon-carbon bonds have higher p character. This results in a weaker bond and an increased carbon-carbon bond length. A Urey-Bradley term allows for these structural changes and recognizes the unique 1–3 interactions which occur in strained molecules.

HyperChem supplements the standard MM2 force field (see “References” on page 106) by providing additional parameters (force constants) using two alternative schemes (see the second part of this book, *Theory and Methods*). This extends the range of chemical compounds that MM+ can accommodate. MM+ also provides cut-offs for calculating nonbonded interactions and periodic boundary conditions.

Note: MM+ is derived from the public domain code developed by Dr. Norman Allinger, referred to as MM2(1977), and distributed by the Quantum Chemistry Program Exchange (QCPE). The code for MM+ is not derived from Dr. Allinger’s present version of code, which is trademarked MM2™. Specifically, QCMP010 was used as a starting point for HyperChem MM+ code. The code was extensively modified and extended over several years to include molecular dynamics, switching functions for cubic stretch terms, periodic boundary conditions, superimposed restraints, a default (additional) parameter scheme, and so on.

The HyperChem MM+ code and program also differ from MM2(1977) by having parameters in text files separate from the code. These parameter files are available for your modification and additions. The parameters distributed with HyperChem include the public domain values, generally referred to as the MM2(1991) parameter set, that Dr. Allinger contributed to HyperCube, Inc. Parameters not obtained from Dr. Allinger are appropriately labeled in the distributed parameter files.

Electrostatic Interactions

Another difference between the force fields is the calculation of electrostatic interactions. AMBER, BIO+, and OPLS use point charges to model electrostatic interactions. MM+ calculates electrostatic interactions using bond dipoles. The bond dipole method may not adequately simulate very polar or charged systems.

Accuracy of Force Fields

For biological polymers, molecular mechanics force fields are not well substantiated by experimental data. You should be cautious about relying on predictions from these calculations.

Use the force fields that have demonstrated accuracy for particular molecules or simulations. For example, OPLS reproduces physical properties in liquid simulations extremely well. MM+ reproduces the structure and thermodynamic properties of small, nonpolar molecules better than AMBER, BIO+, and OPLS.

Previous Experiences

Previous investigations might influence the choice of a molecular mechanics method. If molecular mechanics calculations of a particular compound or molecule type already exist, choose the same force field so you can make comparisons easily.

Choosing Force Field Options

The *HyperChem Reference* manual and *Getting Started* discuss the sequence of steps to perform a molecular mechanics calculation. These steps include choosing a force field, force field options, and possible restraints.

Dielectric Function

You can use two types of dielectric functions: a constant and a distance-dependent dielectric. Use constant dielectric for *in vacuo* systems and for molecular systems with explicit solvent molecules.

Also use constant dielectric for MM+ and OPLS calculations. Use the distance-dependent dielectric for AMBER and BIO+ to mimic the screening effects of solvation when no explicit solvent molecules are present. The scale factor for the dielectric permittivity, ϵ , can vary from 1 to 80. HyperChem sets ϵ to 1.5 for MM+. Use 1.0 for AMBER and OPLS, and 1.0–2.5 for BIO+.

1–4 Nonbonded Scale Factors

AMBER, BIO+, and OPLS scale 1–4 van der Waals and 1–4 electrostatic interactions. Although the value of the 1–4 nonbonded scale factors is an option in HyperChem, you should generally use recommended values. This is because during parameterization, the force field developers used particular values for the 1–4 nonbonded scale factors, and their parameters may not be correct for other scale factors.

The van der Waals scale factors used during force field parameterization are 0.5 for AMBER, 1.0 for BIO+, and 0.125 for OPLS. For 1–4 electrostatic interactions, use 0.5 for AMBER, BIO+, and OPLS.

Nonbonded Cutoffs

You can choose to calculate all nonbonded interactions or to truncate (cut off) the nonbonded interaction calculations using a switched or shifted function. Computing time for molecular mechanics calculations is largely a function of the number of nonbonded interactions, so truncating nonbonded interactions reduces computing time. You must also truncate nonbonded interactions for periodic boundary conditions to prevent interaction problems between nearest neighbor images.

Use these guidelines for nonbonded interactions:

- For small and medium-sized molecules, calculate all nonbonded interactions.
- For larger molecules, such as proteins, use a switching function to dramatically decrease computing time.
- Use a switching function for periodic boundary conditions.
- Use a shifted function only to reproduce reported results. Since a shifted dielectric potential affects the entire potential energy surface, it is not recommended.

A switched function extends over the range of inner (R_{on}) to outer (R_{off}) radius and a shifted function from zero to outer (R_{off}) radius. Beyond the outer radius, HyperChem does not calculate non-bonded interactions. The suggested outer radius is approximately 14 Ångstroms or, in the case of periodic boundary conditions, less than half the smallest box dimension. The inner radius should be approximately 4 Ångstroms less than the outer radius. An inner radius less than 2 Ångstroms may introduce artifacts to the structure.

Restraints

You can restrain atoms during molecular mechanics or quantum mechanics calculations. Choosing restraints, via the Restraint Forces dialog box, applies additional harmonic forces—which you specify, to interatomic distances, angles, or dihedrals that you have set up as named selections.

Note: Restraints apply to distances, angles and dihedrals between bonded or nonbonded atoms. You can also restrain atoms to points in space.

You need to specify two parameters: the equilibrium value of the internal coordinate and the force constant for the harmonic potential. The equilibrium restraint value depends on the reason you choose a restraint. If, for example, you would like a particular bond length to remain constant during a simulation, then the equilibrium restraint value would probably be the initial length of the bond. If you want to force an internal coordinate to a new value, the equilibrium internal coordinate is the new value.

Recommended values for the force constant are 7.0 kcal/mol Å² for an interatomic distance, 12.5 kcal/mol degree² for an angle, and 16.0 kcal/mol degree² for a dihedral angle. Use the recommended values and then, if the internal coordinate is not sufficiently restrained, try a larger force constant.

See “Using Geometric Restraints” on page 81 for examples of using restraints.

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Chapter 9

Using Quantum Mechanics Methods

There are three steps in carrying out any quantum mechanical calculation in HyperChem. First, prepare a molecule with an appropriate starting geometry. Second, choose a calculation method and its associated (Setup menu) options. Third, choose the type of calculation (single point, geometry optimization, molecular dynamics, Langevin dynamics, Monte Carlo, or vibrational analysis) with the relevant (Compute menu) options.

Obtaining a Starting Structure

Use the HyperChem Model Builder to construct an approximate geometry. If you want to look at the relative energies of a set of molecules, you may want to carry out the calculations using fully optimized molecular geometries. These geometry optimization calculations can use either molecular mechanics or quantum mechanics to further refine the molecular geometry beyond that given by the Model Builder.

Geometry optimization using an *ab initio* quantum mechanical method may take much longer than using a semi-empirical quantum mechanical method. In turn, semi-empirical quantum mechanical calculations take longer than molecular mechanics (force field) calculations. You might first run a molecular mechanics optimization to get close to the optimized geometry and then refine with a semi-empirical optimization. Similarly, you might run a semi-empirical optimization before you run an *ab initio* geometry optimization. The closer the starting geometry is to the final geometry, the faster HyperChem can reach an optimized structure. For some molecules, such as certain inorganic molecules, molecular mechanics methods may not have appropriate parameters and will yield poor geometries. In those cases, use the

Model Builder to get a reasonable starting geometry, with the possibility of refining the geometry by semi-empirical calculations before submitting it to *ab initio* computation.

Calculating Part of a Molecular System

You can perform quantum mechanical calculations on a part of a molecular system, such as a solute, while using molecular mechanics for the rest of the system, such as the solvent surrounding the solute. This boundary technique is available in HyperChem for all quantum mechanical methods. It is somewhat less complete with *ab initio* calculations than with semi-empirical calculations, however. With *ab initio* calculations the boundary must occur between molecules rather than inside a molecule.

Choose the region (single or multiple molecules) of interest for an *ab initio* calculation from the total molecular system. HyperChem performs the *ab initio* calculation for the selected region using the perturbation of an electrostatic potential arising from the net charges on the atoms of the unselected part. (For further details of this electrostatic potential perturbation implemented in HyperChem, please see the second part of this book, *Theory and Methods*).

Choose the atoms of interest for the semi-empirical calculation, then use the Extend to sp^3 option on the Select menu to establish the appropriate atomic boundaries for the quantum mechanics calculation. HyperChem substitutes parameterized pseudo-fluorine atoms for the portions of the molecule not included directly in the calculation (see the second part of this book, *Theory and Methods*).

The algorithms of the mixed classical-quantum model used in HyperChem are different for semi-empirical and *ab initio* methods. The semi-empirical methods in HyperChem treat boundary atoms (atoms that are used to terminate a subset quantum mechanical region inside a single molecule) as specially parameterized pseudo-fluorine atoms. However, HyperChem will not carry on mixed model calculations, using *ab initio* quantum mechanical methods, if there are any boundary atoms in the molecular system. Thus, if you would like to compute a wavefunction for only a portion of a molecular system using *ab initio* methods, you must select single or multiple isolated molecules as your selected quantum mechanical region, without any boundary atoms.

Semi-empirical methods could thus treat the receptor portion of a single protein molecule as a quantum mechanical region but *ab initio* methods cannot. However, both semi-empirical and *ab initio* methods could treat solvents as a perturbation on a quantum mechanical solute. In the future, HyperChem may have an algorithm for correctly treating the boundary between a classical region and an *ab initio* quantum mechanical region in the same molecule. For the time being it does not.

Setting Up Options

Certain options are needed to setup for running quantum mechanics calculations in HyperChem via the corresponding option dialog boxes on the Setup menu.

Selecting Options for the *Ab Initio* Method

The *ab initio* options are available via the Ab Initio menu item on the Setup menu.

Choosing a Basis Set

Any set of one-electron functions can be a basis set in the LCAO approximation. However, a well-defined basis set will predict electronic properties using fewer terms than a poorly-defined basis set. So, choosing a proper basis set in *ab initio* calculations is critical to the reliability and accuracy of the calculated results.

There may be as many basis sets defined for polyatomic calculations as there are quantum chemists! One would like to define, in advance, the standard basis sets that will be suitable to most users. However, one also wants to allow sophisticated users the capability to modify existing basis sets or define their own basis sets. We have thus defined a HyperChem basis set file format and included with HyperChem a number of these *.BAS files that define standard basis sets. Users, however, can define as many of their own basis sets as they like using this file format. The details of the HyperChem basis set file format are described in the *HyperChem Reference manual*.

Many conventional and commonly-used *ab initio* basis sets are supported in HyperChem. These basis sets include:

- STO-1G and STO-1G* (H and He)^{22,23,24};
- STO-2G and STO-2G* (H to Xe);
- STO-3G and STO-3G* (H to Xe);
- STO-4G and STO-4G* (H to Xe);
- STO-5G and STO-5G* (H to Xe);
- STO-6G and STO-6G* (H to Xe);
- 3-21G, 3-21G*, and 3-21G** (H to Ar)^{25,26,27};
- 4-21G, 4-21G*, and 4-21G** (H to Ne)^{28,29,30};
- 6-21G, 6-21G*, and 6-21G** (H to Ar);
- 4-31G, 4-31G*, and 4-31G** (H to Ne);
- 5-31G, 5-31G*, and 5-31G** (H to F);
- 6-31G, 6-31G*, and 6-31G** (H to Ar);
- 6-311G, 6-311G*, and 6-311G** (H to Ar)^{31,32};

22. Hehre, W.J.; Stewart, R.F.; Pople, J.A. Self-consistent molecular-orbital methods. I. Use of Gaussian expressions of Slater-Type Atomic Orbitals *J. Chem. Phys.* 51:2657-2664, 1969.

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- D95, D95* and D95** (H to Cl)³³.

Add Extra Basis Function

HyperChem offers an easy way to interactively add certain basis functions to a molecular system. The Extra Basis Function dialog box can be used to add an S, P, D, SP, or SPD shell to the selected atom(s). These extra basis functions are primitives with no contractions. Thus, the extra basis functions are uniquely defined by the shell type and the value of the exponent.

One and only one extra shell can be applied to any atom in the current version of HyperChem. Different extra shells can be applied to different atoms but any atom can receive only one extra shell. If you would like to add more than one extra shell to any atom, you will need to modify a basis set file and create a new basis set. To use this new basis set you will need to include it in the [basisset] section of the CHEM.INI file.

A basis set for an atom thus consists of a standard basis set (3-21G, for example) and an optional extra shell.

Applying a Basis Set

You can use multiple basis sets in a single molecular system. The Apply Basis Set in HyperChem applies the currently selected basis set to the selected atoms or to all the atoms in HyperChem if there is no current selection. For example, some heavy atoms might have a 6-31G basis set (s and p only) while other heavy atoms might use a 6-31G* basis set (with d-orbitals). This is an unusual but flexible option for *ab initio* calculations.

Charge and Spin Multiplicity

Specify the extra (net) charge and the spin multiplicity in the Ab Initio Options dialog box.

The extra charge defines whether the current molecular system is a neutral system, positively charged system (cation), or negatively charged system (anion).

Closed-shell molecules have a multiplicity of one (a singlet). A radical, with one unpaired electron, has a spin multiplicity of two (a doublet). A molecular system with two unpaired electrons (usually

33. Dunning, T.H.; Hay, P.J. in *Modern Theoretical Chemistry* Plenum, New York, 1976.

a triplet) has a multiplicity of three. In some cases, however, such as a biradical, two unpaired electrons may also be a singlet.

Convergence Criteria

Convergence limit and Iteration limit specify the precision of the SCF calculation. Convergence limit refers to the difference in total electronic energy (in kcal/mol) between two successive SCF iterations yielding a converged result. Iteration limit specifies the maximum number of iterations allowed to reach that goal.

You can always use the default values. If the calculation exceeds the iteration limit before it reaches the convergence limit, then most likely there is a convergence failure. Simply increasing this limit is unlikely to help. The DIIS convergence accelerator may help in some cases.

UHF versus RHF

Choose UHF (spin Unrestricted Hartree-Fock) or RHF (spin Restricted Hartree-Fock) calculations according to your molecular system. HyperChem supports UHF for both open-shell and closed-shell calculations and RHF for closed-shell calculations only. The closed-shell UHF calculation may be useful for studying dissociation of molecular systems. ROHF (spin Restricted Open-shell Hartree-Fock) is not supported in the current version of HyperChem (for *ab initio* calculations).

One would normally choose RHF for closed-shell singlets and UHF for open-shell doublets and triplets.

Convergence Acceleration

Choose the DIIS SCF convergence accelerator to potentially speed up SCF convergence. DIIS often reduces the number of iterations required to reach a convergence limit. However, it takes memory to store the Fock matrices from the previous iterations and this option may increase the computational time for individual iterations because the Fock matrix has to be calculated as a linear combination of the current Fock matrix and Fock matrices from previous iterations.

Calculate Gradient

Specifies the calculation of gradients (the first derivatives of the total energy with respect to the nuclear positions). The RMS gradient gives an indication of the deviation from an optimized structure. The computations of two-electron integrals and their derivatives are time-consuming, because of the huge number of the two-electron integrals even for a medium size of molecule. You may not be interested in gradients for single point calculations, so you can turn off (not check) gradient calculation to speed up your task. This option applies to single point calculations only. HyperGauss always computes the gradients in doing geometry optimization, molecular dynamics, and vibration calculations.

Calculate MP2 Correlation Energy

Specifies the calculation of electron correlation energy using the Møller-Plesset second order perturbation theory (MP2). This option can only be applied to Single Point calculations.

MP2 correlation energy calculations may increase the computational time because a two-electron integral transformation from atomic orbitals (AO's) to molecular orbitals (MO's) is required. HyperChem may also need additional main memory and/or extra disk space to store the two-electron integrals of the MO's.

Two-Electron Repulsion Integrals

The calculation of the two-electron repulsion integrals in *ab initio* method is inevitable and time-consuming. The computational time is mainly dominated by the performance of the two-electron integral calculation. The following items can control the performance of the two-electron integrals.

Two-electron Integral Cutoff

Set this threshold to a small positive constant (the default value is 10^{-10} Hartree). This threshold is used by HyperChem to ignore all two-electron repulsion integrals with an absolute value less than this value. This option controls the performance of the SCF iterations and the accuracy of the wave function and energies since it can decrease the number of calculated two-electron integrals.

Two-electron Integral Buffer Size

HyperChem computes two-electron integrals and saves them in main memory (two-electron integral buffer). The units of this buffer are in double-precision words (8 bytes per double-precision word in Windows). Once this buffer is full, these two-electron integrals are written to a temporary file on a disk (the selected disk can be set in the CHEM.INI file, before you start HyperChem, or with a script command, after you start HyperChem). A large buffer may reduce the processing time through fewer disk accesses. If the two-electron integral buffer size is big enough to hold all the integrals, HyperChem does not use the disk.

Regular Two-Electron Integral Format

Specifies the use of a “regular” format for saving the two-electron integrals. HyperChem uses 16 bytes to store every integral. The first 8 bytes stores the four indices of an integral and the second 8 bytes stores its value. HyperChem only stores an integral and its associated indices when the integral's absolute value is greater than or equal to the two-electron integral cutoff. The two-electron integral and its indices are stored without any modification when you choose this regular two-electron integral format. These two-electron integrals and their indices can be printed out to a log file by choosing a proper setting for QuantumPrintLevel in the CHEM.INI file.

Raffenetti Two-Electron Integral Format

Specifies the use of the Raffenetti two-electron integral format³⁴. HyperChem can calculate all two-electron integrals and store them in a special form that makes it easier to generate a Fock matrix during the SCF iterations. The Raffenetti two-electron integral format may take more main memory or disk space for the two-electron integrals, particularly in a UHF calculation, but may still be faster than the regular two-electron integral format for the same calculation.

The Raffenetti format is not available when performing MP2 and CI calculations.

34. Raffenetti, R.C. Pre-processing two-electron integrals for efficient utilization in many-electron self-consistent field calculations. *Chem. Phys. Letters* 20:335-338, 1973.

Direct SCF Calculation

When the Direct SCF calculation³⁵ option is chosen, the two-electron integrals are recomputed in every iteration. A Direct SCF calculation will be considerably slower than a regular SCF calculation which computes all the two-electron integrals and then saves them, retrieving the saved integrals every iteration to form the Fock matrices. The Direct SCF calculation avoids using disk space or a large main memory. This option may be practical for large molecular systems run on a desk-top PC where there is little available space on the disk.

Initial Guess of MO Coefficients

An initial guess at the molecular orbital coefficients is necessary for an SCF calculation. Usually, the initial guess is obtained by solving the Hartree-Fock-Roothaan equations with the replacement of the Fock matrix by the core Hamiltonian. This initial guess of the MO coefficients is usually acceptable. However, in some cases, the core Hamiltonian leads to incorrect occupied orbitals or the initial guess may be far from the final converged SCF MO coefficients. Hence, HyperChem supports a few alternative methods for generating an initial guess at the MO coefficients. These alternative methods are:

- Projected Hückel: the initial guess at the MO coefficients is obtained from an extended Hückel calculation;
- Projected CNDO: the initial guess at the MO coefficients is obtained from a CNDO calculation;
- Projected INDO: the initial guess at the MO coefficients is obtained from an INDO calculation.

However, these alternative methods can be only applied to certain elements. For example, the projected CNDO/INDO may be used only for molecular systems with atomic numbers less than or equal to 18 (Ar). Elements beyond 18 are not available in the projected CNDO/INDO initial guess.

Number of d Orbitals

There are two different sets of d-type functions (d orbitals) used in *ab initio* calculations. One 3d set consists of five 3d functions —

35. Almlof, J.; Faegri Jr., K.; Korsell, K. *J. Comp. Chem.* 3:385, 1982.

$3d_0$, $3d_{+1}$, $3d_{-1}$, $3d_{+2}$, and $3d_{-2}$ and is normally used in STO-NG basis sets. The other is a set of six 3d functions — $3d_{xx}$, $3d_{yy}$, $3d_{zz}$, $3d_{xy}$, $3d_{xz}$, and $3d_{yz}$, and is used in the split-valence basis sets, such as, 3-21G, 4-31G, 6-31G, etc.

The contraction exponents and coefficients of the d-type functions were optimized using five d-primitives (the first set of d-type functions) for the STO-NG basis sets and six d-primitives (the second set of d-type functions) for the split-valence basis sets. Thus, five d orbitals are recommended for the STO-NG basis sets and six d orbitals for the split-valence basis sets.

Ghost-Atoms

With HyperChem you can always name a selection of atoms using the Name Selection item of the Select menu. A named selection called “**ghost-atoms**” has a special meaning, however. In most situations any atom that is a “ghost” atom, i.e. is a member of the ghost-atom set is treated just like any other atom and the named selection “ghost-atoms” is treated like any other named selection. However HyperChem may treat the ghost atoms differently from the regular atoms when performing certain *ab initio* calculations. If you have specified the use of “ghost-atoms” in the Ab Initio Advanced Options dialog box, then a ghost atom is represented in *ab initio* calculations by its basis set only and does not have any nucleus or electrons associated with it. Since there are atomic orbitals (basis functions) belonging to a ghost atom, there will be Mulliken charges attached to the ghost atoms after performing an *ab initio* calculation.

The concept of “ghost-atoms” only applies to Single Point calculations in the current version of HyperChem.

A major use of ghost atoms is to be able to offset the effect of basis set superposition effects (BSSE). For example, as two monomers come together the basis set of one monomer extends the basis set of the other, lowering the dimer energy more than just from the physical monomer-monomer interaction. A way to offset this in computing the dimerization energy is to use the same basis set in both monomer and dimer calculations. That is, the monomer energy is the energy of the dimer with ghost-atoms for the atoms of one of the monomers and “real” atoms for the other monomer.

Configuration Interaction

Use Configuration Interaction to predict the electronic spectra of molecules. The Configuration Interaction wave function computes a ground state plus low lying excited states. You can obtain electronic absorption frequencies from the differences between the energies of the ground state and the excited states.

A configuration interaction calculation is available only for single points when the reference ground state is obtained from an RHF calculation.

The calculation mixes all single determinant wavefunctions that can be obtained from the ground state by exciting electrons from a subset of the occupied orbitals (of the ground state) to a subset of the unoccupied orbitals. The subsets are specified as a fixed number (highest occupied or lowest unoccupied) or by an energy criterion associated with the energy difference between the occupied orbital and the unoccupied orbital.

Selecting Options for the Extended Hückel Method

Charge and Spin Multiplicity

Specify the extra (net) charge and spin multiplicity in the Semi-empirical Options dialog box.

The extra charge defines whether the current molecular system is a neutral system, positively charged system (cation), or negatively charged system (anion).

Closed-shell molecules have a multiplicity of one (a singlet). A radical, with one unpaired electron, has a multiplicity of two (a doublet). A molecular system with two unpaired electrons (usually a triplet) has a multiplicity of three. In some cases, however, such as a biradical, two unpaired electrons may also be a singlet.

Hückel Constant

The Hückel constant (k) scales the interaction energy between two atomic orbitals (see “Extended Hückel Method” on page 125). HyperChem uses the default value of 1.75 (see the second part of this book, *Theory and Methods*). You should use this value for most cases. A suggested range for experimental adjustment of this constant is 1.6–2.0.³⁶

You can select Unweighted constant or Weight diffuseness for the Hückel constant. The unweighted option uses only the scale factor k . The Weight diffuseness option weighs the contributions from the two binding energies differently, but absorbs this weighting into the Hückel constant. The option you choose makes little difference in cases of orbitals with similar diffuseness, as for most organic molecules. It may be useful in calculations involving third row elements.

d Orbitals

The Extended Hückel method also allows the inclusion of d orbitals for third row elements (specifically, Si, P, S and Cl) in the basis set. Since there are more atomic orbitals, choosing this option results in a longer calculation. The major reason to include d orbitals is to improve the description of the molecular system.

In some situations, using this option may be important. For example, if p orbitals on electronegative atoms interact with d orbitals, (as for a silicon atom bonded to an amine group), you may want to include d orbitals.

Selecting Options for NDO Methods

After you select a method for a semi-empirical calculation (using the Semi-empirical item on the Setup menu), choose Options in the dialog box to set conditions for the calculation. You see the Semi-empirical Options dialog box. The following sections explain these options.

Convergence Criteria

Convergence limit and Iteration limit specify the precision of the calculation. Convergence limit refers to the difference in energy (in kcal/mol) between two successive SCF cycles. Iteration limit specifies the maximum number of cycles allowed to reach that goal.

You can usually use the default values. If the calculation exceeds the iteration limit before it reaches the convergence limit, then there is most likely convergence failure. Simply increasing the limits is unlikely to help. The DIIS convergence accelerator, (see “SCF Convergence” on page 47), which is available for all the SCF

36. Hoffmann, R. An Extended Hückel Theory. I. Hydrocarbons *J. Chem. Phys.* 39(6):1397-1412, 1963.

semiempirical methods, might help in some cases. Most often, however, the reason for convergence failure lies in the molecular geometry. For example, two nuclei very close together often lead to convergence failure. If convergence problems arise, check the starting geometry for unrealistic features.

Charge, Spin, and Excited State

Specify the charge and spin multiplicity in the Semi-empirical Options dialog box.

Closed-shell molecules have a multiplicity of one (a singlet). A radical, with one unpaired electron, has a multiplicity of two (a doublet). A molecular system with two unpaired electrons (usually a triplet) has a multiplicity of three. In some cases, however, such as a biradical, two unpaired electrons may also be a singlet.

This dialog box also contains the option for specifying that the molecular system is in the first excited singlet state (Next lowest) or the Lowest electronic state.

UHF versus RHF

Next, you choose a UHF or RHF calculation. HyperChem can compute open-shell (non-singlet) systems with either the half-electron RHF or the UHF method (see “Hartree-Fock Wave Functions” on page 37).

Convergence Acceleration

The DIIS convergence accelerator is available for all the SCF semiempirical methods. This accelerator may be helpful in curing convergence problems. It often reduces the number of iteration cycles required to reach convergence. However, it may be slower because it requires time to form a linear combination of the Fock matrices during the SCF calculation. The performance of the DIIS accelerator depends, in part, on the power of your computer.

Configuration Interaction

Configuration Interaction (or electron correlation) improves energy calculations using CNDO, INDO, MINDO/3, MNDO, AM1, PM3, ZINDO/1, and ZINDO/S for these electron configurations

- closed-shell singlet ground states

- half-electron, excited singlet states
- half-electron, doublet, triplet, and quartet open-shell ground states.

See also “Extending the Wave Function Calculation” on page 37.

Use Configuration Interaction to predict electronic spectra of molecules. The Configuration Interaction wave function provides a ground state plus some excited state energies. You can obtain electronic absorption frequencies from the differences between the energies of the ground state and the excited states.

You can also use a RHF wave function with Configuration Interaction for calculations involving bond breaking, instead of using a UHF wave function. Using RHF plus Configuration Interaction conserves spin symmetry.

Note: Configuration Interaction significantly increases computing time. For calculations of ground-state energies, MINDO/3, MNDO, AM1, and PM3 methods may already include in their parameters some effects of Configuration Interaction.

Log File for Results

Log File for Results

After you choose the computation method and options, you can use Start Log on the File menu to record results, such as total energies, orbital energies, dipole moments, atomic charges, enthalpies of formation (for the CNDO, INDO, MINDO/3, MNDO, AM1, PM3, ZINDO/1, and ZINDO/S methods), etc.

Before starting HyperChem, use the QuantumPrintLevel setting in the chem.ini file to set the amount of information recorded in a log file.

For more information about log files, see Appendix A in the *HyperChem Reference manual*.

Types of Calculations

Single-point, geometry optimization, molecular dynamics and vibration calculations are all available with either *ab initio* or semi-empirical SCF methods. After obtaining a wavefunction via any of

these calculations, you can plot two-dimensional contour diagrams of the electrostatic potential surrounding a molecule, the total electronic density, the spin density, one or more molecular orbitals, and the electron densities of individual orbitals. After a vibration calculation, you can display a predicted infrared spectrum and display normal modes as vector attached to atoms or by animation of each mode. If you have performed a single-point calculation with a singly-excited configuration interaction, you can display a simulated ultraviolet-visible spectrum.

The setup of these calculations is very similar for both quantum and molecular mechanics. In practice, molecular dynamics calculations using the *ab initio* and semi-empirical quantum mechanical SCF methods are limited to relatively small systems. Each time step requires a complete calculation of the wave function and the forces.

Note: You can superimpose harmonic restraining forces to interatomic distances, angles, or dihedrals that you have set up as named selections. You can also restrain atoms to points in space. See “Using Geometric Restraints” on page 81 and “Restraints” on page 105.

Single Point Calculations and CI

HyperChem always computes the electronic properties for the molecule as the last step of a geometry optimization or molecular dynamics calculation. However, if you would like to perform a configuration interaction calculation at the optimized geometry, an additional single point calculation is required with the CI option being turned on.

For quantum mechanical methods, many more options are available for a single point calculation than for molecular mechanics. This is because the quantum mechanical methods yield various electronic properties. Among the options available following a Single Point calculation is the plotting of contour diagrams. These plots include the electrostatic potential surrounding a molecule, the total electronic density, the spin density, and the contour diagrams describing individual molecular orbitals. HyperChem can produce different plots in succession without repeating the single point calculation, as long as the coordinates of the molecule are unaltered. To plot these pictures after a calculation, choose either Contour Plots or Orbitals from the Compute menu of HyperChem.

Optimization Methods

Four optimization techniques are available for geometry optimizations with quantum mechanical methods: a steepest descent method, two conjugate gradient methods, and eigenvector following. To select these methods, choose Geometry Optimization on the Compute menu. The Semi-empirical Optimization or Ab Initio Optimization dialog box appears. You have the choice of the same methods as for molecular mechanics calculations (see “Geometry Optimizations” on page 57).

In general, the steepest descent method is useful when a molecule is far from a minimum. Conjugate gradient methods are better when the minimum is nearby. You choose the precision of the optimization in the Semi-empirical Optimization or Ab Initio Optimization dialog box. Suitable default values for ending an optimization calculation are either an RMS gradient of 0.1 kcal/mol/Å or a maximum number of cycles that is 15 times the number of atoms involved in the calculation. In general, you must use a gradient limit. For improved precision, use a lower gradient limit.

Note: You cannot use the Extended Hückel method or any one of the SCF methods with the CI option being turned on for geometry optimizations, molecular dynamics simulations or vibrational calculations, in the current version of HyperChem.

Transition State Search

You can use the *ab initio* method (with any basis set), and all semi-empirical methods except Extended Hückel, to perform a transition state search. Two different methods are available: eigenvector following and synchronous transit. In the synchronous transit method, both linear synchronous transit (LST) and quadratic synchronous transit (QST) are available. To select any of these methods, choose Transition State on the Compute menu. If you choose eigenvector following, the calculation will start with the calculation of the Hessian matrix. Then the dialog box will appear, in which you can choose the mode to be followed, and specify the calculation termination conditions (RMS gradient and number of SCF cycles). If the synchronous transit method is chosen, the dialog box appears, in which you can specify a linear or quadratic search, and can specify convergence criteria.

In general, *ab initio* calculations are preferable for transition state searching. The time required for the calculation to finish may sometimes be the limiting factor in the choice of the calculation method. Semi-empirical methods may be less successful in transition state searching, since they were originally parametrized for energy minimization searching. (The ZINDO/S method is especially likely to give poor results for transition state searching since it was parameterized for spectral calculations.) Many times, a tighter SCF convergence criteria may be needed, as well as a larger number of SCF cycles, in order to locate the transition state successfully with a semi-empirical method.

Note: You can not use the Extended Hückel method, nor any of the other SCF methods with the CI option turned on, for geometry optimization or molecular dynamics simulations.

Molecular Dynamics

You can use any *ab initio* SCF calculation and all the semi-empirical methods, except Extended Hückel, for molecular dynamics simulations. The procedures and considerations are similar for simulations using molecular mechanics methods (see “Molecular Dynamics” on page 69).

These simulations take much longer than molecular mechanics simulations. They may, however, model bond breaking and formation more accurately. While HyperChem doesn't rearrange its molecular graph dynamically, you can detect the changes by monitoring interatomic distances (see “Bond Breaking” on page 90).

Energy Conservation in Molecular Dynamics Calculations

In order to conserve the total energy in molecular dynamics calculations using semi-empirical methods, the gradient needs to be very accurate. Although the gradient is calculated analytically, it is a function of wavefunction, so its accuracy depends on that of the wavefunction. Tests for CH₄ show that the convergence limit needs to be at most 1e-6 for CNDO and INDO and 1e-7 for MINDO/3, MNDO, AM1, and PM3 for accurate energy conservation. ZINDO/S is not suitable for molecular dynamics calculations.

Vibrations

A vibrations calculation is the first step of a vibrational analysis. It involves the time consuming step of evaluating the Hessian matrix (the second derivatives of the energy with respect to atomic Cartesian coordinates) and diagonalizing it to determine normal modes and harmonic frequencies. For the SCF methods the Hessian matrix is evaluated by finite difference of analytic gradients, so the time required quickly grows with system size.

Once the vibration calculation completes, you can analyze and display the results by using Vibrational Spectrum menu item.

Contour Plots and Orbitals

Once you have calculated an *ab initio* or a semi-empirical wave function via a single point calculation, geometry optimization, molecular dynamics or vibrations, you can plot the electrostatic potential surrounding the molecule, the total electronic density, the spin density, one or more molecular orbitals ψ_i , and the electron densities of individual orbitals ψ_i^2 . You can examine orbital energies and select orbitals for plotting from an orbital energy level diagram.

Vibrational Spectrum

To perform a vibrational analysis, choose Vibrations on the Compute menu to invoke a vibrational analysis calculation, and then choose Vibrational Spectrum to visualize the results. The Vibrational Spectrum dialog box displays all vibrational frequencies and a simulated infrared spectrum. You can zoom and pan in the spectrum and pick normal modes for display, using vectors (using the Rendering dialog box from Display/Rendering menu item) and/or animation.

Generally, a vibration analysis calculation should be performed after a geometry optimization with the same method. This ensures that the calculation of second derivatives is performed at a configuration for which all first derivatives are zero.

Electronic Spectrum

Use the Electronic Spectrum dialog box to display and analyze the UV-visible spectrum produced by a singly excited CI calculation. This dialog box is available from the Compute menu only after you do a single point CI semi-empirical or *ab initio* calculation. Electronic Spectrum is then activated on the Compute menu.

Saving Information in a Log File

You can obtain detailed results of calculations by using Start Log on the File menu. The amount of calculational results is controlled by the QuantumPrintLevel. The QuantumPrintLevel can be changed in the CHEM.INI file before you run HyperChem or by a script command after you are running HyperChem. For more details of the log file and information saved in the log file, see the HyperChem *Reference* manual.

Extended Hückel Method

Extended Hückel is the simplest and fastest semi-empirical method included in HyperChem, but it is also the least accurate. It is particularly simple in its treatment of electron-electron interactions: it has no explicit treatment of these interactions, although it may include some of their effects by parameterization.

Extended Hückel provides the approximate shape and energy ordering of molecular orbitals. It also yields the approximate form of an electron density map. This is the only requirement for many qualitative applications of quantum mechanics calculations, such as Frontier Orbital estimates of chemical reactivity (see “Frontier Molecular Orbitals” on page 141).

HyperChem determines the energy and form of the molecular orbitals using a single set of parameters that represents the binding energies of electrons in each atomic orbital. Binding energy refers to the attraction between an electron in an atomic orbital and the nucleus of the same atom. These energies are the diagonal elements of the Hamiltonian matrix. The off-diagonal elements are the interaction energies between two atomic orbitals. Interaction energies are the average of the binding energies multiplied by the

overlap integral over the two atomic orbitals. HyperChem scales this result by the Hückel constant, k , which has a default value of 1.75 (see the second part of this book, *Theory and Methods*).

Limitations of Extended Hückel

The neglect of electron-electron interactions in the Extended Hückel model has several consequences. For example, the atomic orbital binding energies are fixed and do not depend on charge density. With the more accurate NDO semi-empirical treatments, these energies are appropriately sensitive to the surrounding molecular environment.

HyperChem cannot perform a geometry optimization or molecular dynamics simulation using Extended Hückel. Stable molecules can collapse, with nuclei piled on top of one another, or they can dissociate into atoms. With the commonly used parameters, the water molecule is predicted to be linear.

NDO Methods

The Extended Hückel method neglects all electron-electron interactions. More accurate calculations are possible with HyperChem by using methods that neglect some, but not all, of the electron-electron interactions. These methods are called Neglect of Differential Overlap or NDO methods. In some parts of the calculation they neglect the effects of any overlap density between atomic orbitals. This reduces the number of electron-electron interaction integrals to calculate, which would otherwise be too time-consuming for all but the smallest molecules.

Defining Electron-Electron Interactions

NDO calculations use the Hartree-Fock (HF) approximation to solve the Schrödinger equation. HF methods deal with several kinds of electron-electron interactions. By understanding these interactions, you can appreciate differences between the NDO methods and gain insight into why the NDO approximation works well or fails.

Electrons repel each other electrostatically, and the repulsion between an electron in one atomic orbital and an electron in

another (or the same, if doubly occupied) is called a coulomb interaction. The identical nature of electrons requires a correction for electrons of the same spin, and this is often described as if it were a real interaction. The contributions to matrix elements describing this correction are called atomic exchange integrals. This is because they arise from terms in the many-electron wave function involving the interchange of coordinates of an electron pair (see “Exclusion Principle” on page 34). In a typical calculation, there are many more exchange-type integrals than coulomb integrals. Think of an exchange integral as an electron in the overlap region between two atomic orbitals interacting with an electron in an overlap region between two other atomic orbitals.

Treatment of Electron-Electron Interactions

The NDO methods in HyperChem are built on three different approximations to the treatment of electron-electron interactions. The NDO methods are discussed in the following sections.

CNDO, INDO, MINDO/3, ZINDO/1, and ZINDO/S Methods

The simplest method is CNDO (Complete Neglect of Differential Overlap). The electron repulsion between electrons in different orbitals depends only on the nature of the atoms involved, and not on the particular orbital. This creates a very simple picture. One of its disadvantages is that because it neglects almost all exchange integrals, it cannot calculate differences between states of multiplicity arising from the same electronic configuration. CNDO treats singlet-triplet energy gaps poorly.

The INDO method (Intermediate NDO) corrects some of the worst problems with CNDO. For example, INDO exchange integrals between electrons on the same atom need not be equal, but can depend on the orbitals involved. Though this introduces more parameters, additional computation time is negligible. INDO and MINDO/3 (Modified INDO, version 3) methods are different implementations of the same approximation.

ZINDO/1 and ZINDO/S are Dr. Michael Zerner’s INDO versions and used for molecular systems with transition metals. ZINDO/1 is expected to give geometries of molecules, and ZINDO/S is parametrized to give UV spectra.

MNDO, AM1, and PM3 Methods

The NDDO (Neglect of Diatomic Differential Overlap) approximation is the basis for the MNDO, AM1, and PM3 methods. In addition to the integrals used in the INDO methods, they have an additional class of electron repulsion integrals. This class includes the overlap density between two orbitals centered on the same atom interacting with the overlap density between two orbitals also centered on a single (but possibly different) atom. This is a significant step toward calculating the effects of electron-electron interactions on different atoms.

Calculating the extra integrals takes time. MNDO, AM1, and PM3 calculations typically take about one and one-half times as long as INDO or MINDO/3 calculations.

AM1 is generally the most accurate computational method included in HyperChem and is often the best method for collecting quantitative information. PM3 is functionally similar to AM1, but uses an alternative parameter set (see “PM3” on page 150).

Practical Uses of NDO Methods

NDO methods work best for molecules with electrons that are spread evenly throughout, with no significant charge polarization. Hydrocarbons are classic examples: all NDO methods work well on nonpolar hydrocarbons. Molecular systems with heteroatoms provide a better test of these methods. Groups with several electronegative atoms close together, such as NO_2 , are the most difficult to treat. Among inorganic, main group compounds, even the best semi-empirical methods can fail dramatically with, for example, interhalogen molecules.

Parameterization

The five semi-empirical methods in HyperChem differ in many technical details. Treatment of electron-electron interactions is one major distinguishing feature. Another important distinguishing feature is the approach used to parameterize the methods. Based on the methods used for obtaining parameters, the NDO methods fall into two classes:

- CNDO and INDO were developed by the Pople group at Carnegie Mellon University. This group chose parameters based pri-

marily on theory. Their intent was to give them values as close as possible to those possibly obtained by an exact Hartree-Fock calculation, using the same basis set.

- MINDO/3, MNDO, and AM1 were developed by the Dewar group at the University of Texas at Austin. This group chose many parameters, such as heats of formation and geometries of sample molecules, to reproduce experimental quantities. The Dewar methods yield results that are closer to experiment than the CNDO and INDO methods.
- PM3, developed by James J.P. Stewart³⁷, is a reparameterization of AM1, which is based on the neglect of diatomic differential overlap (NDDO) approximation. NDDO retains all one-center differential overlap terms when Coulomb and exchange integrals are computed. PM3 differs from AM1 only in the values of the parameters. The parameters for PM3 were derived by comparing a much larger number and wider variety of experimental versus computed molecular properties. Typically, non-bonded interactions are less repulsive in PM3 than in AM1. PM3 is primarily used for organic molecules, but is also parameterized for many main group elements.
- ZINDO/1 is based on a modified version of the intermediate neglect of differential overlap (INDO), which was developed by Michael Zerner of the Quantum Theory Project at the University of Florida. Zerner's original INDO/1 used the Slater orbital exponents with a distance dependence for the first row transition metals only. However, in HyperChem constant orbital exponents are used for all the available elements, as recommended by Anderson, Edwards, and Zerner, *Inorg. Chem.* 28, 2728-2732, 1986.
- ZINDO/S is an INDO method parameterized to reproduce UV visible spectroscopic transitions when used with the singly excited CI method. It was developed in the research group of Michael Zerner of the Quantum Theory Project at the University of Florida.

37. Stewart, J. J. P. Optimization of Parameters for Semiempirical Methods. I. Method *J. Comput. Chem.* 10:209, 1989 and Stewart, J. J. P. Optimization of Parameters for Semiempirical Methods. II. Applications *J. Comput. Chem.* 10:221, 1989.

Results of Semi-Empirical Calculations

You can use the information obtained from semi-empirical calculations to investigate many thermodynamic and kinetic aspects of chemical processes. Energies and geometries of molecules have clear relationships to chemical phenomena. Other quantities, like atomic charges and Frontier Orbitals, are less defined but provide useful qualitative results.

Energies of Molecules

The total energy in an Molecular Orbital calculation is the net result of electronic kinetic energies and the interactions between all electrons and atomic cores in the system. This is the potential energy for nuclear motion in the Born-Oppenheimer approximation (see page 32).

The stable geometry of a molecule has a minimal total energy. Geometries at different energy minima (local minima plus the global minimum) describe different stable or metastable conformations and isomers of a molecule. Geometry optimizations with NDO methods generally yield geometries corresponding to energy minima.

While the HyperChem status line reports the binding energy of the electrons, all the SCF methods also supply heat of formation. MINDO/3, MNDO, AM1, and PM3 are parameterized by fitting to experimentally determined heats (enthalpies) of formation for a set of molecules at 298 K. The heat of formation is calculated for these methods by subtracting atomic heats of formation from the binding energy. Results are reported in the log file for a calculation (see page 120). Heat of formation is the value usually reported when describing results and is more useful than the directly calculated binding energy.

The following data (Table 1) for molecules, including hydrocarbons, strained ring systems, molecules with heteroatoms, radicals, and ions comes from a review by Stewart.³⁸ For most organic molecules, AM1 reports heats of formation accurate to within a few kilocalories per mol. For some molecules (particularly inorganic compounds with several halogens, such as perchloryl fluoride, even the best semi-empirical method fails completely.

38. Stewart, J. J. P. MOPAC: A Semiempirical Molecular Orbital Program *J. Computer-Aided Mol. Design* 4, 1-105:1990.

Table 8-1. Heats of formation of selected molecules from AM1 calculations

Molecular Formula	Name	Heat of Formation (experiment, kcal/mol)	Heat of Formation (AM1, kcal/mol)
C ₇ H ₆ O ₂	Benzoic Acid	-70.1	-68.0
C ₇ H ₈	Norbornadiene	+59.7	+67.7
C ₅ H ₈ O	Cyclopentanone	-46.0	-36.1
C ₂ H ₄ O	Ethylene oxide	-12.6	-9.0
C ₅ H ₈	Spiropentane	+44.3	+50.5
C ₄ H ₁₀	n-butane	-30.4	-31.2
CF ₄	Carbon tetrafluoride	-223.3	-225.7
C ₃ H ₅	Allyl radical	+40.0	+38.6
CH ₂ (triplet)	Methylene	+92.3	+80.8
CH ₃ O	Methoxy radical	-0.5	-3.7
C ₇ H ₇ ⁺	Benzyl cation	+216.0	+222.1
CH ₂ F ₂ ⁺	Difluoromethane cation	+185.2	+151.6
O ₃ FCI	Perchloryl fluoride	-5.1	+246.5

You can investigate the energetics of chemical equilibrium by comparing the heats of formation of reactants and products. This produces one of the most useful results of a chemical calculation. The accuracy and reliability of the heats of formation depend on the method used (see “Choosing a Semi-Empirical Method” on page 148).

A common application of the direct calculation of molecular energy is the study of organic reaction mechanisms. You can investigate the energies of different potential intermediates, species not easily studied by experiment. A review by Thiel³⁹ lists many such

39. Thiel, W. Semiempirical Methods: Current Status and Perspectives *Tetrahedron*, 44:7393, 1988.

applications for MNDO, including studies of rearrangements, questions of stereoselectivity, regioselectivity, and photochemical reactions. The accuracy of calculations in predicting relative energies of related species is generally greater than the absolute heats of formation (see Tables 1 and 2). This shows how much interest there is in the study of reaction mechanisms.

Data on proton affinities (gas phase) of many different compounds (see Table 2) demonstrate the high level of accuracy possible in determining energies of related species. In this report by Dewar and Dieter⁴⁰, the enthalpy of formation of H⁺ is the experimental value (367.2 kcal/mol). The calculated value for H⁺ is unreliable.

Table 8-2. Proton affinities of selected compounds, from AM1 calculations

Base	Conjugate Acid	Proton Affinity (experimental, kcal/mol)	Proton Affinity (AM1, kcal/mol)
CH ₄	CH ₅ ⁺	132.0	134.0
C ₆ H ₆ (benzene)	C ₆ H ₇ ⁺	181.3	183.2
CH ₃ NH ₂	CH ₃ NH ₃ ⁺	214.1	211.1
Ph-NH ₂	Ph-NH ₃ ⁺	209.5	211.4
CH ₃ CN	CH ₃ CNH ⁺	188.4	190.4
H ₂ O	H ₃ O ⁺	166.5	164.5
CH ₃ CHO	CH ₃ CHOH ⁺	186.6	184.9

Geometries of Molecules

The geometries obtained from optimizations with semi-empirical calculations describe the shapes of molecules. The calculations have varying degrees of accuracy and take more time than molecular mechanics methods. The accuracy of the results depends on the molecule.

Molecular mechanics force fields have much information built into them and can be accurate for the molecules used in their parameterization. For molecules outside the limited scope for

40. Dewar, J. S.; Dieter, K. M. *J. Am. Chem. Soc.* 108: 8075, 1986.

which they were designed, semi-empirical methods are more reliable. Stewart³⁸ reports a statistical study of geometries obtained using MNDO and AM1. For second row elements, the calculations of bond lengths are accurate to an average of approximately 0.01 Ångstrom for AM1, and almost twice this error for MNDO. For third row elements, the error is about twice that of the second row elements. Bond angles are predicted correctly to within a few degrees for almost all organic molecules.

Energies of Transition States

Many transition states of chemical reactions contain symmetry elements not present in the reactants and products. For example, in the umbrella inversion of ammonia, a plane of symmetry exists only in the transition state.

Symmetrical transition states are the lowest energy configuration within that symmetry. If a geometry optimization starts off within that symmetry, then the calculation can find the transition state.

Example: If you start an optimization of a planar ammonia molecule and constrain it to that geometry, the calculation finds the transition state.

Example: Ethane is stable in the staggered (*gauche*) conformation. The transition state for rotating a methyl group in ethane has the eclipsed conformation. A geometry optimization starting from an eclipsed conformation yields the transition state.

Semi-empirical methods take their parameters from data on stable molecules, so the parameters are less suited to describing transition states than to describing minimum energy geometries. Activation energies derived from these methods are generally less reliable than are reaction energies. Calculations of rotational barriers using MNDO and AM1 provide examples of the accuracy of activation energies (Table 3). The following data is from Stewart's review.³⁸

Table 8-3. Barriers to rotation and inversions, from AM1 calculations

Molecule	Barrier to	Experiment (kcal/mol)	AM1 (kcal/mol)	MNDO (kcal/mol)
Ethane	Methyl rotation	2.9	1.25	1.01
Ammonia	Inversion	6	4.24	11.58

Molecule	Barrier to	Experiment (kcal/mol)	AM1 (kcal/mol)	MNDO (kcal/mol)
Methanol	Methyl rotation	1.1	1.04	0.74

Molecular Orbital Energies and Ionization Potentials

Koopmans' Theorem states that the first ionization energy of a closed-shell molecule is approximated to second order by the energy of the highest occupied orbital (HOMO). During ionization, the remaining electrons are reorganized, contributing an additional energy term not considered in this theorem. However, Koopmans' theorem does hold for many situations and enables interpretation of photoelectron spectra from Molecular Orbital calculations. It is also true that orbital energies can reasonably approximate higher ionization potentials.

Errors in ionization potentials are typically a few tenths of an electron volt, a small percentage of the total. Stewart gives tables with sample values.^{24, 41}

Dipole Moments

The molecular dipole moment is perhaps the simplest experimental measure of charge density in a molecule. The accuracy of the overall distribution of electrons in a molecule is hard to quantify, since it involves all of the multipole moments. Experimental measures of accuracy are necessary to evaluate results. The values for the magnitudes of dipole moments from AM1 calculations for a small sample of molecules (Table 4) indicate the accuracy you may expect. This data is a sampling from Stewart's review.³⁸

41. Stewart, J.J.P. in *Reviews of Computational Chemistry*, Lipkowitz, K.; Boyd, D.B., Eds. VCM Publishers, New York, 1990.

Table 8-4. Dipole moments of selected molecules, from AM1 calculations

Formula	Name	Experiment (Debyes)	AM1 (Debyes)
C ₃ H ₄ O	Acrolein	3.12	2.53
NH ₃	Ammonia	1.47	1.85
H ₂ O	Water	1.85	1.86
C ₆ H ₆ O	Phenol	1.45	1.23
HSiF ₃	Trifluorosilane	1.27	1.55
C ₆ H ₄ F ₂	o-difluorobenzene	2.59	2.68

The value for water in Table 4 is particularly interesting. AM1 reproduces the water molecule's electron distribution very well and can give accurate results for hydrogen bonds.

The HyperChem log file includes calculated dipole moments of molecules. To set the amount of information collected in the log file, change the value of the QuantumPrintLevel setting in the chem.ini file. Note that the sign convention used in the quantum mechanical calculation of dipoles is opposite to that used in molecular mechanics dipole calculations; this reflects the differing sign conventions of physics and chemistry.

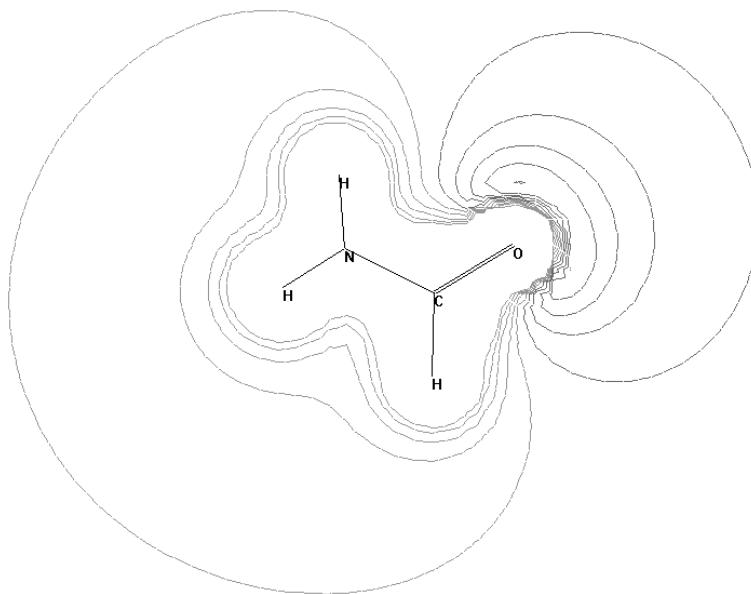
Electrostatic Potential

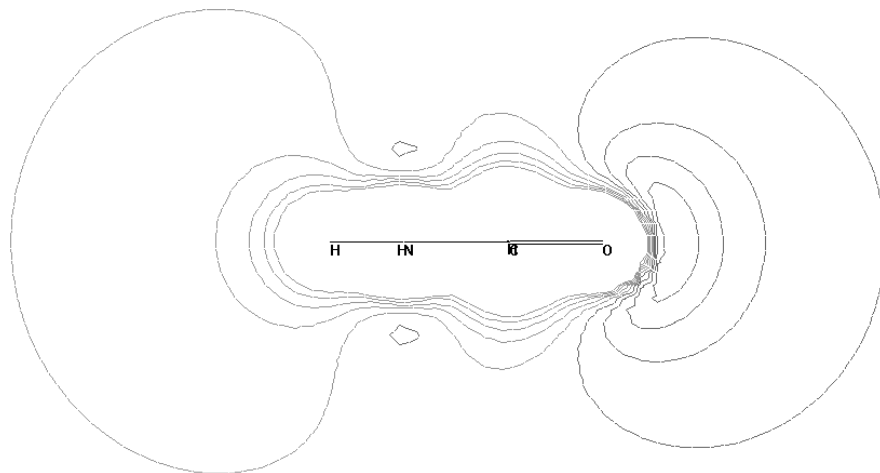
Electron distribution governs the electrostatic potential of molecules. The electrostatic potential describes the interaction of energy of the molecular system with a positive point charge. Electrostatic potential is useful for finding sites of reaction in a molecule: positively charged species tend to attack where the electrostatic potential is strongly negative (electrophilic attack).

HyperChem displays the electrostatic potential as a contour plot when you select the appropriate option in the Contour Plot dialog box. Choose the values for the starting contour and the contour increment so that you can observe the minimum (typically about -0.5 for polar organic molecules) and so that the zero potential line appears.

View the contour map in several planes to see the general form of the distribution. As long as you don't alter the molecular coordinates, you don't need to repeat the wave function calculation. Use the left mouse button and the HyperChem Rotation or Translation tools (or Tool icons) to change the view of a molecule without changing its atomic coordinates.

Atomic charges indicate where large negative values (sites for electrophilic attack) are likely to occur. However, the largest negative value of the electrostatic potential is not necessarily adjacent to the atom with the largest negative charge. An example is formamide (NH_2CHO). The largest negative atomic charge occurs on the nitrogen, but the most negative values of the electrostatic potential occur at the oxygen lone pair sites. Protonation most favorably occurs at these sites. This illustrates the value of electrostatic potential compared to simple atomic charges in predicting reactivity.





In this example, the deepest minimum occurs at oxygen lone pair sites. The contour starting value is -0.4 and the increment is 0.04 . Fifteen contour levels were calculated on a 60 by 60 grid. The most negative (Mulliken) atomic charge in this system is that of the nitrogen (-0.448), with oxygen (-0.371) being the only other negative atom in the system. Electrostatic potential predicts protonation on the oxygen atom.

Atomic Charges

Energy, geometry, dipole moment, and the electrostatic potential all have a clear relation to experimental values. Calculated atomic charges are a different matter. There are various ways to define atomic charges. HyperChem uses Mulliken atomic charges, which are commonly used in Molecular Orbital theory. These quantities have only an approximate relation to experiment; their values are sensitive to the basis set and to the method of calculation.

It is interesting to calculate the atomic charges of the water molecule using the various methods in HyperChem, and compare the results to the optimized point charges for the TIP3P model of water. The TIP3P model, which HyperChem uses in its periodic box, gives atomic charges that reproduce accurately the electrostatic interactions between water molecules. The charge on the oxygen atom is -0.834 , while the charges on the oxygens from the semi-empirical calculations at optimized geometries are -0.383 (AM1), -0.326 (MNDO), -0.505 (MINDO/3), -0.312 (INDO), and

-0.266 (CNDO). At the CNDO geometry, the Extended Hückel charge on oxygen is -0.884. Extended Hückel, which gives the least accurate results of any method, yields a charge closest to the electrostatic potential values of TIP3P. Note that the TIP3P values are appropriate for a particular use; it would be incorrect to call them the proper atomic charges. However, it is clear that reliable energies and geometries do not translate into a meaningful set of atomic charges.

Despite these reservations, Mulliken population-derived atomic charges are easy to compute. Empirical investigation shows that they have various uses; they provide approximate representation of the 3D charge distribution within a molecule.

AMBER, BIO+, and OPLS calculations use information on atomic charges. Atomic charges can come from these sources:

- HyperChem residue templates. HyperChem uses these templates when it reads a Protein Data Bank file or when you construct a molecule from residues.
- Set Charge on the Build menu. You can use this command to assign charges to individual atoms.
- Semi-empirical calculations.
- *Ab initio* calculations

For example, semi-empirical calculations on a substrate molecule provide a set of charges that you can use in a molecular mechanics calculation of the interaction of that substrate with another molecule. To include the effects of polarization, repeated semi-empirical calculations can provide a set of charges that respond to the environment.

If the MM+ option to use bond dipoles for nonbonded electrostatic calculations is set, then MM+ ignores atomic charges but uses dipole moments supplied in its parameter set (in the mmpstr.* files).

One of the common uses of Mulliken atomic charges is to indicate chemical reactivity.

Chemical Reactivity

Because of thermodynamic forces, many elementary reactions (those that take place in a single step) favor the most stable prod-

uct. In these cases, calculating energies of the reaction products yields straightforward, well-defined information about the likely products. Electrophilic, aromatic substitutions are an example of this type of reaction.

Other reactions are controlled kinetically, and the most stable product is not the major one observed. In these cases, you must look at the reactant side of the reaction coordinate to discover factors determining the outcome. Klopman⁴² and Salem⁴³ developed an analysis of reactivity in terms of two factors: an electrostatic interaction approximated by atomic charges and a Frontier orbital interaction. Fleming's book provides an excellent introduction to these ideas.⁴⁴

The Klopman-Salem equation partitions contributions to the interaction energy of two molecules into two teams, as they approach each other (equation 29).

$$\Delta E = \sum_{A < B} \frac{q_A q_B}{R_{AB}} + \left(\sum_r^{\text{occ}} \sum_s^{\text{unocc}} - \sum_s^{\text{occ}} \sum_r^{\text{unocc}} \frac{2 \left(\sum_{\mu\nu} C_{\mu r} \cdot C_{\nu s} \cdot H_{\mu\nu} \right)}{\epsilon_r - \epsilon_s} \right) \quad (29)$$

ΔE is the interaction energy; q_A and q_B are charges on atoms A and B, separated by R_{AB} , on different molecules. r and s are molecular orbitals on the two different molecules. μ and ν label the atomic orbitals that contribute to these molecular orbitals, with coefficients $C_{\mu r}$ and $C_{\nu s}$. $H_{\mu\nu}$ is the matrix element between atomic orbitals μ and ν , which is a measure of the energy of their interaction, roughly proportional to their overlap. The energies of the molecular orbitals are ϵ_r and ϵ_s .

The first term includes the electrostatic attractions and repulsions between the net charges on pairs of atoms, one from each molecule. The second involves interactions between occupied and vacant molecular orbitals on the two molecules. The hypothesis is that the reaction proceeds in a way to produce the most favorable

42. Klopman, G. *J. Am. Chem. Soc.* 90:223, 1968.

43. Salem, L. *J. Am. Chem. Soc.* 90:543,90:553, 1968.

44. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions* Wiley and Sons, London, 1976.

interaction energy. In one extreme, this can be accomplished by a favorable electrostatic interaction between charges. At the other extreme, it is accomplished by a favorable overlap of Frontier orbitals. Note that the Klopman-Salem equation is approximate, and that even within the framework of the equation, both factors are always at work.

Frontier Orbital theory supplies an additional assumption to this calculation. It considers only the interactions between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). These orbitals have the smallest energy separation, leading to a small denominator in the Klopman-Salem equation. The Frontier orbitals are generally diffuse, so the numerator in the equation has large terms.

The interaction between charges favors reaction between sites (on the two species) that have extreme charge values: the most positive charge interacts with the most negative. This ionic reaction generally involves strongly polar reactants. The second term favors interactions where the HOMO and the LUMO can overlap most favorably. This generally occurs for less polar reactants and is important when the two have similar energies, so that the denominator is small.

Atomic Charges and Reactivity

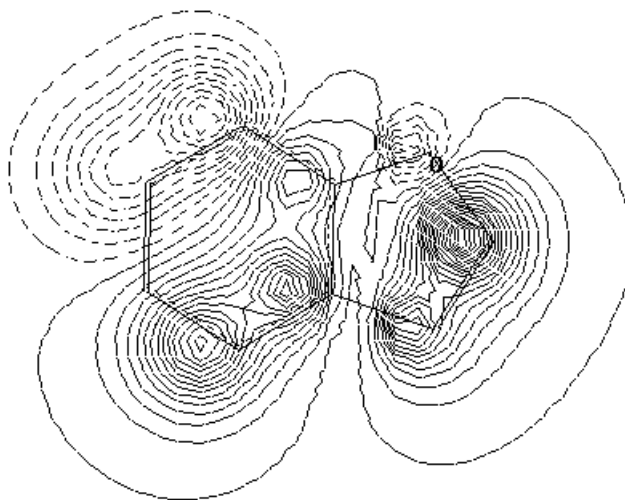
It is generally true that nucleophiles attack molecules at sites of positive charge, and that electrophiles attack sites of negative charge. You can estimate sites of ionic reactivity from the atomic charges in a molecule, particularly for reactions involving “hard” nucleophiles and electrophiles. While the electrostatic potential is a rigorous expression of this idea, the charges provide a quick summary of the main features of the electron distribution. Predictions of ionic reactivity based on atomic charges are generally more reliable when comparing different atoms of the same element.

Caution: For ionic reactions in solution, solvent effects can play a significant role. These, of course, are neglected in calculations on a single molecule. You can obtain an indication of solvent effects from semi-empirical calculations by carefully adding water molecules to the solute molecule.

Frontier Molecular Orbitals

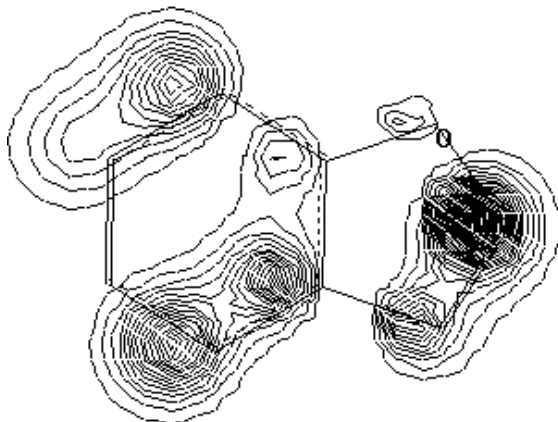
You can interpret the stereochemistry and rates of many reactions involving “soft” electrophiles and nucleophiles—in particular pericyclic reactions—in terms of the properties of Frontier orbitals. This applies in particular to pericyclic reactions. Overlap between the HOMO and the LUMO is a governing factor in many reactions. HyperChem can show the forms of orbitals such as HOMO and LUMO in two ways: a plot at a slice through the molecule and as values in a log file of the orbital coefficients for each atom.

Example: An example of Frontier Orbital theory is in predicting sites of nitration (electrophilic attack) on aromatic compounds. If you plot the HOMO as a contour map, the region of highest density (regardless of sign) is generally the site of electrophilic attack. Alternatively, you can look in the log file for the atom with the largest molecular orbital coefficient. This is generally the site of reaction.



In this example, the HOMO is plotted one Ångström above the plane of the molecule. Since it is of π symmetry, it has a node in the plane of the molecule. It shows the site of electrophilic attack at the carbon adjacent to the oxygen atom. This is also the experimentally observed site. The orbital comes from an Extended Hückel calculation of an MM+ optimized geometry.

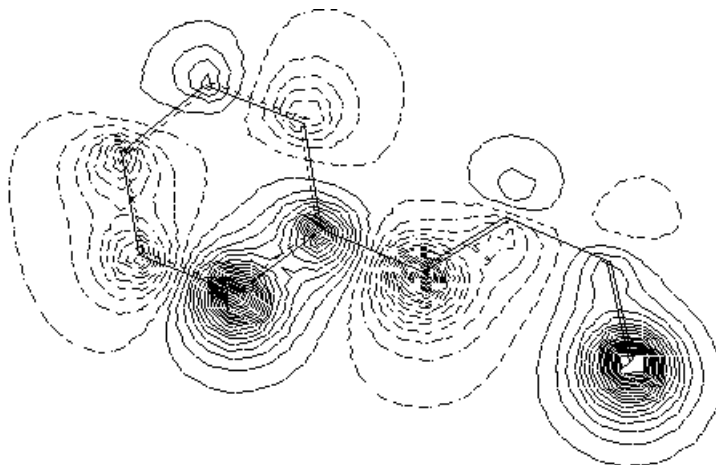
Plotting the same orbital as its density, which is the square of the wave function, emphasizes the difference in magnitude at the different sites.



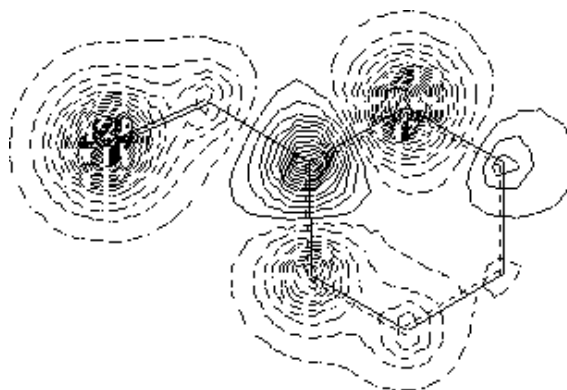
Frontier Orbital theory is qualitative, so there is no need for great accuracy in the calculation as long as it produces the approximate form of the orbitals.

Example: Another example of frontier orbital theory uses the reaction of phenyl-butadiene with phenylethylene. This reaction is a [4 + 2] pericyclic addition to form a six-membered ring. It could proceed with the two phenyl rings close to each other (head to head) or further away from each other (head to tail).

An initial assumption is that the reaction takes place with maximum overlap between the HOMO on one molecule and the LUMO on the other. The HOMO of phenylbutadiene has most density on the terminal carbon atom.



The LUMO of phenylethylene also has most density at the terminal (beta) carbon, so that these two atoms attach to each other, yielding the sterically unfavorable product.



This example uses AM1 for optimization and orbital calculations. For more examples of Frontier Orbital theory, see Fleming's book.²⁹

Vibrational Analysis and Infrared Spectroscopy

The quality of the vibrational frequencies varies widely with the semi-empirical method that is used. Generally, AM1, and PM3 are in closer agreement with experiment than methods based on CNDO or INDO.

The vibrational frequencies are derived from the harmonic approximation, which assumes that the potential surface has a quadratic form.

Large amplitude (floppy) vibrational modes often exhibit significant anharmonicity that may increase errors in computed frequencies. In addition to anharmonicity, usually there is coupling between vibrational modes.

If there are negative frequencies in an IR spectrum, it is a sign that you are not at a minimum energy structure. A valid minimum energy structure possesses only positive frequencies.

Results of a recent literature study indicate that frequencies computed using semi-empirical PM3, AM1, and MNDO methods compare well to values obtained at the *ab initio* level using medium size basis sets. Of these three methods, PM3 showed the closest correspondence to experimental values, which is generally about 10 percent too high in value from stretches (Seeger, D.M.; Korzeniewski, C.; Kowalchuk, W., *J. Phys. Chem.* 95:68-71, 1991).

The following table shows the accuracy of computed fundamental frequencies for CO₂ (cm⁻¹):

Normal Mode	CNDO	INDO	AM1	PM3	Experiment
bend	571	553	525	521	667
asymmetric stretch	1888	2080	1480	1406	1340
symmetric stretch	6427	5737	2565	2386	2349

Experimental Characteristic IR Fundamental Frequencies

After you compute an IR spectrum with HyperChem, you can use the table below to assign computed IR lines and qualitatively assess the accuracy of the computation.

Functional Group	Frequency, cm^{-1}	Intensity ^a	Assignment
1. Alkanes	2850-3000	s	C - H stretch
	1450-1470	s	CH ₂ and CH ₃ bend
	1370-1380	s	
	720-725	m	
2. Alkenes			
a) (RCH = CH ₂)	3080-3140	m	= C - H stretch
	1645	m	C = C stretch
	990	s	C - H out-of-plane bend
	910	s	
b) R ₂ C = CH ₂	3080-3140	m	= C - H stretch
	1650	m	C = C stretch
	890	s	C - H out-of-plane bend
c) <i>cis</i> -RCH = CHR	3020	w	= C - H stretch
	1660	m	C = C stretch
	675-725	m	C - H out-of-plane bend
d) <i>trans</i> -RCH = CHR	3020	w	= C - H stretch
	1675	vw	C = C stretch
	970	s	C - H out-of-plane bend
e) R ₂ C = CHR	3020	w	= C - H stretch
	1670	w	C = C stretch
	790-840	s	C - H out-of-plane bend
f) R ₂ C = CR ₂	1670	vw	C = C stretch

Functional Group	Frequency, cm^{-1}	Intensity ^a	Assignment
3. Alkynes			
a) $\text{RC} \equiv \text{CH}$	3300	s	$\equiv \text{C} - \text{H}$ stretch
	2100-2140	m	$\text{C} \equiv \text{C}$ stretch
	600-700	s	$\equiv \text{C} - \text{H}$ bend
b) $\text{RC} \equiv \text{CR}$	2190-2260	vw	$\text{C} \equiv \text{C}$ stretch
4. Alkyl Halides			
a) $\text{R} - \text{F}$	1000-1350	vs	$\text{C} - \text{F}$ stretch
b) $\text{R} - \text{Cl}$	750-850	s	$\text{C} - \text{Cl}$ stretch
c) $\text{R} - \text{Br}$	500-680	s	$\text{C} - \text{Br}$ stretch
d) $\text{R} - \text{I}$	200-500	s	$\text{C} - \text{I}$ stretch
5. Alcohols			
a) RCH_2OH	3600	var	free $\text{O} - \text{H}$ stretch
	3400	s	bonded $\text{O} - \text{H}$ stretch
	1050		$\text{C} - \text{O}$ stretch
b) R_2CHOH	3600	var	free $\text{O} - \text{H}$ stretch
	3400	s	bonded $\text{O} - \text{H}$ stretch
	1150	s	$\text{C} - \text{O}$ stretch
c) R_3COH	3600	var	free $\text{O} - \text{H}$ stretch
	3400	s	bonded $\text{O} - \text{H}$ stretch
	1200	s	$\text{C} - \text{O}$ stretch
6. Ethers	1070-1150	s	$\text{C} - \text{O}$ stretch
7. Aldehydes	1725	s	$\text{C} = \text{O}$ stretch
	2720, 2820	m	$\text{C} - \text{H}$ stretch

Functional Group	Frequency, cm^{-1}	Intensity ^a	Assignment
8. Ketones			
a) acyclic	1715	s	C = O stretch
b) three-membered	1850	s	C = O stretch
c) four-membered	1780	s	C = O stretch
d) five-membered	1745	s	C = O stretch
e) six-membered	1715	s	C = O stretch
f) seven-membered	1705	s	C = O stretch

a. vs=very strong, s=strong, m=medium, w=weak, vw=very weak, v=variable

UV-visible Spectra

The longest wavelength absorption transition for ethene calculated by HyperChem using PM3 is 207 nm, which compares favorably with the experimental value of 190-200 nm.

After you compute an electronic spectrum with HyperChem, you can use the table below to assign computed transitions and qualitatively assess the accuracy of the computation.:

Substrates	Absorption maxima (nm)
Simple alkenes	190-200
Acyclic dienes	220-250
Cyclic dienes	250-270
Styrenes	270-300
Saturated ketones	270-280
α , β - Unsaturated ketones	310-330
Aromatic ketones and aldehydes	280-300
Aromatic compounds	250-280

Choosing a Semi-Empirical Method

The choice of the NDO method depends on several factors including your previous experience and preferences. If you want to compare the results to other studies, you must use the same semi-empirical method. Since some methods can converge much more quickly than others, you might want to use a fast method to obtain an approximation of the final answer, and then a more accurate method for the final result.

Extended Hückel

Extended Hückel (EHT) is the computational equivalent of the orbital interaction pictures familiar to chemists (see “Generating and Viewing Orbitals and Electronic Plots” on page 9). The energies of atomic orbitals are well defined, and the total energy is the sum of occupied orbital energies. Neither factor is true for other methods. Extended Hückel is useful for examining the general form and energy ordering of molecular orbitals. The method is simple and it provides qualitative answers to questions about electronic structure.

For transition metals the splitting of the d orbitals in a ligand field is most readily done using EHT. In all other semi-empirical methods, the orbital energies depend on the electron occupation. HyperChem’s molecular orbital calculations give orbital energy spacings that differ from simple crystal field theory predictions. The total molecular wavefunction is an antisymmetrized product of the occupied molecular orbitals. The virtual set of orbitals are the residue of SCF calculations, in that they are deemed least suitable to describe the molecular wavefunction.

Normally, you would expect all 2p orbitals in a given first row atom to be identical, regardless of their occupancy. This is only true when you perform calculations using Extended Hückel. The orbitals derived from SCF calculations depend sensitively on their occupation. For example, the 2px, 2py, and 2pz orbitals are not degenerate for a CNDO calculation of atomic oxygen. This is especially important when you look at d orbital splittings in transition metals. To see a clear delineation between t_{2u} and e_g levels you must use EHT, rather than other semiempirical methods.

See also “Limitations of Extended Hückel” on page 126.

CNDO

Although CNDO is less accurate than other NDO methods, there are two common reasons for using it:

- CNDO and INDO are generally faster than the MINDO/3, MNDO, AM1, and PM3 and require much less memory. You can apply them to molecules that are too large for MINDO/3, MNDO, AM1, and PM3.
- Apart from speed, an appealing aspect of CNDO is its simplicity. It uses fewer parameters than any other method except for Extended Hückel and, consequently, it is easier to understand the results of modifying a calculation.

Note: Do not use CNDO on any problem where electron-spin is critically important. Its complete neglect of atomic exchange integrals makes it incapable of dealing with these problems.

INDO

INDO is faster than MINDO/3, MNDO, AM1, and PM3 and, unlike CNDO, can deal with spin effects. It is a particularly appealing choice for UHF calculations on open-shell molecules. It is also available for mixed mode calculations (see the previous section). INDO shares the speed and storage advantages of CNDO and is also more accurate. Although it is preferred for numerical results, it loses some of the simplicity and interpretability of CNDO.

MINDO/3

MINDO/3 is the earliest of the Dewar methods. It provides more accurate geometries and heats of formation than CNDO or INDO, and has been used widely. The limitations of the INDO approximation, on which MINDO/3 is based, frequently lead to problems of accuracy when dealing with molecules containing heteroatoms.

MINDO/3 is particularly good for describing carbocations, including nonclassical carbocations, and polynitro organic compounds. For these problems it gives better results than MNDO and AM1, even though those methods are generally more accurate. Stewart²³ reports that for a set of 11 nitro and polynitro organic compounds, the average error in heats of formation is 3.5 kcal/mol for

MINDO/3, compared to 34.5 kcal/mol for MNDO or 13.7 kcal/mol for AM1.

MNDO

MNDO was introduced to correct some of the problems with MINDO/3. It has been used widely to calculate heats of formation, molecular geometries, dipole moments, ionization energies, electron affinities, and other properties. It has problems dealing with sterically crowded molecules (too unstable), four-membered rings (too stable), hydrogen bonding (almost nonexistent), and hypervalent compounds (too unstable). Also, nitrobenzene incorrectly yields an out-of-plane nitro group, and the peroxide bond is too short by about 0.17 Ångstrom.

Although AM1 is generally a significant improvement over MNDO, MNDO gives better results for some classes of molecule, such as some phosphorus compounds.

AM1

Many problems with MNDO involve cases where the NDO approximation electron-electron repulsion is most important. AM1 is an improvement over MNDO, even though it uses the same basic approximation. It is generally the most accurate semi-empirical method in HyperChem and is the method of choice for most problems. Altering part of the theoretical framework (the function describing repulsion between atomic cores) and assigning new parameters improves the performance of AM1. It deals with hydrogen bonds properly, produces accurate predictions of activation barriers for many reactions, and predicts heats of formation of molecules with an error that is about 40 percent smaller than with MNDO.

Problems still exist with AM1. Treatment of phosphorus-oxygen bonds is inaccurate, nitro compounds are still too positive in energy, and the peroxide bond, for example, is still too short. In many cases, PM3 is an improvement over AM1.

PM3

PM3 is a reparameterization of AM1, which is based on the neglect of diatomic differential overlap (NDDO) approximation. NDDO

retains all one-center differential overlap terms when Coulomb and exchange integrals are computed. PM3 differs from AM1 only in the values of the parameters. The parameters for PM3 were derived by comparing a much larger number and wider variety of experimental versus computed molecular properties. Typically, nonbonded interactions are less repulsive in PM3 than in AM1. PM3 is primarily used for organic molecules, but is also parameterized for many main group elements.

ZINDO/1

The ZINDO/1 method is the most suitable semi-empirical method in HyperChem for determining structures and energies of molecules with first or second transition row metals.

The ability to perform molecular orbital (MO) calculations on metals is extremely useful because molecular mechanics methods are generally unable to treat metals. This is because metals have a wide range of valences, oxidation states, spin multiplicities, and have unusual bonding situations (e.g., $d\pi$ - $p\pi$ back bonding). In addition, the nondirectional nature of metallic bonding is less amenable to a ball and spring interpretation.

Conversely, these factors dictate that molecular orbital calculations on metals yield less reliable results than with organic compounds.

ZINDO/S

ZINDO/S is parameterized to reproduce spectroscopic transitions, therefore we do not recommend using this method for geometry optimization. You can obtain better results by performing a single-point calculation with ZINDO/S on a geometry obtained from the Model Builder, an optimization using one of HyperChem's other methods, or an external source.

For transition metal complexes with several possible spin arrangements, a separate calculation within each spin multiplicity may be required to find the ground state of the complex.

When computing UV visible spectra, you should do a CI singles calculation. RHF or UHF calculations are sufficient to reproduce the proper order of molecular orbitals in most complexes.

Further Reading

Documentation on the reliability of the different NDO methods for various applications is scattered throughout the chemistry literature. Original papers describing the methods present relevant material. The CNDO and INDO methods are discussed in books by Pople and Beveridge⁴⁵ and by Murrell and Harget⁴⁶. Compilations exist for MINDO/3 and MNDO in a book by Clark.⁴⁷ For MNDO, AM1, and PM3²³, see the MOPAC documentation by Stewart²⁴ and a review article by Stewart²⁷.

45. Pople, J. A.; Beveridge, D. L. *Approximate Molecular Orbital Theory* McGraw-Hill, New York, 1970.

46. Murrell, J. N.; Harget, A. J. *Semi-empirical Self-consistent-field Molecular Orbital Theory of Molecules* Wiley Interscience, New York, 1971.

47. Clark, T. A. *Handbook of Computational Chemistry*, John Wiley and Sons, New York, 1985.

HyperChem[®] **Computational Chemistry**

Part 2
Theory and Methods

Chapter 10

Theory and Methods Introduction

This part describes the essentials of HyperChem's theoretical and computational chemistry or how HyperChem performs chemical calculations that you request from the Setup and Compute menus. While it has pedagogical value, it is not a textbook of computational chemistry; the discussions are restricted to topics of immediate relevance to HyperChem only. Nevertheless, you can learn much about computational chemistry by reading this manual while using HyperChem.

The theory and methods discussed in this book are HyperChem's two fundamental force-energy-generator modules: one for molecular mechanics and one for quantum mechanics. Molecular mechanics and quantum mechanics are described in subsequent chapters as modules capable of delivering an energy, or derivatives of the energy. Other chapters describe the uses for these energies and their derivatives in more generic parts of HyperChem.

HyperChem Architecture

While you may not necessarily perceive the difference, HyperChem is designed to consist of two basic components: a *front end* and a *back end*.

The front end is what you see and what you interact with. It provides a user interface to molecular modeling and provides the visualization of molecules and the results of computations. The front end can be thought of as the molecular modeling component of HyperChem.

The back end is the component of HyperChem that performs the more time-consuming scientific calculations. This is where molecular mechanical and quantum mechanical calculations are performed. The back end can be thought of as the computational chemistry component of HyperChem.

The Back Ends

As an aid in understanding how to use HyperChem effectively, this section describes the essentials of the front end and back end architecture. While this may not be necessary, an intuition as to how the program operates can be useful in optimizing its efficient use. A network version of HyperChem will allow the front end to run on a local workstation or personal computer with the back end running somewhere else in the network, possibly on a large, parallel-processing machine at a different geographical location. The non-network version simply merges the front end and back end into the same machine.

The user only interacts with the front end. The front end collects input from the user, initiates back end calculations, collects results from the back end, and then, if requested, displays these results to the user. The front end launches a back end program, sends it input data, and then receives output results from it. The back end programs included with HyperChem are HyperMM+, HyperNewton (performs AMBER, BIO+, and OPLS calculations), HyperEHT (performs Extended Hückel calculations), HyperNDO (performs CNDO, INDO, MINDO/3, MNDO, AM1, PM3, ZINDO/1, and ZINDO/S calculations), and HyperGauss (performs *ab initio* quantum mechanical calculations). When the front end initiates a back end program, an icon will appear (for the Microsoft Windows version only) representing the back end program. The icons are a falling red apple, indicating a molecular mechanics calculation and an orbiting electron rendering of an atom, indicating a semi-empirical quantum mechanical calculation. While the icon is visible, a back end program is active. The user can explicitly stop a back end program but only the front end can start a program.

A back end program essentially acts as a computational server for the front end. It receives input, computes something, sends it back to the front end and then looks for further input or commands from the front end. It can be used over and over for different calculations. If it has been explicitly stopped, the front end will start

the back end executing again as necessary. If the front end determines that it needs to stop a back end program or start another copy it will do so. In particular, switching between calculation methods may stop a back end program and start another one.

For example, if the user requests a molecular dynamics calculation using the AMBER force field, HyperChem starts a copy of HyperNewton running and sends it a copy of the chosen AMBER parameter set. It then sends it a copy of the current molecular system in the work space and the appropriate parameters for the molecular dynamics run. The back end runs the dynamics trajectory periodically sending back results to the front end to update the display of the molecule, plot structural or energetic values, etc. The front end and back end communicate via messages that are as appropriate to a distributed computing environment as they are to the single machine configuration.

The internal architecture of HyperChem back ends is different from that expected to be used by third-party packages. To a third-party agent wishing to interface with HyperChem, HyperChem always acts as a server. Thus a third-party molecular dynamics package would ask HyperChem to send the coordinates of a molecule rather than HyperChem determining on its own that it should send coordinates at the appropriate time.

HyperChem Philosophy

The HyperChem philosophy associated with back end computations is one which is intended to instill confidence, as far as is possible, in the scientific results emanating from HyperChem. This philosophy is one of openness — openness about the product, the calculations being performed, the science embodied in the product, etc. Apart from protecting the proprietary code associated with a commercial product, Hypercube wishes to document and describe as fully as is possible the calculations that HyperChem performs. There should be no mystery about the scientific results obtained with HyperChem.

HyperChem should not be viewed as a black box that computes only what its designers thought correct. It has an open architecture that makes it possible to customize it many ways. As far as is possible, the parameters of molecular mechanics and semi-empirical calculations are in the user's hands. As the techniques of software engineering advance and our expertise in building new

releases of HyperChem progresses, we intend to make as many facets of HyperChem computations available to the user as possible. In the past, it was thought necessary to provide source code to users to allow them to customize a product. The ability to customize a product to one's own use is now attainable much more simply by means of an open architecture and well-defined, documented ways to use and customize the product.

In order to balance public domain science with a high quality commercial software product it has been necessary for us to re-implement almost every aspect of computational chemistry embodied in HyperChem. All HyperChem source code is written in C or C++, specified, designed, and implemented by HyperChem's developers. We have stood on the scientific shoulders of giants, but we have not used their FORTRAN code! Thus, although we have had access to MOPAC and other public domain codes for testing and other purposes, HyperChem computes MINDO, MNDO, and AM1 wave functions, for example, with HyperChem code, not MOPAC code. We have made the effort to implement modern chemical science in a modern software-engineered product.

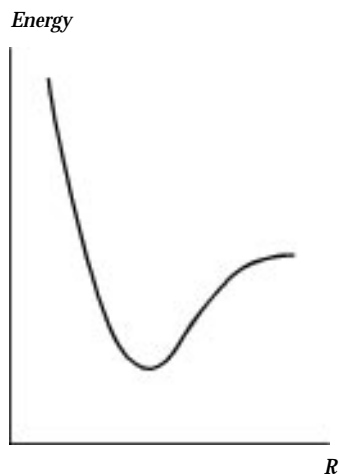
Background on Computational Chemistry

The principal theory behind HyperChem is the concept of a potential energy surface and the distinction between classical and quantum energies, kinetic and potential energies, energies of electrons versus energies of nuclei, etc. This section provides a concise approach to the problem of defining a potential energy surface for the motion of nuclei and begins with the usual quantum mechanical definitions prior to a more rigorous quantum mechanical definition.

Potential Energy Surfaces

A potential energy surface is simply a specification of the classical potential energy, V , as a function of molecular structure. For example, the potential surface (in this case a potential curve) for a diatomic molecule is sketched qualitatively in the following illustration. The potential energy curve shows the potential energy of the molecule as a function of the internuclear distance R . Now, in fact, there are six degrees of freedom on which the energy might depend—for instance the X , Y , and Z coordinates of each of the

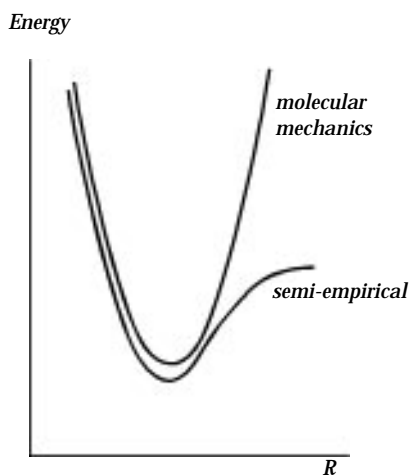
two atoms. However, five of these degrees of freedom correspond to translations (3) and rotations (2) of the rigid molecule and do not affect the energy of the system. This leaves only the internuclear distance as the variable upon which the potential energy depends.



The curve above shows that as $R \rightarrow \infty$, the potential energy approaches a constant, which is the energy of the two individual atoms. Further, there is a global minimum for this potential surface at intermediate distances. At very short distances, the energy rises to $+\infty$ as the two atoms repel each other.

The semi-empirical methods of HyperChem are quantum mechanical methods that can describe the breaking and formation of chemical bonds, as well as provide information about the distribution of electrons in the system. HyperChem's molecular mechanics techniques, on the other hand, do not explicitly treat the electrons, but instead describe the energetics only as interactions among the nuclei. Since these approximations result in substantial computational savings, the molecular mechanics methods can be applied to much larger systems than the quantum mechanical methods. There are many molecular properties, however, which are not accurately described by these methods. For instance, molecular bonds are neither formed nor broken during HyperChem's molecular mechanics computations; the set of fixed bonds is provided as input to the computation.

This difference is shown in the next illustration which presents the qualitative form of a potential curve for a diatomic molecule for both a molecular mechanics method (like AMBER) or a semi-empirical method (like AM1). At large internuclear distances, the differences between the two methods are obvious. With AM1, the molecule properly dissociates into atoms, while the AMBER potential continues to rise. However, in explorations of the potential curve only around the minimum, results from the two methods might be rather similar. Indeed, it is quite possible that AMBER will give more accurate structural results than AM1. This is due to the closer link between experimental data and computed results of molecular mechanics calculations.



HyperChem provides three types of potential energy surface sampling algorithms. These are found in the HyperChem Compute menu: Single Point, Geometry Optimization, and Molecular Dynamics.

Single Point

A single point calculation, as its name suggests, performs a calculation at only a single point on the potential surface. For a diatomic molecule, this might be a calculation at $R=2.0 \text{ \AA}$, for example. The results of a single point calculation give the potential energy of the system at that geometry, as well as the gradient at that point. For single parameter potential curves like that shown above, the gradient describes the steepness of the potential curve at that point along the direction in which the energy decreases. For a poly-

atomic system, the situation is more complicated, but essentially the same — the gradient gives the direction in which the energy goes most steeply downhill, along with the steepness of the downhill slope. The RMS gradient that is reported is just the root-mean-square average of the Cartesian components of the gradient vector.

Geometry Optimization

A geometry optimization samples single points on the potential surface, searching for a minimum. At a potential minimum, the gradient is zero, and any small change in geometry causes the potential energy to rise. The technique used to search for the minimum is called the optimization algorithm, and several of these are available for selection in the optimization dialog box. The optimization algorithms are recipes for using the past history of points sampled from the potential surface to determine the next point to examine.

Molecular Dynamics

Molecular dynamics involves the addition of kinetic energy to the above potential energy surface description and the subsequent motion of the molecular system over the potential surface. This motion follows the laws of classical mechanics according to Newton. Normally (except for the constant temperature algorithm of HyperChem), the classical total energy (sum of kinetic energy and potential energy) is conserved and the motion is faster (larger kinetic energy) near minima in the potential surface (smaller potential energy). If a set of initial conditions is defined (initial velocities and a particular point on the potential surface), then Newton's laws cause the molecular system to evolve along a path that is referred to as the molecular dynamics trajectory. This trajectory traverses the potential surface in ways that are of considerable interest to explore. Both the end point of a trajectory and the path taken to get there are of interest in molecular modeling.

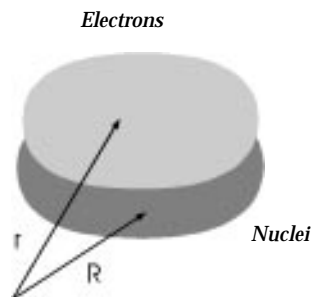
The Born-Oppenheimer Approximation

The first basic approximation of quantum chemistry is the Born-Oppenheimer Approximation (also referred to as the clamped-nuclei approximation). The Born-Oppenheimer Approximation is used to define and calculate potential energy surfaces. It uses the heavier mass of nuclei compared with electrons to separate the

problem of computing the energy of a collection of nuclei and electrons (a molecular system) into two problems: an electronic problem and a nuclear motion problem. The electronic problem solves for the wave function of the electrons in the field of fixed (clamped) nuclei. The nuclear motion problem subsequently solves for the motion of nuclei (which can be referred to as atoms here) on a potential energy surface. The potential energy surface is the energy of the associated electronic problem, as a function of the position of the clamped nuclei (clamped only during each single energy calculation).

The Hamiltonian of a Collection of Nuclei and Electrons

A molecular system in HyperChem consists of N nuclei A (having positive charges, $+Z_A$) and M electrons i (each with negative charge, $q_i = -1$). The nuclei are described by a vector, \mathbf{R} , with $3N$ Cartesian X , Y , and Z components. The electrons are described by a vector, \mathbf{r} , with $3M$ Cartesian x , y , and z components. The electrons are explicitly considered only in semi-empirical calculations.



A Hamiltonian is the quantum mechanical description of an energy contribution. The *exact* Hamiltonian for a molecular system is:

$$\mathcal{H}(\mathbf{R}, \mathbf{r}) = \mathcal{T}_n(\mathbf{R}) + \mathcal{T}_e(\mathbf{r}) + \mathcal{V}_{ee}(\mathbf{r}, \mathbf{r}) + \mathcal{V}_{ne}(\mathbf{R}, \mathbf{r}) + \mathcal{V}_{nn}(\mathbf{R}, \mathbf{R}) \quad (1)$$

where $\mathcal{T}_n(\mathbf{R})$ is the total kinetic energy of the nuclei, $\mathcal{T}_e(\mathbf{r})$ is the total kinetic energy of the electrons, $\mathcal{V}_{ee}(\mathbf{r}, \mathbf{r})$ is the potential energy of interaction of electrons with electrons, $\mathcal{V}_{ne}(\mathbf{R}, \mathbf{r})$ is the potential energy of interaction of the nuclei with electrons, and $\mathcal{V}_{nn}(\mathbf{R}, \mathbf{R})$ is the potential energy of interaction of nuclei with nuclei.

The Electronic Hamiltonian

Since nuclei are much heavier than electrons and move slower, the Born-Oppenheimer Approximation suggests that nuclei are stationary and thus that we can solve for the motion of electrons only. This leads to the concept of an *electronic Hamiltonian*, describing the motion of electrons in the potential of fixed nuclei.

$$\mathcal{H}_{\text{elec}}(\mathbf{r}) = \mathcal{J}_{\text{e}}(\mathbf{r}) + \mathcal{V}_{\text{ee}}(\mathbf{r}, \mathbf{r}) + \mathcal{V}_{\text{ne}}(\mathbf{R}, \mathbf{r}) \quad (2)$$

HyperChem's semi-empirical calculations solve (approximately) the Schrödinger equation for this electronic Hamiltonian leading to an electronic wave function $\Psi_{\text{elec}}(\mathbf{r})$ for the electrons:

$$\mathcal{H}_{\text{elec}}(\mathbf{r})\Psi_{\text{elec}}(\mathbf{r}) = E_{\text{elec}}(\mathbf{R})\Psi_{\text{elec}}(\mathbf{r}) \quad (3)$$

The eigenvalue of this Schrödinger equation, the electronic energy E_{elec} , depends parametrically, as shown, on the coordinates of the nuclei (assumed to be fixed for the purposes of calculating each $E_{\text{elec}}(\mathbf{R})$, but variable in general). The electronic energy, $E_{\text{elec}}(\mathbf{R})$ combined with $\mathcal{V}_{\text{nn}}(\mathbf{R}, \mathbf{R})$ is the total energy of Single Point semi-empirical calculations.

The Nuclear Hamiltonian

In the same way that we assumed nuclei move much slower than electrons, we can assume electrons move much faster than nuclei and the detailed motion of electrons might be replaced by their average position. Thus Equation (1) above becomes:

$$\mathcal{H}(\mathbf{R}) = \mathcal{H}(\mathbf{R}, \langle \mathbf{r} \rangle) = \mathcal{J}_{\text{n}}(\mathbf{R}) + \langle \mathcal{H}_{\text{elec}} \rangle + \mathcal{V}_{\text{nn}}(\mathbf{R}, \mathbf{R}) \quad (4)$$

or

$$\mathcal{H}(\mathbf{R}) = \mathcal{J}_{\text{n}}(\mathbf{R}) + E_{\text{elec}}(\mathbf{R}) + \mathcal{V}_{\text{nn}}(\mathbf{R}, \mathbf{R}) \quad (5)$$

This last equation is the nuclear Schrödinger equation describing the motion of nuclei. The electronic energy computed from solving the electronic Schrödinger equation (3) on page 163 plus the nuclear-nuclear interactions $\mathcal{V}_{\text{nn}}(\mathbf{R}, \mathbf{R})$ provide a potential for nuclear motion, a Potential Energy Surface (PES).

$$\mathcal{V}_{\text{PES}}(\mathbf{R}) = \mathcal{V}(\mathbf{R}) = E_{\text{elec}}(\mathbf{R}) + \mathcal{V}_{\text{nn}}(\mathbf{R}, \mathbf{R}) \quad (6)$$

This potential energy surface, which is just values of the Single Point energy of HyperChem, can be thought of as describing the

interactions between the atoms (described by coordinates \mathbf{R}) of a molecular system. It is commonly referred to in quantum mechanical calculations as the total energy, although it is only the potential energy as far as the motion of a collection of atoms is concerned. It provides a potential for a nuclear Hamiltonian:

$$\mathcal{H}(\mathbf{R}) = \mathcal{T}_n(\mathbf{R}) + \mathcal{V}(\mathbf{R}) \quad (7)$$

Solutions to a Schrödinger equation for this last Hamiltonian (7) describe the vibrational, rotational, and translational states of a molecular system. This release of HyperChem does not specifically explore solutions to the nuclear Schrödinger equation, although future releases may. Instead, as is often the case, a classical approximation is made replacing the Hamiltonian by the classical energy:

$$E = T + \mathcal{V}(\mathbf{R}) \quad (8)$$

where T is the classical kinetic energy and \mathcal{V} is the potential energy. The potential energy \mathcal{V} is either the total energy, $E_{\text{elec}}(\mathbf{R}) + \mathcal{V}_{\text{nn}}(\mathbf{R}, \mathbf{R})$, reported from a semi-empirical quantum mechanical calculation or the (potential) energy of a molecular mechanics calculation. In either case, \mathcal{V} is the energy computed in Single Point or Optimization calculations. The kinetic energy, T , is only computed during Molecular Dynamics calculations, where a distinction must be made between kinetic and potential energy. Elsewhere, the total energy usually means the total potential energy of the nuclei (atoms) as a function of the coordinates of the nuclei (atoms).

The quantity, $\mathcal{V}(\mathbf{R})$, the sum of the electronic energy E_{elec} computed in a wave function calculation and the nuclear-nuclear coulomb interaction $\mathcal{V}(\mathbf{R}, \mathbf{R})$, constitutes a potential energy surface having $3N$ independent variables (the coordinates \mathbf{R}). The independent variables are the coordinates of the nuclei; but having made the Born-Oppenheimer approximation, we can think of them as the coordinates of the atoms in a molecule.

Molecular Mechanics versus Quantum Mechanics

Molecular quantum mechanics finds the solution to a Schrödinger equation for an electronic Hamiltonian, H_{elec} , that gives a total energy, $E_{\text{elec}}(\mathbf{R}) + \mathcal{V}(\mathbf{R}, \mathbf{R})$. Repeated solutions at different nuclear configurations, \mathbf{R} , lead to some approximate potential energy sur-

face $\mathcal{V}(\mathbf{R})$. This procedure requires the solution, albeit a very approximate solution, of some Schrödinger equation for every value of \mathbf{R} . This can be very time consuming and impractical for large molecular systems.

Molecular mechanics approximates $\mathcal{V}(\mathbf{R})$ by analytical functions that are deduced and subsequently parameterized via accurate calculations or experimental results. In many situations, the potential energy surface obtained is more accurate than that calculated from first principles because of resorting to experiment for defining the parameters of the analytical functions. The analytical function (potential energy surface) $\mathcal{V}(\mathbf{R})$ is sometimes referred to as a force field. Most force fields contain terms associated with bond stretching, angle bending, torsional twisting, and other terms that have chemical significance. The common difficulty with molecular mechanics is that a $\mathcal{V}(\mathbf{R})$ may not have been defined or parameterized for the molecular system of interest.

Classical Mechanics on a Potential Energy Surface

Rather than solve a Schrödinger equation with the Nuclear Hamiltonian (above), a common approximation is to assume that atoms are heavy enough so that classical mechanics is a good enough approximation. Motion of the particles on the potential surface, according to the laws of classical mechanics, is then the subject of classical trajectory analysis or molecular dynamics. These come about by replacing Equation (7) on page 164 with its classical equivalent:

$$E(\mathbf{R}) = \sum_i \frac{1}{2} m_i (d\mathbf{R}_i/dt)^2 + \mathcal{V}(\mathbf{R}) \quad (9)$$

In this context, E is the total classical energy including kinetic energy. You can then investigate the potential energy surface in a purely classical way using the positions (\mathbf{R}_i) and velocities ($\mathbf{V}_i = d\mathbf{R}_i/dt$) of the constituent atoms.

Force-Energy Generators

HyperChem performs a number of different types of calculations such as geometry optimization, molecular dynamics, etc. Each of these types of calculations is designed to be, as far as is possible, independent of the technology that produces the potential energy surface. The technology that produces the potential energy surface is referred to here as a force-energy generator. Thus, geometry optimization of a molecule is fed by routines that compute the potential energy $\psi(\mathbf{R})$ and its derivatives $d\psi(\mathbf{R})/d\mathbf{R}$, $d^2\psi(\mathbf{R})/d\mathbf{R}^2$, etc. without concern whether these force-energy generators are molecular mechanics or semi-empirical quantum mechanics. New force-energy generators could, in principle, be added easily. An example would be the addition of an *ab initio* force-energy generator for which all the other methodology of HyperChem, such as molecular dynamics, would become available.

Chapter 11

Molecular Mechanics

Molecular Mechanics uses an analytical, differentiable, and relatively simple potential energy function, $\mathcal{V}(\mathbf{R})$, for describing the interactions between a set of atoms specified by their Cartesian coordinates \mathbf{R} .

Unlike first principles of quantum mechanical calculations, molecular mechanics might be thought of as simply a fitting procedure, attempting to obtain as accurately as possible a representation of $\mathcal{V}(\mathbf{R})$ with no particular regard for theoretical foundations. However, it is found that the most successful fitting procedures, having generic utility, lead to terms in the potential that can be ascribed to chemically meaningful interactions. For example, molecular mechanics potentials typically have simple analytic terms that provide an energetic penalty for deviations from standard bond lengths, bond angles, and bond dihedral angles, together with simple analytic terms for long-range coulombic and van der Waals interactions.

To be useful, molecular mechanics potentials have to balance the simplicity of the analytical form of the potential (so that the energy and its derivatives can be rapidly evaluated, even for large molecules) with the accuracy of describing important characteristics of the exact $\mathcal{V}(\mathbf{R})$. Developing these molecular mechanics force fields has been an active and important activity for many years, resulting in a number of standard methodologies as described below. None of the standard force fields used in HyperChem, however, have complete general utility and they must be used with care. Force fields are usually developed for specific types of molecules and their use in other situations will either fail (for lack of parameters for the analytic expressions) or give poor results (because it is employed beyond the original range of molecular situations for which the force field was developed).

Background

Molecular mechanics has three important concepts:

- Functional form
- Atom types
- Parameter sets

Each molecular mechanics method has its own functional form: MM+, AMBER, OPLS, and BIO+. The functional form describes the analytic form of each of the terms in the potential. For example, MM+ has both a quadratic and a cubic stretch term in the potential whereas AMBER, OPLS, and BIO+ have only quadratic stretch terms. The functional form is referred to here as the force field. For example, the functional form of a quadratic stretch with force constant K_r and equilibrium distance r_0 is:

$$E_{\text{quadratic stretch}} = K_r(r - r_0)^2 \quad (10)$$

Each force field includes a set of atom types. Consider the quadratic stretch term shown above. In principle, every different bond in every molecule would have its own parameters r_0 and K_r . This would be unmanageable for a generic method that attempts to compare molecules. Instead, atoms are classified as having a given type. Thus, you can distinguish an sp -hybridized carbon from an sp^2 -hybridized carbon from an sp^3 -hybridized carbon by saying they are different types (C2, C3, and C4 in MM+, for example). You can then describe quadratic stretching constants r_0 and K_r for each pair of atoms types (C2-C2, C2-C3, C3-C3, etc. as in MM+). The atom types in HyperChem are a characteristic of the force field with one set of atom types for each force field.

Finally, each force field may have multiple parameter sets (the values of r_0 and K_r , for example). The AMBER force field and AMBER set of types may be used with, for example, the AMBER/2 or AMBER/3 set of parameters.

These ideas plus others related to the molecular mechanics options of HyperChem are discussed in this chapter.

Atom Types

The concept of atom types might be considered the most fundamental topic in molecular mechanics and lies behind all aspects of the approach. Atom types, not atoms, are the fundamental basis for calculating interactions in molecular mechanics.

Definition of Atom Type

The atom type defines the chemical environment of an atom. The basic idea is that not all carbon atoms in molecules are the same and can be distinguished by the following:

- Hybridization
- Formal charge on the atom
- Immediate bonded neighbors

The chemical environment for an atom in a molecule is probably unique to that molecule. Chemistry tries to find unifying concepts and the atom type is one of those unifying concepts. For example, the AMBER force field defines five atom types for oxygens:

- O** carbonyl oxygen
- OH** hydroxyl (alcohol) oxygen
- O2** carboxylic acid oxygen or phosphate oxygen
- OS** ester or ether oxygen
- OW** oxygen in water

The molecular mechanics interactions are computed between types not elements. Thus, you would compute different values for the long range nonbonded interaction of two water oxygens than you would for the interaction of water oxygen and an ester oxygen. These values would differ from the values for the interaction of two ester oxygens. Of course, if you want to neglect the chemical environment in calculating interactions, you could define some default type for all oxygens to make all oxygens identical.

In principle, atom types could be associated with a particular parameter set rather than the functional form or force field. In HyperChem, however, atoms types are rigorously tied to a force field: MM+, AMBER, OPLS, and BIO+. Each of the force fields has a

default set of atom types and all parameter sets for a given force field must use the same set of atom types. It is possible, however, to redefine or modify the atom types associated with a force field as described in the next section.

Atom types are defined in the file `chem.rul`. The atom types for each of the force fields are listed in the files pointed to by the `AtomTypeMass` entries associated with the specific force fields in the Registry or the `chem.ini` file. They are usually named `*typ.txt` or `*typ.dbf`, depending on whether text or dBASE format is used. For the AMBER force field, all variations use the same type file, defined in the [Amber] section of the Registry or the `chem.ini` file. It is usually called `ambertyp.txt`, if a text format file is used, indicated by `FileFormat=Text` or `ambertyp.dbf`, if a dBASE III format file is used, indicated by `FileFormat=dbf`.

The concept of atom types is particularly relevant to the united atom approach. In AMBER, for example, an all atom treatment of a methyl group uses the type `CT` to describe the carbon and the type `HC` to describe the hydrogens. A united atom approach collapses the hydrogens into the carbon nucleus to represent the whole methyl group as one type, `C3`, located at the position of the carbon but with quite different interaction characteristics (parameters). For each force field, the list of types and their atomic masses is stored in the file pointed to by the `AtomTypeMass` entry in the Registry or `chem.ini`. The masses of `CT` and `C3` are respectively 12.01 and 15.03, with the larger number including the mass of the hydrogen atoms.

While atom types are tied to a specific force fields, it is easy to modify each force field's atom types; the functional form cannot be modified but atom types can. The next section describes how atom types are defined.

The Typing Rules

Atom types represent the chemical environment of an atom. The atom types associated with a given force field could be hard-wired to have specific values and meaning. HyperChem also allows flexible definitions of the atom types and the associated chemical environments. The chemical environment of an atom (a set of rules for defining a type) and the default rules are in a standard ASCII text file, `chem.rul`, included with HyperChem. You can modify this file and compile it in a binary form that HyperChem

uses to calculate the atom types from the chemical environment of an atom.

The syntax and semantics of the typing rules in a chem.rul file are included in the *HyperChem Reference Manual*. The following example illustrates their use. The five AMBER types for oxygen atoms shown above are defined in chem.rul by the following rules:

```
O:
    ; carbonyl
    connected to =C?
    =O.

    ; neutral carboxylic acid
    connected to (H)C(=O)?
    =OH.

    ; negative carboxylic acid
    connected to ~C~O?
    =O2.

    ; ether
    connected to (-C)-C?
    =OS.

    ; ester
    connected to (C=O)C?
    =OS.

    ; water
    connected to H2?
    =OW.

    ; hydroxyl
    connected to H?
    =OH.

    ; phospho ester
    connected to (C)P?
    =OS.
```

```
; phosphate  
connected to P?  
=O2.  
  
; default  
=OS.
```

These rules are executed in order until a set of rules is satisfied. If all the rules fail then the last default type OS is assigned. The tests on neighboring lines are AND'ed together and sets of tests (clauses) separated by blank lines are OR'ed.

The above rules state that if an oxygen is connected to a carbon by a double bond it is a carbonyl oxygen with type O. Otherwise, if it is connected to both a hydrogen and a carbon that is itself connected by a double bond to another oxygen then it is a neutral carboxylic oxygen with type OH. Otherwise, if it is connected by an aromatic bond to a carbon which in turn is connected by an aromatic bond to another oxygen then it is a negative carboxylic oxygen with type O2. Otherwise, if it is connected by single bonds to two carbon atoms it is an ether oxygen of type OS. Otherwise, if it is connected to a carbonyl group and to a carbon it is an ester oxygen with type OS. Otherwise, if it is connected to two hydrogens it is a water oxygen with type OW. Otherwise, if it is connected to a hydrogen it is an hydroxyl oxygen with type OH. Otherwise, if it is connected to a carbon and a phosphorus it is a phospho ester oxygen with type OS. Otherwise, if it is connected to a phosphorus it is a phosphate oxygen with type O2. Otherwise, for lack of other information it is defined to be of type OS.

Note that two different environments, although they might be distinguished by tests (such as for ether and ester) can share an atom type (such as OS). A refinement of the AMBER force field would use separate types for these two along with different parameters for the different types.

Redefining or Adding Types

To redefine an atom type associated with a force field, adjust the rules in the chem.rul file to represent the new chemical environment for a particular type and then compile the new types. It is always desirable to save the original chem.rul under another name prior to modifying chem.rul. Having modified chem.rul, you can

start a copy of HyperChem and click Build/Compile Type Rules to create a new typerule.bin, the binary file which HyperChem always uses to calculate atom types.

To add new types to a force field, follow this procedure:

1. Add the new type to the chem.rul file.
2. Add the new type and its mass to the file pointed to by the AtomTypeMass entry of the Registry or the chem.ini file for the appropriate force field.
3. Compile the chem.rul file to a new typerule.bin file as described in the previous paragraph.
4. Add nonbonded and other parameters to the appropriate files.

The new parameter files must be compiled for each parameter set used with the particular force field that has the new type, as follows:

1. Start HyperChem.
2. Choose the appropriate force field (MM+, AMBER, OPLS, or BIO+).
3. Select Setup/Select Parameter Set and specify a particular parameter set.
4. Select Setup/Compile Parameter File to create a new binary *.par parameter file that includes the new type.
5. Repeat steps 3 and 4 for each of the parameter sets available with the particular force field being modified.

Force Fields

This section describes HyperChem's four force fields, MM+, AMBER, OPLS, and BIO+, providing auxiliary information for all force field calculations.

Note: All of the force fields provided in HyperChem are built on new implementations of force fields developed by various computational chemistry research groups. However, HyperChem improves on the original force fields and uses new code.

Background

Many of the ideas and issues surrounding the use of molecular mechanics (or force field technology) in computational chemistry are common to all force fields and in this section we describe many of these basic ideas.

Energetic Terms in the Potential

The interaction potential $\mathcal{V}(\mathbf{R})$ describes both bonding and non-bonding interactions. The bonding interactions are usually formulated as a strain energy that is zero at some ideal configuration of the atoms and describe how the energy increases as the ideal configuration is deformed. Bonding interactions usually refer to atoms in the following relationships:

- Directly bonded (a 1-2 bond stretch relationship)
- Geminal to each other (a 1-3 angle bending relationship)
- Vicinal to each other (a 1-4 dihedral angle rotation relationship)

The nonbonded interactions usually include the following:

- An exchange repulsion when atoms get too close
- A long range attraction arising from dispersion forces
- Electrostatic interactions coming from the interaction of charges, dipoles, quadrupoles, etc.

The exchange repulsion and dispersive attraction combine in what is referred to as a van der Waals term. Sometimes a potential is added to account for hydrogen bonding explicitly; while in other situations this is expected to fall out of ordinary electrostatic interactions.

In addition to these basic terms, force fields often have cross terms that combine the above interactions. For example there may be a term which causes an angle bend to interact with a bond stretch term (opening a bond angle may tend to lengthen the bonds involved).

The interaction potential $\mathcal{V}(\mathbf{R})$ in used by the force fields in HyperChem share the following types of terms:

Bond Stretching

This term is associated with deformation of a bond from its standard equilibrium length. For small displacements from equilibrium, a harmonic function is often used:

$$E_{\text{bond}} = \sum_{\text{bonds}} K_r (r - r_0)^2 \quad (11)$$

A larger value for the stretch force constant K_r leads to a greater tendency for the bond to remain at its equilibrium distance r_0 . Higher powers of $r - r_0$, giving cubic, quartic, or higher terms are also common. A Morse function might also be employed.

Bond Angle Bending

This term is associated with the deformation of an angle from its normal value. For small displacements from equilibrium, a harmonic function is often used:

$$E_{\text{bond angle}} = \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 \quad (12)$$

A larger value for the bending force constant K_θ leads to a greater tendency for the angle to remain at its equilibrium value θ_0 . There may be cubic, quartic, etc. terms as with the corresponding bond stretch term in addition to the quadratic term shown here.

Dihedrals

This term is associated with the tendency of dihedral angles to have a certain n -fold symmetry and to have minimum energy for the *cis*-, *gauche*-, or *trans*-conformation, etc.

$$E_{\text{dihedral}} = \sum_{\text{dihedral}} \frac{V_n}{2} [1 + \cos(n\phi - \phi_0)] \quad (13)$$

The period of the interaction is $360/n$. The phase angle ϕ_0 shifts the curve to the left or right. For $n=1$ and $\phi_0=0$, the curve represents the situation where the energy is a minimum for the *trans*-conformation with a barrier of V_n to the highest energy *cis*-conformation. A

phase angle of $\phi_0=180$ represents the opposite situation with a minimum at the *cis*-conformation and a maximum at the *trans*-conformation. By including sums of terms of the above kind, dihedral angle interactions of arbitrary complexity can be described. In HyperChem, n is restricted to values from 1 to 6, so up to six Fourier terms may be used for a particular dihedral angle.

Improper Dihedrals

This term is associated with maintaining the planarity of planar atoms, or preventing inversion of tetrahedral carbons with one hydrogen in a united atom representation. This type of term usually employs an energetic penalty for deformation of a dihedral angle defined by the central atom and its three bonded neighbors. The functional form employed may be that of equation (12) or equation (13) on page 175, or a different scheme altogether (as in MM+).

van der Waals

This term describes the repulsive forces keeping two nonbonded atoms apart at close range and the attractive force drawing them together at long range.

$$E_{\text{vanderWaals}} = \sum_{ii \in \text{vdW}} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} \right] \quad (14)$$

The above potential is referred to as a Lennard-Jones or 6–12 potential and is summed over all nonbonded pairs of atoms ij . The first positive term is the short range repulsion and the second negative term is the long range attraction. The parameters of the interaction are A_{ij} and B_{ij} . The convenient analytical form of the 6–12 potential means that it is often used, although an exponential repulsion term is usually considered to be a more accurate representation of the repulsive forces (as used in MM+).

The force fields in HyperChem that use the above 6–12 potential allow six ways of specifying the constants A_{ij} and B_{ij} : three by single atom type and three by pairs of atom types. Single atom type means that there are constants for individual atom types, i , that are combined by a combining rule that results in a parameters for a specific pair, ij , of atom types. Pairs of atom types means that parameter files contain explicit parameters for a pair of atom types

ij and that no combining of single atom type parameters is necessary. If in the first case, there were N parameters, the second case would require N(N-1)/2 parameters for an equivalent set. If present, the constants specified by pairs of atoms types are used to override the values generated from single atom types.

The form that single atom type constants take is selected by setting the Registry/chem.ini parameter set entry 6-12AtomVDWFormat to one of RStarEpsilon, SigmaEpsilon or SlaterKirkwood. This specifies the combination rules that are used for the file pointed to by the 6-12AtomVDW entry in the Registry or the chem.ini file for the same parameter set.

For the 6-12AtomVDWFormat entry set to RStarEpsilon, the combination rules used are:

$$A_{ij} = \left(\frac{r_i^*}{2} + \frac{r_j^*}{2} \right)^{12} \sqrt{\epsilon_i \epsilon_j} \quad (15)$$

$$B_{ij} = 2 \left(\frac{r_i^*}{2} + \frac{r_j^*}{2} \right)^6 \sqrt{\epsilon_i \epsilon_j} \quad (16)$$

where $r_i^*/2$ is half the minimum energy separation for two atoms of type i, ϵ_i is the well depth for two atoms of type i. These parameters are found in the parameter file.

For the 6-12AtomVDWFormat entry set to SigmaEpsilon, the combination rules used are:

$$A_{ij} = 4(\sigma_i \sigma_j)^6 \sqrt{\epsilon_i \epsilon_j} \quad (17)$$

$$B_{ij} = 4(\sigma_i \sigma_j)^3 \sqrt{\epsilon_i \epsilon_j} \quad (18)$$

where σ_i , the zero energy separation for two atoms of type i

($r = \sqrt[6]{2} \sigma_i$), and ϵ_i , the well depth for two atoms of type i, are the parameters from the parameter file.

For the 6-12AtomVDWFormat entry set to SlaterKirkwood, the combination rules used are:

$$B_{ij} = \frac{C \alpha_i \alpha_j}{\sqrt{\frac{\alpha_i}{N_i}} + \sqrt{\frac{\alpha_j}{N_j}}} \quad (19)$$

$$A_{ij} = \frac{1}{2}B_{ij}(R_i + R_j)^6 \quad (20)$$

where α_i , the polarizability of an atom of type i , N_i , the effective number of valence electrons for an atom of type i , and R_i , the van der Waals radius of an atom of type i , are the parameters from the parameter file. The constant C combines the permittivity of free space (ϵ_0), the charge of an electron (e), the mass of an electron (m_e) and Planck's constant (h):

$$C = \frac{3eh}{4\sqrt{\pi\epsilon_0 m_e}} \quad (21)$$

The form of Lennard-Jones constants specified by pairs of atom types is selected by setting the parameter set entry 6-12PairVDWFormat in the Registry or the chem.ini file to one of RStarEpsilon, SigmaEpsilon or AijBij. This specifies the interpretation of the file, if any, pointed to by the 6-12PairVDW entry in the Registry or the chem.ini file for the same parameter set. Values specified in this fashion override the values generated by single atom type constraints, so they are typically used just to specify parameters for certain cases where the atom combination rules don't give acceptable results.

For the 6-12PairVDWFormat entry set to RStarEpsilon, the values are converted by:

$$A_{ij} = r_{ij}^{*12} \epsilon_{ij} \quad (22)$$

$$B_{ij} = 2r_{ij}^{*6} \epsilon_{ij} \quad (23)$$

where r_{ij}^* , the minimum energy separation for two atoms of type i and j , and ϵ_{ij} , the well depth for two atoms of type i and j , are the parameters from the parameter file.

For the 6-12PairVDWFormat entry set to SigmaEpsilon, the values are converted by:

$$A_{ij} = 4\sigma_{ij}^{12} \epsilon_{ij} \quad (24)$$

$$B_{ij} = 4\sigma_{ij}^6 \epsilon_{ij} \quad (25)$$

where σ_{ij} , the zero energy separation for two atoms of type i and j ($r = \sqrt[6]{2}\sigma_{ij}$), and ϵ_{ij} , the well depth for two atoms of type i and j , are the parameters from the parameter file.

For the 6-12PairVDWFormat entry set to AijBij, the values in the parameter file are not converted.

Usually, atoms with a 1-4 vicinal relationship or more are considered to be nonbonded. Sometimes, however, only atoms with a 1-5 relationship are considered to be fully nonbonded and the atoms with a 1-4 relationship have scaled down nonbonded interactions or are deleted completely from the nonbonded computations, or different parameters are used.

Electrostatic

This term describes the classical nonbonded electrostatic interactions of charge distributions.

$$E_{\text{electrostatic}} = \sum_{ii \in \text{electrostatic}} \left[\frac{q_i q_j}{\epsilon R_{ij}} \right] \quad (26)$$

The above potential describes the monopole-monopole interactions of atomic charges q_i and q_j a distance R_{ij} apart. Normally these charge interactions are computed only for nonbonded atoms and once again the 1-4 interactions might be treated differently from the more normal nonbonded interactions (1-5 relationship or more). The dielectric constant ϵ used in the calculation is sometimes scaled or made distance-dependent, as described in the next section.

Electrostatic terms other than the simple charge interactions above are commonly included in molecular mechanics calculations, particularly dipole-dipole interactions. More recently, second-order electrostatic interactions like those describing polarizability have been added to some force fields.

Hydrogen Bonding

This term is an explicit recognition of the importance of hydrogen bonding to molecular interactions.

$$E_{\text{H-bonded}} = \sum_{ij \in \text{H-bond}} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right] \quad (27)$$

Not all force fields add a specific hydrogen bonding term, as there is evidence from accurate quantum mechanical calculations that hydrogen bonding is accounted for by normal electrostatic interactions. In HyperChem, only the AMBER force field employs an explicit hydrogen bonding term. The 12–10 form was suggested by Pauling but other functional forms for explicit hydrogen bonding have also been used.

Effective Dielectric Constants

Many molecular mechanics potentials were developed at a time when it was computationally impractical to add large numbers of discrete water molecules to the calculation to simulate the effect of aqueous media. As such, techniques came into place that were intended to take into account the effect of solvent in some fashion. These techniques were difficult to justify physically but they were used nevertheless.

The first modification is to simply scale the dielectric permittivity of free space (ϵ_0) by a scale factor D to mediate or dampen the long range electrostatic interactions. Its value was often set to be between 1.0 and 78.0, the macroscopic value for water. A value of $D=2.5$, so that $\epsilon = 2.5\epsilon_0$, was often used in early CHARMM calculations.

Alternatively, a distance dependent dielectric constant is often used in the absence of explicit water molecules. This sets ϵ in equation (26) to $D \epsilon_0 R_{ij}$, proportional to the distance between charges. The electrostatic interaction then uses R_{ij}^{-2} and does not require the evaluation of a square root. To quote Weiner *et al.*, the developers of AMBER, “A rationale for using a distance-dependent dielectric constant is that it mimics the polarization effect in attractive interactions, with closer interactions weighted more heavily. Second, it helps compensate for the lack of explicit solvation by implicitly damping longer range charge interactions more than shorter range ones. There is empirical and computational support for such a model, given that solvent (water) is not explicitly included in the calculation.”

Cutoffs

When dealing with large systems where the number of nonbonded interactions dominate the calculation time, a time-saving approximation introduces a cutoff distance. This neglects nonbonded interactions beyond this distance. While this approximation is particularly difficult to justify for long range coulombic interactions (unit charges separated by 20 Å still contribute 17 kcal/mol to the energy), a cutoff in the range of 8–15 Å is still commonly used.

For the periodic boundary conditions described below, the cutoff distance is fixed by the nearest image approximation to be less than half the smallest box length. With a cutoff any larger, more than nearest images would be included.

When the cutoff is sharp, discontinuities in the forces and resultant loss of conservation of energy in molecular dynamics calculations can result. To minimize edge effects of a cutoff, often the cutoff is implemented with a switching or shifting function to allow the interactions to go smoothly to zero.

The switching function used by HyperChem, called *switch* below, alters the nonbonded energy (van der Waals, hydrogen bond, and electrostatic) in the following way:

$$E(\text{switched}) = E(\text{non-switched}) \times \text{switch}(R_{ij}^2, R_{\text{inner}}^2, R_{\text{outer}}^2) \quad (28)$$

where:

$$\text{switch}(x, a, b) = 1 \quad x \leq a \quad (29)$$

$$\text{switch}(x, a, b) = 0 \quad x \geq b$$

$$\text{switch}(x, a, b) = \frac{(b-x)^2(b+2x-3a)}{(b-a)^3} \quad a < x < b$$

Between the inner radius R_{inner} of the switch and the outer radius R_{outer} of the switch the interaction goes smoothly to zero.

HyperChem uses as its default an inner radius of 10 Å and an outer radius of 14 Å.

HyperChem can also use a *shifted* nonbonded potential, where the nonbonded energy is modified by:

$$E(\text{shifted}) = E(\text{unshifted})(1 - 2R_{ij}^2/R_{\text{outer}}^2 + R_{ij}^4/R_{\text{outer}}^4) \quad (30)$$

for R_{ij} less than or equal to R_{outer} and E (shifted) = 0 for R_{ij} greater than R_{outer} . Shifted cutoffs apply to van der Waals, hydrogen bonding and electrostatic interactions, but not to 1–4 interactions with the BIO+ force field.

Terms Involving Vicinal 1–4 Interactions

Although interactions between vicinal 1–4 atoms are nominally treated as nonbonded interactions, most of the force fields treat these somewhat differently from normal 1–5 and greater nonbonded interactions. HyperChem allows each of these 1–4 nonbonded interactions to be scaled down by a scale factor < 1.0 with AMBER or OPLS. For BIO+ the electrostatic may be scaled and different parameters may be used for 1–4 van der Waals interactions. The AMBER force field, for example, normally uses a scaling factor of 0.5 for both van der Waals and electrostatic interactions.

MM+

The MM+ force field is an extension of MM2 which was developed by Allinger and co-workers [N. L. Allinger, *J. Am. Chem. Soc.*, 99, 8127 (1977), N. L. Allinger and Y. H. Yuh, Quantum Chemistry Program Exchange, Bloomington, Indiana, Program #395, U. Burkert and N. L. Allinger, *Molecular Mechanics*, ACS Monograph 177 (1982).] and is designed primarily for small organic molecules although it is being expanded to peptides [J. Lii et. al., *J. Comp. Chem.* 10, 503 (1989)] and other systems as well [K. B. Lipkowitz, QCPE Bulletin, Indiana University, 12, 1, (Feb., 1992)]. The efforts of the Allinger group have been focused more on very accurate results for certain classes of molecules than on developing a generic (but less accurate) method that can be applied to almost all situations in organic chemistry. Thus, the MM2 force field will fail in many situations where no parameters exist. With the MM+ force field specified, HyperChem first tries to perform a calculation with MM2 (1991) parameters but has a default scheme when there are no MM2 parameters. A message in the status line and log file indicates that default parameters are being used. These default calculations are described later in this chapter.

HyperChem's MM+ force field uses the latest MM2 (1991) parameters and atom types (provided directly by Dr. Allinger) with the 1977 functional form [N. L. Allinger, *J. Am. Chem. Soc.*, 99, 8127 (1977), N. L. Allinger and Y. H. Yuh, Quantum Chemistry Program

Exchange, Bloomington, Indiana, Program #395, U. Burkert and N. L. Allinger, *Molecular Mechanics*, ACS Monograph 177 (1982).] modified to incorporate nonbonded cutoffs (using switched or shifted smoothing), periodic boundary conditions, and the bond stretch term switched from cubic form to quadratic form at long range (to avoid the long range repulsive region of standard MM2).

Units

Like MM2, MM+ internally uses ergs for energy and reports its force constants (a stretching force constant, for example) in units of millidynes per Ångstrom. Other force fields in HyperChem report their force constants in kcal/mol per Å². In addition, there is a factor of 1/2 in the definition of a stretching force constant when comparing MM+ and other force fields. Thus, it is necessary to be quite careful in comparing force constants between different force fields. In the following discussion (and in HyperChem), every equation uses kcal/mol as the basic unit of energy and appropriate conversion constants are described. For example, a factor of 71.94 must be multiplied to MM+ stretching force constants for comparison with stretching force constants for the other force fields. These details affect the internal operation and the interpretation of the input values in parameter files but HyperChem reports all energetic results in energy units of kcal/mol.

Bond Stretching

MM2 uses a cubic stretch term:

$$E_{\text{bond}} = 143.88 \sum_{\text{bonds}} \frac{1}{2} K_r (r - r_0)^2 [1 + CS(r - r_0)] \quad (31)$$

The cubic stretch term is a factor CS times the quadratic stretch term. This constant CS can be set to an arbitrary value by an entry in the Registry or the chem.ini file. The default value for MM2 and MM+ is CS = -2.0.

However, this form becomes repulsive for $r - r_0 > 2/3 CS$, so it is unsuitable for bond lengths significantly larger than equilibrium. In the MM2 program, this is avoided by temporarily setting CS to zero, reverting to a quadratic form, which leads to discontinuities in the potential surface that are unacceptable for geometry optimi-

zation and molecular dynamics. Thus the MM+ force field applies the switching function from equation (29) on page 181 to give

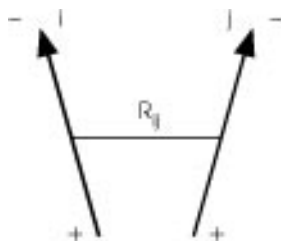
$$E_{\text{bond}} = 143.88 \sum_{\text{bonds}} \frac{1}{2} K_r (r - r_0)^2 \times \left[1 + \text{switch} \left(r - r_0, -\frac{1}{3} CS, -\frac{4}{3} CS \right) CS (r - r_0) \right] \quad (32)$$

Inside the point of inflection of equation (31) equation (32) is identical to MM2 with the cubic stretch term turned on. At very long bond distances, it is identical to MM2 with the cubic stretch term turned off.

Two r_0 values are given for each MM+ bond, r_0^A and r_0^B . If r_0^B is available (has a non-zero value in the parameter file) then it is used in preference to the normal r_0^A for bonds where atom i and atom j have at least two hydrogen atoms directly attached to them. For example, $\text{CH}_2\text{-CH}_2$, $\text{CH}_2\text{-CH}_3$, or $\text{CH}_3\text{-CH}_3$ bonds may have their own equilibrium distance differentiated from the average single bond between carbon atoms.

Bond Dipoles

MM+ calculations do not usually have an electrostatic charge-charge interaction nor define a set of atomic charges for atoms. Instead, the electrostatic contribution comes from defining a set of bond dipole moments associated with polar bonds. These bond moments are defined in the mmpstr.txt(dbf) file along with the bond stretching parameters and are given in units of Debyes. The center of the dipole is defined to be the midpoint of the bond and two dipoles μ_i and μ_j , separated by R_{ij} , as shown below:



The MM+ dipole interaction energy is:

$$E_{\text{dipole}} = 14.39418 \epsilon \sum_{ii \in \text{nolar bonds}} \mu_i \mu_j \left[\frac{\cos \chi - 3 \cos \alpha_i \cos \alpha_j}{R_{ij}^3} \right] \quad (33)$$

where ϵ , the dielectric constant, is assumed to be larger than 1 (even in the gas phase there is assumed to be some screening of dipole interactions by the rest of the molecule). The MM2 value of 1.5 is used by HyperChem. The angle χ is the angle between the two dipole vectors, and α_i and α_j are the angles that the two dipole vectors make with the \mathbf{R}_{ij} vector. The constant 14.39418 converts ergs/molecule to kcal/mol.

Angle Bending

The quadratic angle bending term in MM+ is identical to that of equation (12) on page 175, apart from a factor 1/2. Three θ_0 values are given for each MM+ bond, θ^A , θ^B and θ^C . If θ^B is available (has a non-zero value in the parameter file) then it is used in preference to the normal θ^A , for angles where the central atom has *one* hydrogen atom directly attached to it. If θ^C is available (has a non-zero value in the parameter file) then it is used in preference to the normal θ^A for angles where the central atom has *two* hydrogen atoms directly attached to it. If no hydrogen atoms are attached to the central atom or if θ^A or θ^B values are not available (when they are relevant), the normal θ^A is used.

MM+ also includes a sextic angle bending term. The final form for the angle bending energy is:

$$E_{\text{bond angle}} = 0.043828 \sum_{\text{angles}} \frac{1}{2} K_{\theta} (\theta - \theta_0)^2 [1 + SF(\theta - \theta_0)^4] \quad (34)$$

The sextic bending term is a scale factor SF times the quadratic bending term. This constant SF can be set to an arbitrary value by an entry in the Registry or the chem.ini file. The default value for MM+ is $SF = 7.0 \times 10^{-8}$. The constant 0.043828 converts the MM+ bending constants expressed in millidyne-Å per radian² to

kcal/mol per degree² used by the other force fields. Note that the MM+ expression also includes a factor of 1/2 in the definition that is missing from other force fields.

The MM+ force field uses special values for the bending force constants when the atoms are in a three- or four-membered ring.

Bond Stretch and Angle Bending Cross Term

Like MM2, MM+ includes coupling between bond stretching and angle bending. If the angle is defined to include atoms i, j, and k, where k is the central atom, then MM+ couples stretching of the ik and jk bonds with the angle:

$$E_{\text{stretch-bend}} = 2.51118 \sum_{\text{angles}} K_{\text{sb}} (\theta - \theta_0)_{\text{ikj}} [(r - r_0)_{\text{ik}} + (r - r_0)_{\text{jk}}] \quad (35)$$

If atom i or atom j is a hydrogen, the deformation ($r - r_0$) is considered to be zero. Thus, no stretch-bend interaction is defined for XH₂ groups. The stretch-bend force constants are incorporated into the program and you cannot modify them. If R is an atom other hydrogen, the values of the stretch-bend force constants are:

$$K_{\text{sb}} = 0.120 \text{ for XR}_2$$

X = atom in 1st long row

$$K_{\text{sb}} = 0.090 \text{ for XRH}$$

or

$$K_{\text{sb}} = 0.250 \text{ for XR}_2$$

X = atom in 2nd long row

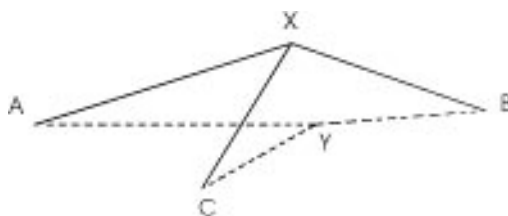
$$K_{\text{sb}} = -0.400 \text{ for XRH}$$

The constant 2.51118 converts between MM+ stretch-bend force constants expressed in millidynes per radian and HyperChem's default, kcal per degree.

Out-of-Plane Bending

An atom that has sp² hybridization tends to be coplanar with its attached atoms. This effect is accounted for by improper torsions in other force fields and by out-of-plane-bending interactions in

MM+. Consider the following situation involving an atom X that is sp^2 hybridized



Y is the projection of X onto the ABC plane. When the central atom (X) of these angles is sp^2 hybridized, the angle bending calculations are modified to use the in-plane angles AYB, AYC, and BYC in equation (34) on page 185 with the standard force constants defined in `mmpben.txt(dbf)` rather than the standard angles AXB, AXC, and BXC. In addition, out-of-plane components are computed as well, for the out-of-plane angles XAY, XBY, and XCY. These last three calculations use equation (34) as well, but with a θ_0 equal to 0 and special out-of-plane bending constants, K_θ , defined in `mmpoop.txt(dbf)`.

Dihedrals

The dihedral angle or torsional energy interaction in MM+ is of the general form of equation (12) on page 175 but explicitly includes $n=1, 2,$ and 3 with a phase angle $\phi_0=0$:

$$E_{\text{dihedral}} = \quad (36)$$

$$\sum_{\text{dihedrals}} \frac{V_1}{2}(1 + \cos\phi) + \frac{V_2}{2}(1 - \cos 2\phi) + \frac{V_3}{2}(1 + \cos 3\phi)$$

The values of $V_1, V_2,$ and V_3 , in kcal/mol, are listed in `mmp-tor.txt(dbf)`. The MM+ force field uses special values for the torsional force constants when the atoms are in a four-member ring.

van der Waals

The MM+ van der Waals interactions do not use a Lennard-Jones potential but combine an exponential repulsion with an attractive $1/R^6$ dispersion interaction. The basic parameters are a van der

Waals radius r_i^* for each atom type and a hardness parameter ϵ_i that determines the depth of the attractive well and how easy (or difficult) it is to push atoms close together. There are interactions for each nonbonded ij pair, including all 1–4 pairs. The parameters for a pair are obtained from individual atom parameters as follows:

$$r_{ij}^* = r_i^* + r_j^* \quad (37)$$

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j} \quad (38)$$

The van der Waals interaction is then calculated as:

$$E_{\text{vanderWaals}} = \sum_{ij \in \text{vdW}} \epsilon_{ij} (2.9 \times 10^5 \exp(-12.5\rho_{ij}) - 2.25\rho_{ij}^{-6}) \quad (39)$$

where

$$\rho_{ij} = \frac{R_{ij}}{r_{ij}^*} \quad (40)$$

At short distances ($r_{ij} \leq 3.311$) the above expression is replaced by:

$$E_{\text{vanderWaals}} = 336.176 \sum_{ij \in \text{vdW}} \epsilon_{ij} \rho_{ij}^{-2} \quad (41)$$

For CH interactions the normal ϵ and r^* values are replaced by special CH values:

$$\epsilon_{\text{CH}} = 0.046 \quad (42)$$

$$r_{\text{CH}}^* = 3.340 \quad (43)$$

For XH bonds, where X is any heavy atom, the hydrogen electron density is not thought to be centered at the position of the hydrogen nucleus but displaced along the bond somewhat, towards X. The MM+ force field reduces the XH bond length by a factor of 0.915 strictly for the purposes of calculating van der Waals interactions with hydrogen atoms.

AMBER

The AMBER (Assisted Model Building and Energy Refinement) is based on a force field developed for protein and nucleic acid computations by members of the Peter Kollman research group at the

University of California, San Francisco. The original AMBER has become one of the more widely used academic force fields and extensive work has gone into developing it — resulting in a number of versions of the method and associated parameters. HyperChem gives results equivalent to Versions 2.0 and 3.0a of the AMBER program distributed by the Kollman group and parameter sets for both these versions are distributed with HyperChem.

AMBER was first developed as a united atom force field [S. J. Weiner et al., *J. Am. Chem. Soc.*, 106, 765 (1984)] and later extended to include an all atom version [S. J. Weiner et al., *J. Comp. Chem.*, 7, 230 (1986)]. HyperChem allows the user to switch back and forth between the united atom and all atom force fields as well as to mix the two force fields within the same molecule. Since the force field was developed for macromolecules, there are few atom types and parameters for small organic systems or inorganic systems, and most calculations on such systems with the AMBER force field will fail from lack of parameters.

Bond Stretching

The functional form for bond stretching in AMBER is quadratic only and is identical to that shown in equation (11) on page 175. The bond stretching force constants are in units of kcal/mol per \AA^2 and are in the file pointed to by the QuadraticStretch entry for the parameter set in the Registry or the chem.ini file, usually called *str.txt(dbf).

Angle Bending

The functional form for angle bending in AMBER is quadratic only and is identical with that shown in equation (12) on page 175. The angle bending force constants are in units of kcal/mol per radian² and are in the file pointed to by the QuadraticBend entry for the parameter set in the Registry or the chem.ini file, usually called *ben.txt(dbf).

Dihedrals

The functional form for dihedral angle (torsional) rotation is identical to that shown in equation (13) on page 175. The barrier heights are in kcal/mol and are in the file pointed to by the FourierTorsion entry for the parameter set in the Registry or the chem.ini file, usually called *tor.txt(dbf). If more than one term is

available for a given dihedral angle in the parameter file, the terms are summed to give the total potential, i.e., the potential can be a Fourier sum over n in equation (14) where n is from 1 to 6.

Improper Dihedrals

The functional form for improper dihedral term is identical to that shown in equation (13) on page 175. The barrier heights are in kcal/mol and are in the file pointed to by the `FourierImpTorsion` entry for the parameter set in the Registry or the `chem.ini` file, usually called `*imp.txt(dbf)`. The central atom in the improper torsion is the second or third atom (i.e. a central atom) in the dihedral angle. For atoms that have the improper flag set (either from templates or editing a HIN file) HyperChem uses the improper dihedral angle formed by neighbor 1 - neighbor 2 - central atom - neighbor 3, where the order of neighbors is how they appear in a HIN file. Not all planar atoms customarily have associated improper torsions, and the order of atoms is arbitrary but was consistently chosen by the authors of the AMBER force field. The templates contain the standard AMBER definitions of improper torsions for amino and nucleic acids.

van der Waals

The functional form for van der Waals interactions in AMBER is identical with that shown in equation (13) on page 175. The coefficients A_{ij} and B_{ij} are computed from the parameters in the file pointed to by the `6-12AtomVDW` entry for the parameter set in the Registry or the `chem.ini` file, usually called `*nbd.txt(dbf)`, and optionally with the file pointed to by the `6-12PairVDW` entry for the parameter set, usually called `*npr.txt(dbf)`. The standard AMBER parameter sets use equations (15) and (16) for the combination rules by setting the `6-12AtomVDWFormat` entry to `RStarEpsilon`. The 1-4 van der Waals interactions are usually scaled in AMBER to half their nominal value (a scale factor of 0.5 in the Force Field Options dialog box).

Electrostatic

The functional form for electrostatic interactions in AMBER is identical with that shown in equation (26) on page 179. You normally use a dielectric scaling of $D=1$ with AMBER combined with a constant functional form when solvent molecules are explicitly

included or a distance dependent form when trying to emulate the effects of solvent without explicitly adding solvent molecules. The charges q_i are not part of any AMBER parameter file. Standard atomic charges are placed on an atom only when the molecular system is created from templates, by using the database menu or reading a PDB file. Otherwise charges must be set manually or by a quantum mechanical calculation, or they default to zero and no electrostatic interactions result. The 1–4 electrostatic interactions are usually scaled in AMBER to half their nominal value (a scale factor of 0.5 in the Force Field Options dialog box).

Hydrogen Bonding

The AMBER force field uses a hydrogen bonding term identical to equation (27) on page 180. The coefficients C_{ij} and D_{ij} for appropriate donor-acceptor pairs are given in the file pointed to by the 10–12PairHBond entry for the parameter set in the Registry or the chem.ini file, usually called *hbd.txt(dbf). If a nonbonded atom pair (excluding 1–4 interactions) has hydrogen bond parameters, the interaction is calculated using the hydrogen bonding term instead of the van der Waals term.

Lone Pairs

The AMBER force field expects lone pairs to be added to all sulfur atoms and computes the interactions as if these lone pairs were atoms with a specific type just like any other atom. The templates automatically add the expected lone pairs to sulfur atoms when using the AMBER force field.

OPLS

OPLS (Optimized Potentials for Liquid Simulations) is based on a force field developed by the research group of Bill Jorgensen now at Yale University and previously at Purdue University. Like AMBER, the OPLS force field is designed for calculations on proteins and nucleic acids. It introduces nonbonded interaction parameters that have been carefully developed from extensive Monte Carlo liquid simulations of small molecules. These nonbonded interactions have been added to the bonding interactions of AMBER to produce a new force field that is expected to be better than AMBER at describing simulations where the solvent is explic-

itly included and nonbonded interactions are particularly important.

The HyperChem OPLS force field gives results equivalent to the original OPLS force field.

The OPLS force field is described in two papers, one discussing parameters for proteins [W. L. Jorgensen and J. Tirado-Rives, *J. Amer. Chem. Soc.*, 110, 1657 (1988)] and one discussing parameters for nucleotide bases [J. Pranata, S. Wierschke, and W. L. Jorgensen, *J. Amer. Chem. Soc.*, 113, 2810 (1991)]. The force field uses the united atom concept for many, but not all, hydrogens attached to carbons to allow faster calculations on macromolecular systems. The amino and nucleic acid residue templates in HyperChem automatically switch to a united atom representation where appropriate when the OPLS option is selected.

The OPLS atom types are a superset of the AMBER united atom types and the bonding parameters are just those of AMBER, supplemented where needed by the OPLS developers. The bond stretch, angle bending, dihedral angle and improper dihedral angle terms are identical to those of AMBER. Unlike AMBER, different combination rules are used for the van der Waals parameters, no hydrogen bonding term is used and no lone pairs are used.

van der Waals

The van der Waals term in the OPLS force field is that of equation (14) on page 176. The coefficients A_{ij} and B_{ij} are computed from the parameters in the file pointed to by the 6-12AtomVDW entry for the parameter set in the Registry or the chem.ini file, usually called *nbd.txt(dbf), and optionally with the file pointed to by the 6-12PairVDW entry for the parameter set, usually called *npr.txt(dbf). The standard OPLS parameter sets use equations (17) and (18) on page 177 for the combination rules by setting the 6-12AtomVDWFormat entry to SigmaEpsilon. The 1-4 van der Waals interactions are usually scaled in OPLS to one-eighth their nominal value (a scale factor of 0.125 in the Force Field Options dialog box).

Electrostatic

The OPLS form of electrostatic interactions is that of equation (26) on page 179. That is, it uses a charge-charge interaction just like AMBER. However, since the nonbonded potentials were developed

from liquid studies with explicit water molecules, the use of a distance-dependent dielectric is excluded. The appropriate dielectric scaling factor for OPLS calculations is $D=1$. A set of charges are defined for protein and nucleic acid residues in the template (*.tpl*) files.

BIO+

The BIO+ force field is an implementation of the CHARMM (Chemistry at HARvard Macromolecular Mechanics) force field developed in the group of Martin Karplus at Harvard University. Like AMBER and OPLS, it is primarily designed to explore macromolecules. It does not use lone pairs.

CHARMM was first developed as a united atom force field and parameters for some amino acids have been published [B. R. Brooks *et al.*, *J. Comp. Chem.*, 4, 187 (1983)]. Subsequent changes to the functional form and parameters have been published [W. Reiher, Ph.D., Harvard 1985], but most recent parameter development remains unpublished and unavailable without purchasing the CHARMM program. (Even the often-referenced PARM19 parameter set has never actually been published and is not made available unless the CHARMM program is purchased). Current parameter development in the Karplus group at Harvard employs an all-atom representation, using all dihedral angles with no hydrogen bonding term [J. C. Smith and M. Karplus, *J. Am. Chem. Soc.* 114, 805-812, 1992]. Since only limited parameter sets have been published, there are atom types and parameters for only a subset of amino acids, so most calculations on such systems with the BIO+ force field fail from lack of parameters.

The HyperChem BIO+ force field gives results equivalent to CHARMM using the same CHARMM parameter sets.

Bond Stretching

The functional form for bond stretching in BIO+, as in CHARMM, is quadratic only and is identical to that shown in equation (11) on page 175. The bond stretching force constants are in units of kcal/mol per \AA^2 and are in the file pointed to by the Quadratic-Stretch entry for the parameter set in the Registry or the chem.ini file, usually called *str.txt(dbf).

Angle Bending

The functional form for angle bending in BIO+ is quadratic only and is identical with that shown in equation (12) on page 175. The angle bending force constants are in units of kcal/mol per radian² and are in the file pointed to by the QuadraticBend entry for the parameter set in the Registry or the chem.ini file, usually called *ben.txt(dbf).

Dihedrals

The functional form for dihedral angle (torsional) rotation is identical to that shown in equation (13) on page 175. The barrier heights are in kcal/mol and are in the file pointed to by the FourierTorsion entry for the parameter set in the Registry or the chem.ini file, usually called *tor.txt(dbf). If more than one term is available for a given dihedral angle in the parameter file, the terms are summed to give the total potential, i.e. the potential can be a Fourier sum over n in equation (13), where n is from 1 to 6. The term in BIO+ is a generalization of that given for CHARMM in B. R. Brooks *et al.*, *J. Comp. Chem.*, 4, 187 (1983), in that ϕ_0 values other than 0° or 180° are allowed. In HyperChem, all bond dihedral angles are included in the energy calculation, equivalent to autogenerating dihedral angles in CHARMM. Thus, parameters developed for use with arbitrary subsets of bond dihedral angles, as is common with CHARMM, need to be scaled or have some parameters set to have zero force constants for use in HyperChem BIO+. Note: An extra column exists in the dihedral parameter file for specifying a factor to divide into the force constant.

Improper Dihedrals

The functional form for an improper dihedral term is that shown in equation (12) on page 175 except that the summation is over improper torsion angles and q represents an improper torsion angle. For angles smaller than 6°, with q_0 equal to 0°, a series expansion is used to avoid a numerically indeterminate derivative. The barrier heights are in kcal/mol and are in the file pointed to by the QuadraticImpTorsion entry for the parameter set in the Registry or the chem.ini file, usually called *imp.txt(dbf). The central atom in the improper torsion is the first or fourth atom (i.e. a terminal atom) in the dihedral angle. For atoms that have the improper flag set (either from templates or editing a HIN file)

HyperChem uses the improper dihedral angle formed by central atom - neighbor 1 - neighbor 2 - neighbor 3, where the order of neighbors is how they appear in a HIN file. Not all planar atoms customarily have associated improper torsions. The order of atoms is arbitrary but has been consistently chosen by the original authors of the CHARMM force field. The templates contain equivalent CHARMM definitions of improper torsions for amino acids. Improper dihedral angles cannot be defined that do not have a central atom, as is sometimes done in CHARMM calculations.

van der Waals

The functional form for van der Waals interactions in BIO+ is identical with that shown in equation (14) on page 176. The coefficients A_{ij} and B_{ij} are computed from the parameters in the file pointed to by the 6-12AtomVDW entry for the parameter set in the Registry or the chem.ini file, usually called *nbd.txt(dbf), and optionally with the file pointed to by the 6-12PairVDW entry for the parameter set, usually called *npr.txt(dbf). When using the newer, published CHARMM parameter sets, BIO+ uses equations (15) and (16) for the combination rules by setting the 6-12AtomVDWFormat entry to RStarEpsilon. When using earlier, published CHARMM parameter sets, BIO+ uses equations (19), (20) and (21) by setting the 6-12AtomVDWFormat entry to SlaterKirkwood.

The 1-4 van der Waals interactions cannot be scaled in CHARMM but in newer CHARMM parameter sets some atom types (usually united atoms) use different parameters for 1-4 interactions. These are specified for BIO+ in the file pointed to by the 6-12Atom14VDW entry, usually called *nbd.txt(dbf). If an atom type is absent in the 6-12Atom14VDW file, the normal parameters are used. The format of the 6-12Atom14VDW file is also specified by the 6-12AtomVDWFormat entry for the parameter set.

Newer, published CHARMM parameter sets override some of the combination rule generated parameters for some atom type pairs. These parameters are found in the file pointed to by the 6-12PairVDW entry for the parameter set, usually called *npr.txt(dbf). The values of A_{ij} and B_{ij} for these are computed using equations (22) and (23) on page 178 by setting the 6-12PairVDWFormat entry to RStarEpsilon.

Electrostatic

The functional form for electrostatic interactions in CHARMM is identical with that shown in equation (26) on page 179. A dielectric scaling of $D=2.5$ was common with older, published CHARMM parameter sets but newer sets seem to use a scaling of $D=1$, combined with a constant functional form when solvent molecules are explicitly included or a distance-dependent form when trying to emulate the effects of solvent without explicitly adding solvent molecules. The charges q_i are not part of any published CHARMM parameter file. Standard atomic charges are placed on an atom only when the molecular system is created from templates, by using the database menu or reading a PDB file. Otherwise charges must be set manually or by a quantum mechanical calculation, or they default to zero and no electrostatic interactions result. The 1-4 electrostatic interactions are scaled with newer, published CHARMM parameter sets to 0.4 or 0.5 times their nominal value (a scale factor of 0.4 or 0.5 in the Force Field Options dialog box).

Hydrogen Bonding

The BIO+ force field option in HyperChem has no hydrogen bonding term. This is consistent with evolution and common use of the CHARMM force field (even the 1983 paper did not use a hydrogen bonding term in its example calculations and mentioned that the functional form used then was unsatisfactory and under review).

Parameter Sets

The concept of a parameter set is an important (but often inconvenient) aspect of molecular mechanics calculations. Molecular mechanics tries to use experimental data to replace *a priori* computation, but in many situations the experimental data is not known and a parameter is missing. Collecting parameters, verification of their validity, and the relationship of these molecular mechanics parameters to chemical and structural moieties are all important and difficult topics.

A molecular mechanics method in HyperChem is defined by a set of atom types and a functional form for the energy and its derivatives— for example AMBER. For the AMBER method, you may use many different default and user-defined parameter sets. Hyper-

Chem comes with default parameter sets, Amber2 and Amber3 in the case of the AMBER method. It is possible, however, to define an arbitrary number of additional parameter sets for the AMBER method (or for any of the other three force field methods). These user-defined parameter sets can be specified in the Parameters dialog box and integrated into HyperChem, in the same way as the default sets.

Text or DBF Form for Parameters

HyperChem provides two forms of parameter sets — an ASCII text form and the *.dbf database form consistent with dBASE IV and a large number of other database packages. Since the principal difficulty with using molecular mechanics is having or obtaining appropriate parameters, you may want to explore parameter sets as a database in the *.dbf form.

The text form for parameters uses white space or commas to separate the fields (columns) of the parameter files. They can be read by ordinary text editors, word processors, etc. In the text form, parameters are easy to modify but not easy to compare, study, etc. Many database programs are capable of reading columns of text as a database, however. While spreadsheets are not, per se, databases, they can be useful for examining parameter sets. Microsoft Excel, for example, can read the text form of a parameter file and put the data in a form easily manipulated as a matrix or a database. The text form of parameters are stored, by default only, in *.txt files.

The dBASE IV (or dBASE III) form of the parameter sets come in *.dbf files analogous to the *.txt files. These dbf files are binary files, so you can't read them directly. They are not required for the product and are provided only as an option. In most situations where there is no extensive use of database operations on parameter sets, the text form is probably more convenient to use. Many spreadsheet programs, including Microsoft Excel, are also capable of reading *.dbf files.

Modifying Existing Parameter Sets

The entries in molecular mechanics parameter files are described in the *HyperChem Reference Manual*. Use the following procedure to modify an existing parameter set:

1. Modify, add, or delete a parameter in the appropriate file. Use a text editor for a *.txt file or a database program for a *.dbf file.
2. Start HyperChem.
3. Specify the modified parameter set with the Setup/Select Parameter Set command.
4. Select the Setup/Compile Parameters command to recompile the set of *.txt files or *.dbf files into a par file, a binary description of all the parameters of a given parameter set.

The modified parameters are then available to the current or future version of HyperChem. For example, the Amber2 set of parameters is described by the amberstr.txt, amberben.txt, etc. set of files. Modifying one or any of these files, saving it, and then, in HyperChem, selecting the Amber2 parameter set and asking for a compilation of parameters produces a new amber2.par file that is used from then on for the Amber2 set of parameters.

Creating New Parameter Sets

New parameter sets can be created by essentially copying an old parameter set (copying the *str.*, *ben.*, etc. files while changing their root name), describing the new parameter set to HyperChem with its new name, via the Registry or the chem.ini file, and then modifying, adding, and deleting entries in the appropriate files prior to a recompilation to the binary form. The difference between creating a new parameter set and modifying a parameter set, is giving a new name to the parameter set and its associated files and describing that new name in the Registry or the chem.ini file.

For example, if an Amber4 parameter set was to be added to the AMBER molecular mechanics method, you could simply copy the files amberstr.txt(dbf), amberben.txt(dbf), etc. to the new files newamstr.txt(dbf), newamben.txt(dbf), etc. and then copy the Amber2 entry (multiple text lines) in the Registry or the chem.ini file into a new Amber4 entry, changing all the names in the Amber2 entry into the appropriate Amber4 names (Amber2 replaced by Amber4, amberben.txt(dbf) replaced by newamben.txt(dbf), etc.). Finally, the new parameter set should be compiled to amber4.par prior to its use.

Compiling Parameters

Compilation of parameters makes HyperChem more efficient. It replaces a set of text or dBASE files (for one parameter set) by a single binary *.par file. The compilation can be performed at any time from within HyperChem by selecting the parameter set (Setup/Select Parameter Set) and requesting a compilation (Setup/Compile Parameters). *If the parameter files are not modified, you do not have to compile them.*

Chem.ini or Registry Setup of Force Field Options

The Registry or the chem.ini file of molecular mechanics parameter sets is best described as it occurs with the default file. The Registry or the chem.ini file contains four sections—[mm+], [amber], [bio+], and [opls]—describing the parameter files for each of the four molecular mechanics methods. Each method section contains as many sections as there are parameter sets for that method. Thus, the [amber] section is followed by [amber, amber2], [amber, amber3], and [amber, ambers] sections that describe the amber2, amber3, and ambers parameter sets associated with the amber method. These CustomNames, amber2, amber3, and ambers, should first be described to the [amber] section as the custom names you choose for the parameter sets.

The force field section (for example [amber]) contains four entries:

- CurrentFiles describes the index of the current parameter set. CurrentFiles=0 says to use the first parameter set, CurrentFiles=1 says to use the second parameter set, etc.
- AtomTypeMass is set to the name of the file that lists the atom types associated with the force field and their masses (masses are associated with a type here not an atomic number). The file can have any name but by convention is named, for example, as ambertyp.txt(dbf).
- FileFormat describes whether this file is in text or dBASE format. This is, by convention, available in the file names, *.txt or *.dbf, but the AtomTypeMass file name is strictly arbitrary and the file is interpreted on the basis of the FileFormat setting.
- CustomNames describes the names of the individual parameter sets.

A section for a particular parameter set, for example, the [amber, amber2] section, lists first of all the force field name, amber, and then one of the CustomNames listed in the [amber] section, i.e. amber2. The entries in a parameter set section are as follows: The FileFormat entry describes the file format, text or dBASE, for the parameter files. The Dielectric, DielectricScale, 1-4ElectrostaticScale, and 1-4vanderWaalsScale entries describe the default settings of the Molecular Mechanics Options dialog box. The 6-12AtomVDWFormat and 6-12PairVDWFormat entries describe the way the Lennard-Jones van der Waals parameters are obtained æ either from SlaterKirkwood, SigmaEpsilon, or RStarEpsilon values listed in the associated nonbonding parameter files. In some situations, Lennard-Jones parameters come from parameters specific to individual *atoms* or to specific *pairs* of atoms as described earlier in the section of the manual that covers generic force fields.

The entries QuadraticStretch, QuadraticBend, FourierTorsion, FourierImpTorsion, QuadraticImpTorsion, 6-12AtomVDW, 6-12PairVDW, 6-12Atom14VDW, and 10-12PairHBond describe the names of the files holding the associated parameters.

In MM+, the parameter files differ sufficiently that they are described by their own entries, MMPStretch, MMPBend, MMPBend3, MMPBend4, MMPOPBend, MMPTorsion, MMPTorsion4, MMPAtomVDW and MMPCubicStretch. MMPBend3 and MMPBend4 refer to bending constants in 3- and 4-membered rings. The OOPBend constants describe out-of-plane bending.

Periodic Boundary Conditions and Solvent

Isolated gas phase molecules are the simplest to treat computationally. Much, if not most, chemistry takes place in the liquid or solid state, however. To treat these condensed phases, you must simulate continuous, constant density, macroscopic conditions. The usual approach is to invoke periodic boundary conditions. These simulate a large system (order of 10^{23} molecules) as a continuous replication in all directions of a small box. Only the molecules in the single small box are simulated and the other boxes are just copies of the single box.

HyperChem allows solvation of arbitrary solutes (including no solute) in water, to simulate aqueous systems. HyperChem uses only rectangular boxes and applies periodic boundary conditions to the central box to simulate a constant-density large system. The solvent water molecules come from a pre-equilibrated box of water. The solute is properly immersed and aligned in the box and then water molecules closer than some prescribed distance are omitted. You can also put a group of non-aqueous molecules into a periodic box.

It is also possible to simulate liquid droplets by surrounding a solute by a finite number of water molecules and performing the simulation without a periodic box. The water, of course, eventually evaporates and moves away from the solute when periodic boundary conditions are not imposed. If the water is initially added via periodic boundary conditions, you must edit the resulting HIN file to remove the periodic boundary conditions, if a droplet approach is desired.

Periodic boundary conditions can also be used to simulate solid state conditions although HyperChem has few specific tools to assist in setting up specific crystal symmetry space groups. The group operations Invert, Reflect, and Rotate can, however, be used to set up a unit cell manually, provided it is rectangular.

The Periodic Boundary Conditions

When you apply periodic boundary conditions to molecular mechanics simulations, the atoms of the system are placed in a rectangular box and treated as if they are surrounded by identically translated images of the box on all sides. A box of dimensions $R_x \times R_y \times R_z$ has 26 nearest images of itself, translated by combinations of $\pm R_x$, $\pm R_y$, and $\pm R_z$. For crystalline systems, further layers of periodic images might be included, to account for long-range periodicity, and an atom would interact with *all* its periodic images. For liquid-phase systems periodic boundary conditions minimize edge effects of a necessarily finite system, rather than include long-range periodicity. HyperChem employs the usual *nearest image* or *minimum image* restriction, where an atom in the box only interacts with the closest image of another atom in the box. Thus with periodic boundary conditions, an atom only interacts with the set of images that are within $\pm 1/2 R_x$, $\pm 1/2 R_y$ and $\pm 1/2 R_z$ of itself.

The nearest image restriction implies a sharp, rectangular cutoff of $\pm 1/2 R_x$, $\pm 1/2 R_y$ and $\pm 1/2 R_z$. This leads to discontinuities in the potential energy surface; if an atom moves too far away on one side it suddenly disappears and reappears on the other side (i.e. a different image becomes closest). The discontinuity at the switch-over point can lead to undesirable artifacts in geometry optimization and molecular dynamics. Another undesirable feature of this implied rectangular cutoff is that it is anisotropic, so that a rotation of the coordinate system changes the energy.

HyperChem avoids the discontinuity and anisotropy problem of the implied cutoff by imposing a smoothed spherical cutoff within the implied cutoff. When a system is placed in a periodic box, a switched cutoff is automatically added. The default outer radius, where the interaction is completely turned off, is the smallest of $1/2 R_x$, $1/2 R_y$ and $1/2 R_z$, so that the cutoff avoids discontinuities and is isotropic. This cutoff may be turned off or modified in the Molecular Mechanics Options dialog box after solvation and before calculation.

Equilibrated Water Box

The water molecules used to solvate a solute comes from Jorgensen's Monte Carlo equilibrated box of 216 water molecules, described by the TIP3P potential function [W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, *J. Chem. Phys.* 79, 926 (1983)]. This box is cubic and 18.70 Å on a side. When the requested box fits into this, it is just carved out of the basic Jorgensen box. When a bigger box (more than 216 water molecules or perhaps an elongated box) is required, then the basic 216 molecule box is duplicated to create 3 x 3 x 3 x 216 water molecules in a box 56.10 Å on a side and the required box is carved out of this.

Details of Solvation Methodology

Prior to solvation, the solute is oriented according to its inertial axes such that the box size needed to accommodate it is minimized (minimizing the number of water molecules). The principal inertial axis is oriented along the viewer's Z axis, for example. Then water molecules are eliminated if any of the three atoms are closer to a solute atom than the contact distance you specify.

Restraints

You can add restraints to any molecular mechanics calculation (single point, optimization or dynamics). These might be NMR restraints, for example, or any situation where a length, angle, or torsion is known or pre-defined. Restraints with large force constants result in high frequency components in a molecular dynamics calculation and can result in instability under some circumstances.

Definition of a Restraint

A restraint (not to be confused with a Model Builder constraint) is a user-specified one-atom tether, two-atom stretch, three-atom bend, or four-atom torsional interaction to add to the list of molecular mechanics interactions computed for a molecule. These added interactions are treated no differently from any other stretch, bend, or torsion, except that they employ a quadratic functional form. They replace no interaction, only add to the computed interactions.

Restraints are commonly used to restrain certain long range conformations. For example, you might restrain a certain end of a large molecule to be near another end. Alternatively, if the added force constant associated with the restraint is large enough, a local geometry, such as a bond length, bond angle, or torsion angle, could be almost forced to remain fixed. These restraints do not actually restrain any specific geometric feature to remain constant but only make the energy rise when the geometric feature deviates from its restrained value. On the other hand, the Model Builder constraints are true constraints, normally fixing a geometric feature of a Model Built structure.

Adding Restraints

Use Named Selections to add restraints:

1. Name any one-atom, two-atom, three-atom, or four-atom selection with the Select/Select command.
2. Use Restraints in the Setup menu to bring up the Restraint Forces dialog box

3. Add any of the currently named 1-, 2-, 3-, or 4-atom selections to the list of restraints.

If it is a two atom restraint, the dialog box requests a restrained 2-atom distance (bond length or nonbonded distance) and a stretching force constant. For a one atom restraint, the dialog box request a point to tether the atom to and a force constant. If the force constant is small, there is only a tendency towards keeping the two atoms at the specified distance. If the force constant is large, the distance remains near the specified distance since it requires a large energy to displace it significantly from that distance. The two atoms need not be bonded and in many restraint situations the two atoms definitely will not be bonded.

The 3-atom and 4-atom restraints behave just like those for two atoms, except that the dialog box requests an angle rather than a distance and the accompanying request for a force constant requires either a bending force constant (3-atom case) or a torsional force constant (4-atom case).

These molecular dynamics restraints are stored with the HIN file and are retained as long as the Named Selections are still active (structural changes not made to molecular system) or the restraints are still requested via the Restraint Forces dialog box.

The default restraints are appropriate for molecular dynamics calculations where larger force constants would create undesirable high frequency motions but much larger force constants may be desired for restrained geometry optimization.

The Default MM+ Force Field

One of the major difficulties with molecular mechanics procedures (MM+ or otherwise) is that they almost always fail. That is, you find that force constants are not available for the molecule of interest. This is both the strength and weakness of molecular mechanics; it uses atom types to introduce specific chemical environments for the atoms within a molecule (to obtain accuracy in the calculations) but then requires knowledge of force constants specific to that chemical environment (as specific as stating that an atom is in a five-member ring containing one oxygen and one carbon, for example). As the number, N , of atom types rises the number of force constants needed to describe all possible occurrences of these atom type becomes very large. For torsions, for

example, N^4 force constants are needed. This does not even include the very real possibility that an atom type has not been defined for the particular chemical situation at hand.

In computational chemistry it can be very useful to have a generic model that you can apply to any situation. Even if less accurate, such a computational tool is very useful for comparing results between molecules and certainly lowers the level of pain in using a model from one that almost always fails. The MM+ force field is meant to apply to general organic chemistry more than the other force fields of HyperChem, which really focus on proteins and nucleic acids. HyperChem includes a default scheme such that when MM+ fails to find a force constant (more generally, force field parameter), HyperChem substitutes a default value. This occurs universally with the periodic table so all conceivable molecules will allow computations. Whether or not the results of such a calculation are realistic can only be determined by close examination of the default parameters and the particular molecular situation.

The Wild Card Approach

The approach used to develop default parameters is best described using torsional parameters as an example. A general torsional rotation involves four connected atoms, atom_A - atom_X - atom_Y - atom_B , where atom_A and atom_B are the atoms at the ends of the torsion and atom_X and atom_Y are the two central atoms. atom_A is atom type A, for example. The parameters for these torsions are described by the atom types, A-X-Y-B in the torsional parameter file with the default name `mmptor.txt(dbf)`. If you have a molecule with a torsion of the type A-X-Y-B, HyperChem searches the `mmp.par` binary equivalent of `mmptor.txt(dbf)` and if there is a match, extracts and uses the parameters for the torsion.

When no explicitly correct force constant is found, HyperChem proceeds to stage two and finally to stage three. In stage two, you can use wildcards to relax the explicitness of the match between the atom types of the torsion in question and the available MM+ parameters. In the torsional case, as many as three searches of the `mmp.par` file are performed. If the exact match between A-X-Y-B and entries in `mmp.par` fails, then a search in `mmp.par` looks for an entry labeled, `**X-Y**`, where `**` is the designation for wildcard, don't-care, any-atom-type, unknown, etc. This search looks

for a torsional parameter associated only with the central atoms of the torsion independent of the terminal vicinal atoms. If this fails, a third search looks for an entry in the mmp.par file that is labeled `**_**_**_**`. If such an entry exists, it indicates that this is the force constant (and additional torsional parameters) to use when no better match is available. Only the above three searches of mmp.par are made with no intermediate searches such as `**_X-Y-B` or `**_X-**_**`, etc. If the `**_**_**_**` entry for the completely generic torsion exists in mmp.par, then the search for torsional parameters for the A-X-Y-B torsion will obviously succeed at this point, if not before. If no `**_**_**_**` entry exists, and the search of mmp.par fails to find appropriate parameters, then HyperChem proceeds to stage three where default parameters are assigned based on perceived hybridization states of X and Y (and possibly A or B), the type of bond between X and Y etc. This last stage generally yields sets of parameters that are more reasonable than ones based on a single unique generic value, `**_**_**_**`, to be used everywhere that more explicit parameters are not available from mmp.par.

The Default Force Field

If suitable parameters cannot be found in the MMP.PAR file, with or without wild cards, i.e. stage one and stage two fail, then the final stage three is entered and HyperChem uses a unique default scheme to find a parameter. At this point the HyperChem status line notes that default parameters are being used. This default scheme is similar to the Dreiding force field proposed by Mayo, Olafson, and Goddard [*J. Phys. Chem.* 94, 8897 (1990)], but has enough differences that it needs to be described in its own right. Specifically, the default scheme retains the MM2 functional form exactly as proposed by the Allinger group, but uses a scheme similar to that proposed for the Dreiding force field to obtain parameters. The parameters are obtained using a generic approach that considers only the hybridization of relevant atoms, the type of a bond (single, double, triple, or aromatic), and standard covalent radii for all elements in the periodic table. This scheme may not yield an optimized parameter but it does not require so specific a criterion as the explicit listing of a parameter in a parameter file associated with specific atom types.

Covalent radii for all the elements are readily available and the bond orders of all bonds are available from the molecular graph. Prior to describing the explicit default parameter scheme, it is nec-

2. If the number of valence electrons is 1 (H, Na, K, etc.), the hybridization is described as s.
3. If the number of valence electrons is 2 (Be, Mg, etc.), the hybridization is set to sp^3 for 4 neighbors, sp^2 for 3 neighbors, and sp for 1 or 2 neighbors.
4. If the number of valence electrons is 3 (B, Al, etc.), the hybridization is set to sp^3 for 4 neighbors, sp^2 for three neighbors, and sp for 1 or 2 neighbors.
5. If the number of valence electrons is 4 (C, Si, etc.), the hybridization is set to sp^3 for 4 neighbors.
6. If there are 3 neighbors and one or more of them is connected by an aromatic bond, then the hybridization is set to $sp^{2.5}$ or the hybridization is set to sp^2 .
7. If there are 2 neighbors and both bonds are single bonds then the hybridization is set to sp^3 , or if one of the bonds is a single bond the hybridization is set to sp^2 , or if neither of the bonds is single the hybridization is set to sp.
8. If there is 1 neighbor, then if the one bond is a triple bond the hybridization is set to sp, or if the one bond is an aromatic bond the hybridization is set to $sp^{2.5}$, or if the one bond is double the hybridization is set to sp^2 , or if the one bond is single the hybridization is set to sp^3 .
9. If the number of valence electrons is 5 (N, P, etc.), the hybridization is set to sp^3 for 4 or 3 neighbors, unless it is attached to an atom with a triple, double, or aromatic bond, in which case it is set to sp^2 .
10. If there are 2 neighbors and one or more of them is connected by an aromatic bond then the hybridization is set to $sp^{2.5}$ or the hybridization is set to sp^2 .
11. If there is 1 neighbor, then if the one bond is triple the hybridization is set to sp, or if the one bond is aromatic the hybridization is set to $sp^{2.5}$, or if the one bond is double the hybridization is set to sp^2 , or if the one bond is single the hybridization is set to sp^3 .
12. If the number of electrons is 6 (O, S, etc.), the hybridization is set to sp^3 for 4, 3, or 2 neighbors, unless it is attached to an atom with a triple, double, or aromatic bond, in which case it is set to sp^2 . If these atoms have 1 neighbor, and if the one

As special cases to these radii, better values are used for the elements boron to oxygen for particular hybridization states.

Atom	Covalent Radius
B (sp ³)	0.880
B (sp ²)	0.790
C (sp ³)	0.770
C (sp ^{2.5})	0.700
C (sp ²)	0.670
C (sp)	0.602
N (sp ³)	0.702
N (sp ^{2.5})	0.650
N (sp ²)	0.615
N (sp)	0.556
O (sp ³)	0.660
O (sp ^{2.5})	0.660
O (sp ²)	0.560
O (sp)	0.528

Parameters for Butadiene and Related Molecules

The normal molecular mechanics approach, as used with the AMBER, MM2, Dreiding or similar force fields, assigns bond length parameters on the basis of the “atom types” of the two bonded atoms. This results in the central sp²-sp² single bond of a molecule like butadiene having the same bond length parameters as each of the two terminal sp²-sp² double bonds in the same molecule. A single bond should, of course, be considerably longer than a double bond. This effect can be corrected by assigning the bond length parameter on the basis of “bond order” in addition to the “atom types” of the bonded atoms. The default MM+ force field applies such a correction, but the correction is not described in the manuals.

The correction is only applied in the default MM+ parameter scheme. When MM+ parameters are available in the `mmp-str.txt(dbf)` file, the normal approach based on only atom types is used. Thus, the correction is applied to butadiene when all the atom types are **, for example, but not when atom types are present and their corresponding parameters available in the parameter files.

MM+ increases the bond length parameter for single bonds that are not sp^3 - sp^3 hybridized. This correction is a sum of two terms, one for each of the bonded atoms. The correction is 0.03 Ångstroms for $sp^{2.5}$ (aromatic) hybridization, 0.06 Ångstroms for sp^2 hybridization, and 0.09 Ångstroms for sp hybridization. Without this correction the bond length parameter for the central sp^2 - sp^2 single bond of butadiene, for example, would be 1.34 Ångstroms, the same as for the terminal double bonds. The correction adds 0.12 Ångstroms (0.06 + 0.06) to this, leading to a bond-length parameter for the central single bond of 1.46 Ångstroms, a considerably more accurate value.

Angle Bending

All default bending force constants are assigned the value 100 kcal/mol/rad²

Stretch-Bends

No default stretch-bending interactions are included.

Out-Of-Plane Bends

The MM+ force field assigns default values for out of plane bending terms around an sp^2 center. If a central atom has some out of plane parameters, then the first out of plane parameter involving that central atom is used if a specific parameter is not found.

Torsions

The functional form for default torsions is the MM+ form with three torsional constants V1, V2, and V3 for 1-fold, 2-fold, and 3-fold contributions. The default values for these constants depend on the particular chemical situation associated with the bond

order of the bond and the hybridization of the relevant atoms. The rules are:

Single Bonds

1. An ordinary sp^3-sp^3 single bond has a three-fold barrier described by $V3=2.0$ kcal/mol.
2. An sp^3-sp^3 single bond where each of the central atoms is in Group VIA (for example, hydrogen peroxide) has a two-fold barrier with optimum torsional angle of 90 degrees, as described by $V2=-2.0$ kcal/mol.
3. An sp^3-sp^2 or $sp^3-sp^{2.5}$ single bond where the sp^3 atom is in Group VIA (for example, the C-O bond of vinyl alcohol) has a two fold barrier with an optimal planar configuration described by $V2=+2.0$ kcal/mol.
4. An sp^3-sp^2 or $sp^3-sp^{2.5}$ single bond where the atom connected to the central sp^2 ($sp^{2.5}$) atom is another sp^2 ($sp^{2.5}$) atom, as in the H-C-C-double bond O torsion of acetic acid, is described by the MM+ parameters of acetic acid, $V1=-0.167$ kcal/mol and $V3=-0.1$ kcal/mol.
5. An sp^3-sp^2 or $sp^3-sp^{2.5}$ single bond where the atom connected to the central sp^2 ($sp^{2.5}$) atom is *not* another sp^2 ($sp^{2.5}$) atom, as in the H-C-C-H torsion of propene, is described by a three-fold barrier $V3=2.0$ kcal/mol.
6. A planar sp^2-sp^2 single bond or planar $sp^2-sp^{2.5}$ single bond (for example, the central bond of butadiene, with isolated double bonds, or phenyl amine, where the nitrogen is sp^2 hybridized) is described by a two-fold barrier, $V2=5$ kcal/mol.
7. A conjugated $sp^{2.5}-sp^{2.5}$ single bond (for example, the bond joining the two phenyl rings of biphenyl, the central bond of butadiene, with delocalized aromatic bonds, or phenyl amine, where N-C bond is labeled aromatic and nitrogen is $sp^{2.5}$ hybridized) is described by a two-fold barrier, $V2=10$ kcal/mol.

Double Bonds

1. Isolated double bonds (as in ethylene) have a two-fold barrier of $V2=45$ kcal/mol.
2. Aromatic bonds (as in benzene) have a two-fold barrier of $V2=25$ kcal/mol.

Chapter 12

Quantum Mechanics

In addition to molecular mechanics calculations, HyperChem can perform various quantum mechanical calculations. These calculations are more universal than molecular mechanics, but are also more time consuming and less empirical.

Molecular mechanics depends on the concept of atom types and parameters associated with these atom types. Since the number of atom types is very large for the universe of possible molecules, parameters will probably be missing for a random new molecule unless a force field has been developed for molecules similar to the new molecule. Molecular mechanics predicts how the new molecule will behave based upon the behavior of known, similar molecules.

Quantum mechanical calculations generally have only *one carbon atom type*, compared with the *many types of carbon atoms* associated with a molecular mechanics force field like AMBER. Therefore, the number of quantum mechanics parameters needed for all possible molecules is much smaller. In principle, very accurate quantum mechanical calculations need no parameters at all, except fundamental constants such as the speed of light, etc.

HyperChem quantum mechanical calculations are *ab initio* and semi-empirical. *Ab initio* calculations use parameters (contracted basis functions) associated with shells, such as an *s* shell, *sp* shell, etc., or atomic numbers (atoms). Semi-empirical calculations use parameters associated with specific atomic numbers. The concept of atom *types* is not used in the conventional quantum mechanics methods. Semi-empirical quantum mechanics methods use a rigorous quantum mechanical formulation combined with the use of empirical parameters obtained from comparison with experiment. If parameters are available for the atoms of a given molecule, the *ab initio* and semi-empirical calculations have an *a priori* aspect when compared with a molecular mechanics calculation, letting

you explore new molecular systems beyond those for which the parameters were generated originally.

HyperChem include the commonly used basis sets. These basis sets are STO-nG and STO-nG* with $n = 1, 2, 3, 4, 5,$ and 6 for all the atoms with atomic numbers less than or equal to 54 (H - Xe) [W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969); J. B. Collins, P. V. Schleyer, J. S. Binkley, and J. A. Pople, *J. Chem. Phys.*, **64**, 5142 (1976); R. F. Stewart, *J. Chem. Phys.*, **52**, 431 (1970)], 3-21G, 3-21G*, 3-21G**, 6-21G, 6-21G*, and 6-21G** for the elements H to Ar [J. S. Binkley, J. A. Pople, and W. J. Hehre, *J. Am. Chem. Soc.*, **102**, 939 (1980); M. S. Gordon, J. S. Binkley, J. A. Pople, W. J. Pietro, and W. J. Hehre, *J. Am. Chem. Soc.*, **104**, 2797 (1982); W. J. Pietro, M. M. Francl, W. J. Hehre, D. J. Defrees, J. A. Pople, and J. S. Binkley, *J. Am. Chem. Soc.*, **104**, 5039 (1982)], 4-21G, 4-21G*, and 4-21G**, 4-31G, 4-31G*, 4-31G**, 6-31G, 6-31G*, and 6-31G** [W. J. Hehre, R. Ditchfield, and J. A. Pople, *J. Chem. Phys.*, **56**, 2257 (1972); P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta.*, **28**, 213 (1973); M. S. Gordon, *Chem. Phys. Lett.*, **76**, 163 (1980)], 6-311G, 6-311G*, 6-311G**, MC-311G, MC-311G*, and MC-311G** for the elements with atomic numbers less than or equal to 18 (H to Ar) [R. Krishnan, J. S. Kinkley, R. Seeger, and J. A. Pople, *J. Chem. Phys.*, **72**, 650 (1980); A. D. McLean and G. S. Chandler, *J. Chem. Phys.*, **72**, 5639 (1980), and D95, D95*, and D95** for the elements H to Cl [T. H. Dunning and P. J. Hay, in *Modern Theoretical Chemistry*, Plenum, New York, 1976.

HyperChem includes semi-empirical parameters for all the atoms with atomic numbers less than or equal to 54 and can perform calculations on any molecule composed of only those atoms. The few restrictions or exceptions to this rule will be pointed out as appropriate. Nevertheless, the probability of having appropriate parameters for a random calculation are much higher for semi-empirical calculations than for molecular mechanics calculations.

Background

This section describes the basics of HyperChem's simple molecular orbital calculations. It interprets HyperChem's results rather than introducing quantum chemistry. For a complete discussion, you should consult textbooks in quantum chemistry, such as I. N. Levine, *Quantum Chemistry*, 3rd Edition, Allyn and Bacon, 1986;

and A. Szabo and N. S. Ostlund, *Modern Quantum Chemistry*, McGraw-Hill Publishing Co., 1989.

Approximate Solutions of the Schrödinger equation

The Schrödinger equation contains the essence of all chemistry. To quote Dirac: “The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known.” [P.A.M. Dirac, *Proc. Roy. Soc. (London)* 123, 714 (1929)]. The Schrödinger equation is

$$\mathcal{H}\Psi = E\Psi \quad (44)$$

The input, the Hamiltonian \mathcal{H} , describes the particles of the system; the output, E , is the total energy of the system; and the wave function, Ψ , constitutes all we can know and learn about the particular molecular system represented by \mathcal{H} .

For small molecules, the accuracy of solutions to the Schrödinger equation competes with the accuracy of experimental results.

However, these accurate *ab initio* calculations require enormous computation and are only suitable for the molecular systems with small or medium size. *Ab initio* calculations for very large molecules are beyond the realm of current computers, so HyperChem also supports semi-empirical quantum mechanics methods. Semi-empirical approximate solutions are appropriate and allow extensive chemical exploration. The inaccuracy of the approximations made in semi-empirical methods is offset to a degree by recourse to experimental data in defining the parameters of the method. Indeed, semi-empirical methods can sometimes be more accurate than some poorer *ab initio* methods, which require much longer computation times.

In making certain mathematical approximations to the Schrödinger equation, we can equate derived terms directly to experiment and replace difficult-to-calculate mathematical expressions with experimental values. In other situations, we introduce a parameter for a mathematical expression and derive values for that parameter by fitting the results of globally calculated results to experiment. Quantum chemistry has developed two groups of researchers:

- Those who fairly successfully obtain improved *a priori* solutions, but are restricted to relatively small molecules.

- Those who want to explore chemistry widely with tools that are not always reliable, but which suggest many chemically interesting possibilities.

Obviously, the *ab initio* method in HyperChem is suitable for the former and the semi-empirical methods are more appropriate for the latter.

Charge and Multiplicity

Once you make a set of approximations and introduce a set of parameters, you have an *a priori* method (a model of chemistry) for exploring arbitrary molecular systems. The input to these calculations is relatively straightforward: it consists of describing the number of nuclei, atomic number and position or configuration of the nuclei, and indicating how many electrons are to be added to the system of nuclei. This last input essentially describes the total charge of the system. For example, in a singly charged anion, there is one more electron than there is total nuclear charge; thus the charge on the system is -1 . The charge of the system is a principal input quantity.

Secondly, you must describe the electron spin state of the system to be calculated. Electrons with their individual spins of $s_i = 1/2$ can combine in various ways to lead to a state of given total spin. The second input quantity needed is a description of the total spin $S = \sum s_i$. Since spin is a vector, there are various ways of combining individual spins, but the net result is that a molecule can have spin S of 0, $1/2$, 1, These states have a *multiplicity* of $2S+1 = 1, 2, 3, \dots$, that is, there is only one way of orienting a spin of 0, two ways of orienting a spin of $1/2$, three ways of orienting a spin of 1, and so on.

To define the state you want to calculate, you must specify the multiplicity. A system with an even number of electrons usually has a closed-shell ground state with a multiplicity of 1 (a singlet). A system with an odd number of electrons (free radical) usually has a multiplicity of 2 (a doublet). The first excited state of a system with an even number of electrons usually has a multiplicity of 3 (a triplet). The states of a given multiplicity have a spectrum of states—the lowest state of the given multiplicity, the next lowest state of the given multiplicity, and so on.

Independent Electron Methods

The simplest approximation to the Schrödinger equation is an independent-electron approximation, such as the Hückel method for π -electron systems, developed by E. Hückel. Later, others, principally Roald Hoffmann of Cornell University, extended the Hückel approximations to arbitrary systems having both π and σ electrons—the Extended Hückel Theory (EHT) approximation. This chapter describes some of the basics of molecular orbital theory with a view to later explaining the specifics of HyperChem EHT calculations.

The Independent Electron Approximation

Within the Born-Oppenheimer approximation discussed earlier, you can solve an electronic Schrödinger equation

$$\mathcal{H}_{\text{elec}} \Psi_{\text{elec}} = E_{\text{elec}} \Psi_{\text{elec}} \quad (45)$$

for Ψ_{elec} , which describes the motion and position of electrons in a molecule. The independent electron approximation assumes that $\mathcal{H}_{\text{elec}}$, collectively describing all electrons, can be approximated as a sum of effective one-electron Hamiltonians, $\mathcal{H}_i^{\text{eff}}$:

$$\mathcal{H}_{\text{elec}} = \sum_i \mathcal{H}_i^{\text{eff}} \quad (46)$$

Molecular Orbitals

Electrons are identical, and each term in this sum is essentially the same operator. You can then solve an independent-electron Schrödinger equation for a wave function ψ , describing an individual electron:

$$\mathcal{H}^{\text{eff}} \psi = \epsilon \psi \quad (47)$$

Multiple solutions ψ_i and ϵ_i are possible for this last equation. The wave functions for individual electrons, ψ_i , are called *molecular orbitals*, and the energy, ϵ_i , of an electron in orbital ψ_i is called the *orbital energy*.

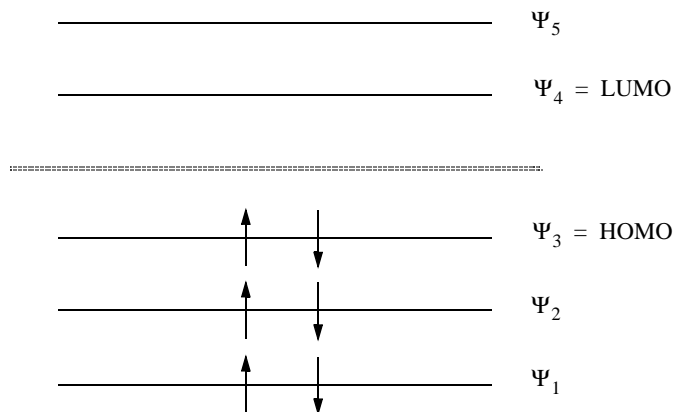
The molecular orbitals describe an electron such that the values of $\psi_i^2(\mathbf{r}) d\mathbf{r}$ at a point \mathbf{r} describe the probability of the electron being in a small volume $d\mathbf{r}$ around that point. The total probability of finding the electron somewhere is

$$\int \psi_i^2(\mathbf{r}) d\mathbf{r} = 1 \quad (48)$$

which says that the molecular orbitals are *normalized*.

Orbital Energy Diagrams

You can order the molecular orbitals that are a solution to equation (47) according to their energy. Electrons populate the orbitals, with the lowest energy orbitals first. A normal, closed-shell, Restricted Hartree Fock (RHF) description has a maximum of two electrons in each molecular orbital, one with electron spin up and one with electron spin down, as shown:



If the number of electrons, N , is even, you can have a closed shell (as shown) where the occupied orbitals each contain two electrons. For an odd number of electrons, at least one orbital must be singly occupied. In the example, three orbitals are occupied by electrons and two orbitals are unoccupied. The highest occupied molecular orbital (HOMO) is ψ_3 , and the lowest unoccupied molecular orbital (LUMO) is ψ_4 . The example above is a singlet, a state of total spin $S=0$. Exciting one electron from the HOMO to the LUMO orbital would give one of the following excited states:

- Total spin $S=0$ (a singlet) if the spins remained the same.
- Total spin $S=1$ (a triplet) if a spin-down electron in the HOMO was promoted to be a spin-up electron in the LUMO. That is, the spin of one of the electrons was reversed when exciting it from the HOMO to the LUMO.
- If you add a single electron to the LUMO orbital above to create an anion, you obtain total spin $S=1/2$ (a doublet).

The MO-LCAO Approximation

To compute molecular orbitals, you must give them mathematical form. The usual approach is to expand them as a linear combination of known functions, such as the atomic orbitals of the constituent atoms of the molecular system. If the atomic orbitals, (1s, 2s, 2px, 2py, 2pz, etc.) are denoted as ϕ_{μ} , then this equation describes the molecular orbitals as linear combination of atomic orbitals (MO-LCAO):

$$\psi_i = \sum_v C_{vi} \phi_v \quad (49)$$

where the elements of a matrix \mathbf{C} are the coefficients in the expansion.

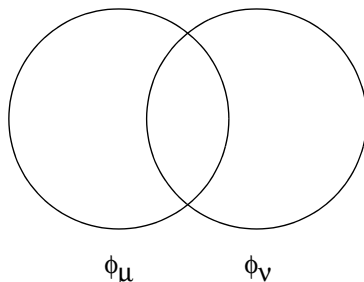
The Matrix equations for the Molecular Orbitals

Now that you know the mathematical form, you can solve the independent-electron Schrödinger equation for the molecular orbitals. First substitute the LCAO form above into equation (47) on page 193, multiply on the left by ϕ_μ and integrate to represent the problem in terms of the matrix elements of a matrix \mathbf{H} ,

$$\mathbf{H}_{\mu\nu} = \int \phi_\mu H^{\text{eff}} \phi_\nu d\tau \quad (50)$$

The overlap between two atomic orbitals ϕ_μ and ϕ_ν ,

$0 < \text{Overlap} < 1$



defines the elements of a matrix \mathbf{S} ,

$$S_{\mu\nu} = \int \phi_\mu \phi_\nu d\tau \quad (51)$$

and the independent electron Schrödinger equation (47) reduces to the following matrix equation:

$$\mathbf{HC} = \mathbf{SC}\epsilon \quad (52)$$

where ϵ is a diagonal matrix of the orbital energies,

$$\epsilon_{ij} = \epsilon_i \delta_{ij} \quad \delta_{ij} \text{ is 1 (i equal j) or 0 (i not equal j)} \quad (53)$$

Solving for the Molecular Orbitals

Solving the previous matrix equation for the coefficients \mathbf{C} describing the LCAO expansion of the orbitals and orbital energies ϵ requires a *matrix diagonalization*. If the overlap matrix were a unit matrix ($S_{\mu\nu} = \delta_{\mu\nu}$), then you would simply diagonalize the matrix \mathbf{H} to yield the eigenvectors \mathbf{C} (the matrix of the diagonalizing unitary transformation), the eigenvalues ϵ , and the resulting diagonal elements of \mathbf{H} :

$$\mathbf{C}^\dagger \mathbf{H} \mathbf{C} = \epsilon \quad (54)$$

Because of the presence of the overlap matrix, however, you must first diagonalize the overlap matrix:

$$\mathbf{U}^\dagger \mathbf{S} \mathbf{U} = \mathbf{s} \quad (55)$$

then form $\mathbf{s}^{-1/2}$ as the diagonal matrix with elements $(\mathbf{s}^{-1/2})_{ii} = [(\mathbf{s})_{ii}]^{-1/2}$

and the nondiagonal matrix $\mathbf{S}^{-1/2}$ by the reverse transformation:

$$\mathbf{S}^{-1/2} = \mathbf{U}\mathbf{s}^{-1/2}\mathbf{U}^t \quad (56)$$

Finally, you must diagonalize $\mathbf{S}^{-1/2}\mathbf{H}\mathbf{S}^{-1/2}$ to obtain the molecular orbitals and orbital energies:

$$(\mathbf{S}^{1/2}\mathbf{C})^t(\mathbf{S}^{-1/2}\mathbf{H}\mathbf{S}^{-1/2})(\mathbf{S}^{1/2}\mathbf{C}) = \epsilon \quad (57)$$

Self-Consistent Field Methods

In the true independent-electron methods you only have to obtain the matrix elements $H_{\mu\nu}$ of some quite unspecified effective one-electron Hamiltonian \mathcal{H}^{eff} . These matrix elements, as in Extended Hückel Theory, can be quite empirical. The Hartree-Fock procedure or Self-Consistent Field (SCF) method, however, introduces very well defined mathematical approximations to end up with a one-electron eigenvalue problem, but one which must be solved iteratively to self-consistency.

Hartree-Fock Method

While the equations of the Hartree-Fock approach can be rigorously derived, we present them *post hoc* and give a physical description of the approximations leading to them. The Hartree-Fock method introduces an effective one-electron Hamiltonian, \mathcal{F} , as in equation (47) on page 193:

$$\mathcal{F}\psi_i = \epsilon_i\psi_i \quad (58)$$

but here the Fock operator, \mathcal{F} , depends implicitly upon the solutions ψ_i . The Fock operator is a sum of the kinetic energy operator for an electron, a potential that a single electron would feel coming from the fixed nuclei, and an average of the effects of all the other $N-1$ electrons.

The procedure is as follows:

1. Guess the position of each electron, that is, you guess each occupied orbital ψ_i .

2. Guess the average potential that a specific electron would feel coming from the other electrons; that is, you guess at the Fock operator.
3. Solve equation (58) for a new guess at the positions of the electrons.
4. Repeat the procedure until the wave function for an electron is consistent with the field that it and the other electrons produce.

The Roothaan equations

The preceding discussion means that the Matrix equations already described are correct, except that the Fock matrix, \mathbf{F} , replaces the effective one-electron Hamiltonian matrix, and that \mathbf{F} depends on the solution \mathbf{C} :

$$\mathbf{F}(\mathbf{C})\mathbf{C} = \mathbf{S}\mathbf{C}\epsilon \quad (59)$$

These are the Roothaan SCF equations, which clearly can be solved iteratively—guess \mathbf{C} , form \mathbf{F} , diagonalize to a new \mathbf{C} , form a new \mathbf{F} , ..., and so on.

If you define a density matrix \mathbf{P} by summing over all occupied molecular orbitals:

$$P_{\mu\nu} = \sum_i^{\text{occ}} C_{\mu i} C_{\nu i} \quad (60)$$

then the rigorous definition of the Fock matrix is

$$F_{\mu\nu} = H_{\mu\nu} + \sum_{\lambda\sigma} P_{\lambda\sigma} \left[(\mu\nu|\lambda\sigma) - \frac{1}{2}(\mu\lambda|\nu\sigma) \right] \quad (61)$$

where $H_{\mu\nu}$ is a true one-electron Hamiltonian representing the kinetic energy and interaction of a single electron with the core of all the nuclei, and $(\mu\nu|\lambda\sigma)$ is a so-called *two-electron integral*. The simpler two-electron integrals are easy to interpret: $(\mu\mu|\nu\nu)$ is just the Coulomb repulsion between one electron described by the probability ϕ_μ^2 and another electron described by the probability

ϕ_v^2 , but others are less intuitive. The density matrix describes the total probability of finding an electron such that

$$\rho(\mathbf{r})d\mathbf{r} = \sum_{\mu\nu} P_{\mu\nu}\phi_\mu(\mathbf{r})\phi_\nu(\mathbf{r})d\mathbf{r} \quad (62)$$

is the probability of finding an electron in the small volume element $d\mathbf{r}$ about the point \mathbf{r} .

Spin Pairing

The Roothaan equations just described are strictly the equations for a closed-shell Restricted Hartree-Fock (RHF) description only, as illustrated by the orbital energy level diagram shown earlier. To be more specific:

- A closed-shell means that every occupied molecular orbital contains exactly two electrons.
- A restricted Hartree-Fock description means that spin-up and spin-down electrons occupy the same spatial orbitals ψ_i —there is no allowance for different spatial orbitals for different electron spins.

The occupancy can be described by

$$\psi_1(1)\bar{\psi}_1(2)\psi_2(3)\bar{\psi}_2(4)\psi_3(5)\bar{\psi}_3(6) \quad (63)$$

The notation here means that electron 1 occupies a spatial orbital ψ_1 with spin up (no bar on top); electron 2 occupies spatial orbital ψ_1 with spin down (a bar on top), and so on. An RHF description of the doublet $S=1/2$ state obtained by adding an electron to ψ_4 would be

$$\psi_1(1)\bar{\psi}_1(2)\psi_2(3)\bar{\psi}_2(4)\psi_3(5)\bar{\psi}_3(6)\psi_4(7) \quad (64)$$

Conversely, an *unrestricted* Hartree-Fock description implies that there are two different sets of spatial molecular orbitals: those molecular orbitals, ψ_i^α , occupied by electrons of spin up (alpha spin) and those molecular orbitals, ψ_i^β , occupied by electrons of spin down (beta spin) as shown next.

tion. A UHF wave function has certain undesirable characteristics as described below. The problem of defining and computing RHF descriptions for open-shell cases, however, is somewhat severe and it is usually necessary to indicate explicitly how open-shell RHF calculations are obtained (in HyperChem, they are obtained via the half-electron approximation). The UHF approximation can be applied universally without such considerations.

The unrestricted approach defines two different sets of spatial molecular orbitals—those that hold electrons with spin up:

$$\psi_i^\alpha = \sum_v C_{vi}^\alpha \phi_v \quad (67)$$

and those that hold electrons with spin down:

$$\psi_i^\beta = \sum_v C_{vi}^\beta \phi_v \quad (68)$$

The two sets of coefficients, one for spin-up alpha electrons and the other for spin-down beta electrons, are solutions of two coupled matrix eigenvalue problems:

$$\mathbf{F}^\alpha(\mathbf{C}^\alpha, \mathbf{C}^\beta)\mathbf{C}^\alpha = \mathbf{S}\mathbf{C}^\alpha \epsilon^\alpha \quad (69)$$

$$\mathbf{F}^\beta(\mathbf{C}^\alpha, \mathbf{C}^\beta)\mathbf{C}^\beta = \mathbf{S}\mathbf{C}^\beta \epsilon^\beta \quad (70)$$

The two equations couple because the alpha Fock matrix \mathbf{F}^α depends on both the alpha and the beta solutions, \mathbf{C}^α and \mathbf{C}^β (and similarly for the beta Fock matrix). The self-consistent dependence of the Fock matrix on molecular orbital coefficients is best represented, as before, via the density matrices \mathbf{P}^α and \mathbf{P}^β , which essentially state the probability of describing an electron of alpha spin, and the probability of finding one of beta spin:

$$P_{\mu\nu}^\alpha = \sum_{i \text{ occ}} C_{\mu i}^\alpha C_{\nu i}^\alpha \quad (71)$$

$$P_{\mu\nu}^{\beta} = \sum_i^{\text{occ}} C_{\mu i}^{\beta} C_{\nu i}^{\beta} \quad (72)$$

$$\mathbf{P}^T = \mathbf{P}^{\alpha} + \mathbf{P}^{\beta} \quad (73)$$

$$F_{\mu\nu}^{\alpha} = H_{\mu\nu}^{\alpha} + \sum_{\lambda\sigma} P_{\lambda\sigma}^T(\mu\nu|\lambda\sigma) - P_{\lambda\sigma}^{\alpha}(\mu\lambda|\nu\sigma) \quad (74)$$

$$F_{\mu\nu}^{\beta} = H_{\mu\nu}^{\beta} + \sum_{\lambda\sigma} P_{\lambda\sigma}^T(\mu\nu|\lambda\sigma) - P_{\lambda\sigma}^{\beta}(\mu\lambda|\nu\sigma) \quad (75)$$

The equations and Roothaan equations are solved by the same techniques.

Convergence

The solution of the RHF or UHF equations is an iterative procedure with two principal issues. First is the question of what to use for an initial guess and second, whether the solutions will converge quickly or at all. The initial guess affects the convergence also, as an exact guess would immediately converge.

An initial guess could be couched in terms of an initial guess at one of \mathbf{C} , \mathbf{P} , or \mathbf{F} , which are equivalent starting points for the **CPFCPF**... procedure. The simplest initial guess is to set $\mathbf{P} = \mathbf{0}$ or equivalently, $\mathbf{F} = \mathbf{H}$. This is referred to as using the *core Hamiltonian* for an initial guess. HyperChem uses something very similar to this for an initial guess for the *ab initio* and semi-empirical methods. Alternatively, HyperChem offers some other methods, such as the projected Hückel, projected CNDO, and projected INDO, for an initial guess of MO for *ab initio* calculations.

The convergence of SCF interactions is not always successful. In the simplest iteration procedure, iterations proceed without the aid of either an external convergence accelerator or an extrapolator. This often leads to slow convergence.

Thus, HyperChem occasionally uses a three-point interpolation of the density matrix to accelerate the convergence of quantum mechanics calculations when the number of iterations is exactly divisible by three and certain criteria are met by the density matrices. The interpolated density matrix is then used to form the Fock matrix used by the next iteration. This method usually accelerates convergent calculations. However, interpolation with the MINDO/3, MNDO, AM1, and PM3 methods can fail on systems that have a significant charge buildup.

When three-point interpolation fails to yield a convergent calculation, you can request a second accelerator for any SCF calculation via the Semi-empirical Options dialog box and the Ab Initio Options dialog box. This alternative method, Direct Inversion in the Iterative Subspace (DIIS), was developed by Peter Pulay [P. Pulay, *Chem. Phys. Lett.*, 73, 393 (1980); *J. Comp. Chem.*, 3, 556(1982)]. DIIS relies on the fact that the eigenvectors of the density and Fock matrices are identical at self-consistency. At SCF convergence, the following condition exists

$$[\mathbf{P} \cdot \mathbf{F}] = 0 \quad (76)$$

The extent to which this condition does not occur is a measure of deviance from self-consistency. The DIIS method uses a linear combination of previous Fock matrices to predict a Fock matrix that minimizes $[\mathbf{P} \cdot \mathbf{F}]$. This new Fock matrix is then used by the SCF calculation.

The DIIS method is not without cost. A history of Fock matrices must be maintained and appropriate memory allocated. In addition, the computational cost of generating a new Fock matrix is significant. Also, in very rare cases, the solution found by this method is very different from that found in other ways.

Spin Pairing—Restricted or Unrestricted?

You will need to decide whether or not to request Restricted (RHF) or Unrestricted (UHF) Hartree-Fock calculations. This question embodies a certain amount of controversy and there is no simple answer. The answer often depends simply on which you prefer or what set of scientific prejudices you have. Ask yourself whether you prefer orbital energy diagrams with one or two electrons per orbital.

To consider the question in more detail, you need to consider spin eigenfunctions. If you have a Hamiltonian \mathcal{H} and a many-electron spin operator δ , then the wave function Ψ for the system is ideally an eigenfunction of both operators:

$$\mathcal{H}\Psi = E\Psi \quad (77)$$

$$\delta^2\Psi = \delta(\delta + 1)\Psi \quad (78)$$

The functions that are exact eigenvalues of the spin operator are described as singlet ($S=0$), doublet ($S=1/2$), and so on. One school of thought says that since we can't obtain exact eigenvalues of \mathcal{H} , we should try to ensure that our wave functions are exact eigenvalues of δ^2 , which we can easily do for RHF wave functions. UHF wave functions relax the restriction of being exact eigenvalues of δ^2 for a lower energy E . A singlet UHF wave function, for example, might have a value of $S=0.06$ and almost be a singlet. Because electron spins are not exactly paired (electrons of opposite spin occupy different spatial orbitals), an exact spin state is not obtained. Nevertheless, UHF wave functions have lower energy than their RHF counterparts. A second school of thought uses the variational principle to justify that UHF wave functions are better solutions (given their better energy).

Of the two, the UHF method provides a more continuous and universal model for chemistry. That is, you can obtain an unrestricted wave function more easily in various chemical situations than you can a restricted solution. An RHF solution for arbitrary bonding situations is sometimes hard to obtain. An example of this is the two-electron bond of, say H_2 , as you stretch and break the bond. At normal bond lengths, the molecule is described as a singlet with two electrons occupying the same spatial molecular orbital. As you stretch and break the bond, however, the two electrons are certainly not best described as having the same spatial distribution—one electron should be on one hydrogen atom (a doublet) and the other electron on the other hydrogen atom (a second spin doublet). You cannot describe two hydrogen atoms by an RHF wave function with both electrons occupying the same spatial orbital; if you do, the hydrogen molecule does not dissociate correctly when you lengthen the bond. A UHF description of H_2 , however, will dissociate correctly, and a UHF wave function with separate-orbitals-for-separate-spins can describe two isolated hydrogen atoms. At normal bond lengths, the UHF solution usually degenerates to the situation where the two spatial orbitals become identical. The UHF solution for H_2 , for example, has a smooth potential energy

surface with no abnormalities. This makes a UHF computation desirable for studying chemical reactions involving the breaking of bonds. Such bond breaking can be poorly handled by RHF wave functions unless the reaction has no change in spin pairing as it proceeds.

A UHF wave function may also be a necessary description when the effects of spin polarization are required. As discussed in “Differences Between INDO and CNDO,” a Restricted Hartree-Fock description will not properly describe a situation such as the methyl radical. The unpaired electron in this molecule occupies a p-orbital with a node in the plane of the molecule. When an RHF description is used (all the s orbitals have paired electrons), then no spin density exists anywhere in the s system. With a UHF description, however, the spin-up electron in the p-orbital interacts differently with spin-up and spin-down electrons in the s system and the s-orbitals become spatially separate for spin-up and spin-down electrons with resultant spin density in the s system.

Electronic States

HyperChem describes electronic states by their spin state (multiplicity, $2S+1$) as either singlet ($S=0$, $2S+1=1$), doublet ($S=1/2$, $2S+1=2$), triplet ($S=1$, $2S+1=3$), or quartet ($S=3/2$, $2S+1=4$). Think of these states as having 0, 1, 2, or 3 unpaired electrons. An *even number of electrons* can lead to a singlet or a triplet, while an *odd number of electrons* leads to a doublet or a quartet. HyperChem does not explicitly consider states of higher multiplicity, such as quintets, and so on. The *ground state* (state of absolutely lowest energy) is not normally a quartet, but can commonly be a singlet, doublet, or a triplet. All other states are *excited states*. Systems with an even number of electrons commonly have a singlet ground state, but a triplet ground state is also possible depending on the arrangement of the molecular orbitals. For example, one of the first successes of molecular orbital theory was to explain why the O₂ oxygen molecule has a triplet ground state (the HOMO orbitals are degenerate and occupied by two electrons). Molecules with an odd number of electrons (free radicals) generally have a doublet ground state.

HyperChem semi-empirical methods usually let you request a calculation on the *lowest energy state of a given multiplicity* or the *next lowest state of a given spin multiplicity*. Since most molecules with an even number of electrons are closed-shell singlets without

unpaired electrons, only the lowest triplet is made available and the next lowest triplet stated is grayed. For example, benzene has an even number of electrons and the ground state is a closed-shell singlet. You can request this ground state (the lowest singlet), the first excited singlet state (next lowest singlet), or the first excited triplet state (the lowest triplet). That is, either the highest occupied molecular orbital (HOMO) is occupied by two electrons or one electron is in the HOMO and one is in the lowest unoccupied molecular orbital (LUMO) leading to excited singlet or triplet states. For doublets and quartets, only the lowest state of the given multiplicity is available as an option.

For open-shell RHF semi-empirical calculations, the half-electron method [H. C. Longuet-Higgins and J. A. Pople, *Proc. Phys. Soc.*, 68, 591 (1955)] recommended by Dewar [M. J. S. Dewar and S. Olivella, *J. Chem. Soc. Fara. II*, 75, 829 (1979)]. It is used in the MOPAC and AMPAC series of programs [J. J. P. Stewart, *Quantum Chem. Prog. Exchange Bull.*, 10(4), 86 (1990); Dewar Research Group, *Quantum Chem. Prog. Exchange Bull.*, 7(2), 85 (1987)] in what amounts to a closed-shell calculation. For example, if the lowest doublet is requested, the orbital holding the unpaired electron is actually occupied by two 1/2-electrons with opposite spin. This is so that the full standard machinery of closed-shell Hartree-Fock calculations can be used to determine the orbitals. A correction is then made to the closed-shell SCF energy to properly represent the doublet state. For molecules with an even number of electrons and a closed-shell ground state this means that the first excited singlet and triplet states have the same orbitals—both being computed by pairs of 1/2-electrons in the HOMO and LUMO orbitals. The correction applied to obtain the energy of the 1/2-electron states, however, leads to the triplet being lower than the singlet, because of the exchange effect (described earlier in conjunction with the difference between CNDO and INDO).

The UHF option allows only the lowest state of a given multiplicity to be requested. Thus, for example, you could explore the lowest Triplet excited state of benzene with the UHF option, but could not ask for calculations on an excited singlet state. This is because the UHF option in HyperChem does not allow arbitrary orbital occupations (possibly leading to an excited single determinant of different spatial symmetry than the lowest determinant of the same multiplicity), nor does it perform a Configuration Interaction (CI) calculation that allows a multitude of states to be described.

For the RHF option, you can request a Configuration Interaction (CI) wave function. These calculations start with a set of computed RHF orbitals, either from the lowest singlet (doublet) or from the half electron singlet and triplet (doublet and quartet) orbitals. This initial calculation is referred to as the reference state. From this reference state, a set of microstates (different single determinants shown in an orbital energy diagram as different occupancies of the orbitals) is generated. These microstates are generated by promoting electrons from occupied orbitals closest to the HOMO orbital into unoccupied orbitals closest to the LUMO orbital until the lowest. Either an orbital criterion or energy criterion can be used to select microstates. A more accurate set of states is then obtained by taking appropriate linear combinations of these microstates. The coefficients of these microstates in the new, more accurate states are obtained by a diagonalization of the Hamiltonian matrix (the CI calculation). The states resulting from the CI calculation can all be inspected in the log file. The CI calculation takes a considerably longer time to obtain than the simple Hartree-Fock (SCF) calculations, and you should use the CI option only if you are prepared to wait for the (possibly) more accurate results.

Thus, in HyperChem a state is described for calculation in this sequence:

1. Define the multiplicity in the Semi-empirical Options dialog box or the Ab Initio Options dialog box.
2. Request one of two computational procedures, either RHF or UHF.
3. Request either the lowest energy state of the specified multiplicity or the next lowest energy state for semi-empirical calculations.
4. Request configuration interaction, if you want it.

Optimization and molecular dynamics cannot be performed when using configuration interaction. When a configuration interaction calculation is performed, gradients of the energy (and hence geometry optimization and molecular dynamics) are not available. For these cases, any geometry optimization should be done with another state or procedure, and then the configuration interaction calculation requested only to obtain spectral information, such as a ultraviolet-visible spectrum.

Post Self-Consistent Field Calculations

Configuration Interaction

For some systems a single determinant (SCF calculation) is insufficient to describe the electronic wave function. For example, square cyclobutadiene and twisted ethylene require at least two configurations to describe their ground states. To allow several configurations to be used, a multi-electron configuration interaction technique has been implemented in HyperChem.

Electronic spectroscopy requires the consideration of multiple electronic states for the same configuration of the nuclei. Configuration interaction is a procedure for generating and mixing many configurations (Slater determinants) together to arrive at a description of not only the ground state, but many excited states of a molecule. To a first approximation, only singly-excited configurations are needed to describe excited electronic states.

HyperChem uses single determinant rather than spin-adapted wave functions to form a basis set for the wave functions in a configuration interaction expansion. That is, HyperChem expands a CI wave function, Φ_a , in a linear combination of single Slater determinants Ψ_i

$$\Phi_a = \sum_i C_{ia} \Psi_i \quad (30)$$

The expansion coefficients C_{ia} are determined by solving the CI secular equation

$$\mathbf{HC} = \mathbf{CE} \quad (31)$$

where \mathbf{E} is the eigenvalue vector and represents the energies of the CI states.

The single Slater determinants are generated by taking an electron from one of the specified occupied orbitals of the ground reference state and placing that electron into one of the specified unoccupied orbitals (of the ground state). The Slater determinants that are mixed together in the CI calculation are completely specified by giving the occupied and unoccupied orbitals to use in generating the configuration, as specified in the Configuration Interaction dialog box.

The elements of the CI matrix are:

$$\langle \hat{\Phi}_a | \hat{H} | \Phi_b \rangle \quad (32)$$

Evaluation of the CI matrix elements is somewhat difficult. Fortunately, most matrix elements are zero because of the orthogonality of the MOs. There are only three types of non-zero elements which are needed to be computed.

1) Diagonal elements:

$$\langle \hat{\Phi}_a | \hat{H} | \Phi_a \rangle \quad (33)$$

2) Off-diagonal elements:

$$\langle \hat{\Phi}_a | \hat{H} | \Phi_b \rangle \quad (34)$$

where $\Phi_a = \Phi_b$ except that Ψ_i in Φ_a is replaced by Ψ_j in Φ_b .

3) Off-diagonal elements:

$$\langle \hat{\Phi}_a | \hat{H} | \Phi_b \rangle \quad (35)$$

where $\Phi_a = \Phi_b$ except that Ψ_i and Ψ_j in Φ_a are replaced by Ψ_k and Ψ_l in Φ_b .

Once the CI expansion coefficients are available, the expectation values of the \hat{S}^2 operator can be obtained by

$$\langle \hat{\Phi}_a | \hat{S}^2 | \Phi_b \rangle \quad (36)$$

For the details of calculation for the matrix elements of operator \hat{H} and expectation values of \hat{S}^2 in equations (33) to (36), please see J. P. Stewart, *J. Comp. Aided Mol. Design*, 4, 1 (1990).

MP2 Correlation Energy

Configuration interaction (CI) is a systematic procedure for going beyond the Hartree-Fock approximation. A different systematic approach for finding the correlation energy is perturbation theory (Rayleigh-Schrödinger many-body perturbation theory — RSPT). In this approach, the total Hamiltonian of the system is divided or partitioned into two parts: a zeroth-order part, H_0 (which has

known eigenfunctions and eigenvalues), and a perturbation, V . The exact energy is then expressed as an infinite sum of contributions of increasing complexity. The expressions for these contributions contain the eigenvalues of H_0 and matrix elements of the perturbation between the eigenfunctions of H_0 . By introducing the ordering parameter λ , the total Hamiltonian can be written as

$$H = H + \lambda V \quad (37)$$

The exact eigenfunctions and eigenvalues can now be expanded in a Taylor series in λ .

$$\Psi_\lambda = \Psi^{(0)} + \lambda \Psi^{(1)} + \lambda^2 \Psi^{(2)} + \dots \quad (38)$$

$$E_\lambda = E^{(0)} + \lambda E^{(1)} + \lambda^2 E^{(2)} + \dots \quad (39)$$

If H_0 is chosen wisely, then the perturbation is small and the perturbation expansion (i.e., the sum of the 1st, 2nd, ..., nth-order energies) converges quickly. To obtain a perturbation expansion for the correlation energy, the best way is to choose the Hartree-Fock Hamiltonian as the zeroth-order Hamiltonian. The application to N -electron molecular systems is sometimes called Møller-Plesset (MP) perturbation theory. These methods, which can be terminated at second (MP2), third (MP3), or fourth order (MP4), with these three being the most frequently used in different *ab initio* programs, calculate the correlation energy and rely on a good description of the virtual orbitals in the original SCF function. The calculated total correlation energy is therefore quite dependent on the quality of the basis set.

Møller-Plesset calculations do not give the full correlation energy, and MP2 is estimated to give only about half of the total correlation energy. They, however, are very fast in comparison with configuration interaction calculations and appear to reproduce well the energetic effects of correlation. The MP2 method probably represents the simplest approximation for the correlation energy. The MP2 energy is given by

$$E^{(2)} = - \sum_{ar} \frac{V_{ar} V_{ra}}{\epsilon_a^{(0)} - \epsilon_r^{(0)}} \quad (40)$$

where ϵ_a and ϵ_r are the eigenvalues of the occupied and unoccupied MOs of the zero-order Hamiltonian and V_{ar} are the matrix elements of the perturbation Hamiltonian operator.

The amount of computation for MP2 is determined by the partial transformation of the two-electron integrals, what can be done in a time proportionally to m^4 (m is the number of basis functions), which is comparable to computations involved in one step of CID (doubly-excited configuration interaction) calculation. To save some computer time and space, the core orbitals are frequently omitted from MP calculations. For more details on perturbation theory please see A. Szabo and N. Ostlund, *Modern Quantum Chemistry*, Macmillan, New York, 1985.

HyperChem supports MP2 (second order Møller-Plesset) correlation energy calculations using any available basis set. In order to save main memory and disk space, the HyperChem MP2 electron correlation calculation normally uses a so called “frozen-core” approximation, i.e. the inner shell (core) orbitals are omitted. A setting in CHEM.INI allows excitations from the core orbitals to be include if necessary (melted core). Only the single point calculation is available for this option.

The Neglect of Differential Overlap Approximation

The principal semi-empirical schemes usually involve one of two approaches. The first uses an *effective* one-electron Hamiltonian, where the Hamiltonian matrix elements are given empirical or semi-empirical values to try to correlate the results of calculations with experiment, but no specified and clear mathematical derivation of the explicit form of this one-electron Hamiltonian is available beyond that given above. The extended Hückel calculations are of this type.

The second approach is based on an explicit mathematical approximation: the neglect of certain *differential overlap* terms. This approximation is not necessarily a valid one in any or all instances but can be justified to an extent. These approximations are offset by introducing empirical parameters and then using the new approximate form of the Schrödinger equation with its adjustable parameters as a fitting procedure for experimental results. A principal difficulty in any attempt to solve the Schrödinger equation for molecules is the large number ($\sim N^4$) of two-electron integrals

(mn|ls) that have to be computed and used in some fashion in the computation. These integrals are defined as

$$(\mu\nu|\lambda\sigma) = \int \phi_{\mu}^A(\mathbf{r}_1)\phi_{\nu}^B(\mathbf{r}_1)r_{12}^{-1}\phi_{\lambda}^C(\mathbf{r}_2)\phi_{\sigma}^D(\mathbf{r}_2)d\mathbf{r}_1d\mathbf{r}_2 \quad (79)$$

where ϕ_{μ}^A is an atomic orbital centered at atom A. In general, these integrals involve atomic orbital basis functions ϕ_{μ} on four different centers A, B, C, and D. The principal function involved can be considered to be the two-center charge distribution, $\phi_{\mu}^A\phi_{\nu}^B$, which when integrated is the overlap integral

$$S_{\mu\nu} = \int \phi_{\mu}^A(\mathbf{r}_1)\phi_{\nu}^B(\mathbf{r}_1)d\mathbf{r}_1 \quad (80)$$

The differential overlap approximation says that $S_{\mu\nu} \ll 1$ in many situations and that the overlap or its original argument under the integrand above can be ignored or approximated in various ways. The simplest approximation is the *complete neglect of differential overlap*

$$\phi_{\mu}\phi_{\nu} = \delta_{\mu\nu}\phi_{\mu}\phi_{\mu} \quad (81)$$

The second basic approximation is the neglect of diatomic differential overlap

$$\phi_{\mu}^A\phi_{\nu}^B = \phi_{\mu}^A\phi_{\nu}^A\delta_{AB} \quad (82)$$

Either of these approximations lead to a great simplification of the general equations, the greatest simplification being that associated with complete neglect of differential overlap (CNDO). An intermediate neglect of differential overlap (INDO, ZINDO/1, and ZINDO/S) scheme retains some of the one-center terms and the neglect of diatomic differential overlap (NDDO) schemes keep all of the one-center terms above. The modified INDO (MINDO/3) method and those that are based on NDDO (MNDO, AM1, and PM3) are all available in HyperChem and are discussed extensively below, in turn. First of all, however, we describe the results of SCF calculations that are independent of the details of whether the specific approximation involved is CNDO, MNDO, or some other approximate treatment of the general SCF equations.

Characterizations of the Wave function

When you perform a single point semi-empirical or *ab initio* calculation, you obtain the energy and the first derivatives of the energy with respect to Cartesian displacement of the atoms. Since the wave function for the molecule is computed in the process, there are a number of other molecular properties that could be available to you. Molecular properties are basically an average over the wave function of certain operators describing the property. For example, the electronic dipole operator is basically just the operator for the position of an electron and the electronic contribution to the dipole moment is

$$\mu = \sum_i \int \psi_i(\mathbf{r}) \mathbf{r} \psi_i(\mathbf{r}) d\mathbf{r} \quad (83)$$

The dipole moment for a calculation is reported and is contained in the log file if logging is turned on. It is also reported on the status line if you Display Dipole Moment on the Display menu. Other expectation values besides the dipole moment (for example, quadrupole moment) could be reported with a wave function but the set reported with this release of HyperChem is limited to only a few. Below we discuss the properties or other characterizations of the calculated wave function that can be interactively visualized.

Contour Plots

HyperChem allows the visualization of two-dimensional contour plots for a certain number of variables. These contour plots show the values of a spatial variable (a property $f(x,y,z)$ in normal three-dimensional Cartesian space) on a plane that is parallel to the screen. To obtain these contour plots the user needs to specify:

- The plane to be contoured
- The contours to be shown
- The number and positioning of the grid of points on the plane to be used in computing values of the variable

The plane is specified as a plane parallel to the screen and offset from the center of mass of the current selection towards the user by a specified number of Ångstroms. For example, if you make no selection and specify an offset of 0.0, the plane is through the cen-

ter of mass of the whole molecular system. If you select a single atom, again with an offset of 0.0, then the plane is that plane parallel to the screen that goes through the selected atom. If you specify an offset of 1.0 instead of 0.0, then the plane is 1.0 Å closer to the viewer than before. You can also specify a negative offset, which pushes the plane away from the user and into the screen.

You can specify the number and values of visible contour lines. You specify the total number of contour lines to be shown by simply stating the number, $n > 0$. You normally specify the values of the contour lines as *default values*. For this case, HyperChem computes the maximum and minimum values on the grid and then draws contours at these values plus $n-2$ contour lines evenly spaced in between these maximum and minimum values. If you need non-default values, you can specify the starting value and then an increment to define the other $n-1$ evenly spaced contour lines. If default values were computed previously, HyperChem suggests the starting value and increment of the previous default computation for the new non-default option.

The grid of computed values for the variable used in defining the contour is a grid of exactly the size of the current working area subdivided evenly such that the total number of grid points is as the user specifies.

When a molecule rotates, HyperChem abandons the current contour map because it is no longer valid and you must explicitly request a new contour map via the Graph check box.

Total Electron Density

The density matrices are a representation, in the basis set ϕ_{μ} of the electron density at a point in space. The electron density $\rho(\mathbf{r})$, described above by equation (62) on page 198, represents a probability distribution function (the probability of an electron being at a particular point in space (rigorously, in a small volume $d\mathbf{r}$ at the point \mathbf{r} in ordinary three-dimensional space). The total density can be subdivided into the probability of finding a spin-up (alpha) electron plus the probability of finding a spin-down (beta) electron:

$$\rho^T(\mathbf{r}) = \rho^{\alpha}(\mathbf{r}) + \rho^{\beta}(\mathbf{r}) \quad (84)$$

where the individual densities are defined to be identical in a closed-shell RHF calculation but can be different in a UHF calculation, according to:

$$\rho^\alpha(\mathbf{r})d\mathbf{r} = \sum_{\mu\nu} P_{\mu\nu}^\alpha \phi_\mu(\mathbf{r})\phi_\nu(\mathbf{r})d\mathbf{r} \quad (85)$$

$$\rho^\beta(\mathbf{r})d\mathbf{r} = \sum_{\mu\nu} P_{\mu\nu}^\beta \phi_\mu(\mathbf{r})\phi_\nu(\mathbf{r})d\mathbf{r} \quad (86)$$

The neglect of diatomic differential overlap approximation used in the semi-empirical methods reduces these formulae to much simpler formulae that can be computed quite rapidly,

$$\rho^\alpha(\mathbf{r})d\mathbf{r} = \sum_{A, \mu\nu \text{ on } A} P_{\mu\nu}^\alpha \phi_\mu(\mathbf{r})\phi_\nu(\mathbf{r})d\mathbf{r} \quad (87)$$

$$\rho^\beta(\mathbf{r})d\mathbf{r} = \sum_{A, \mu\nu \text{ on } A} P_{\mu\nu}^\beta \phi_\mu(\mathbf{r})\phi_\nu(\mathbf{r})d\mathbf{r} \quad (88)$$

where the double sum is over each atom and then the orbitals on that atom. Without this last approximation the electron density calculation can be a long one, even longer than solving the approximate Schrödinger equation in the first place. The reason is the large number of grid points and the double sum over all pairs of atomic orbitals at each grid point. For *ab initio* and extended Hückel calculations where no neglect of overlap (differential or otherwise) is implied in the approximations, the complete calculation is performed and requires considerable patience!

The CNDO/INDO, MINDO/3, ZINDO/1, and ZINDO/S methods might be expected to imply an even simpler equation for the electron density than the above. For example, a rigorous complete neglect of CNDO approximation, suggests that equations (87) and (88) should be replaced by expressions with a sum only over diagonal elements of the density matrix. This would represent a molecular charge density that is the exact sum of atomic densities. Alter-

natively, expectation values like the dipole moment, computed from the this density matrix, would have only monopole charge on each atom contributions. The original authors of the CNDO method recognized that a hybridization term (coming from one-center integrals combining s and p type orbitals) was important to the dipole moment and included it as part of the method. In order to make the electron density consistent with expectation values and take account of these hybridization contributions to dipole moments, electrostatic fields, etc., all the semi-empirical SCF methods in HyperChem use equations (87) and (88) for the electron density and associated expectation values.

Spin Density

For open-shell situations or for some closed-shell UHF situations (A UHF calculation for a normal closed-shell situation will degenerate into the closed-shell RHF solution in most cases. However, a true UHF solution is always obtained when a bond is stretched to such an extent that it is clearly broken and only an unrestricted open-shell descriptions of the two fragments is appropriate) non-zero spin densities exist and can be contoured. The definition of a closed-shell situation has subtleties, but a simplistic definition of it might be that the probability of finding a spin-up electron is identical to the probability of finding a spin-down electron, everywhere in space. Thus, in contrast to the total electron density defined as the sum of alpha and beta densities above, it is convenient to define the *spin density* as the difference:

$$\rho^S(\mathbf{r}) = \rho^\alpha(\mathbf{r}) - \rho^\beta(\mathbf{r})$$

The spin density defines the excess probability of finding spin-up over spin-down electrons at a point in space and is zero everywhere for closed-shell RHF situations. The spin density at the position of a nucleus is a prime determinant of electron spin resonance (ESR) spectra.

Orbital Plots

For many reasons, including the Woodward-Hoffman rules that describe the likelihood of reaction based on arguments about the shapes of orbitals, it is desirable to be able to visualize molecular orbitals.

You can use the semi-empirical and *ab initio* Orbitals dialog box in HyperChem to request a contour plot of any molecular orbital. When requested, the orbital is contoured for a plane that is parallel to the screen and which is specified by a subset selection and a plane offset, as described above. The index of the orbital and its orbital energy (in electron volts, eV) appears in the status line.

If a molecule is rotated by changing the position of the viewer (left mouse button rotation) then the molecule's position in the molecular coordinate system has not changed and another contour plot can be requested without recomputing the wave function. That is, many orbitals can be plotted after a single point *ab initio* or semi-empirical calculation. Any contour map is available without recomputation of the wave function.

When you request an orbital, you also request a plot of either the orbital itself or of its square. The orbital ψ_i is a signed quantity with nodes where the sign changes and the value of the orbital goes to zero. The nodal structure of orbitals has chemical significance. For planar molecules you can distinguish s-orbitals which have non-zero value in the plane of the molecule from π -orbitals which have a node in the plane of the molecule. As energy increases, an orbital generally has more and more nodes. The orbital squared represents the probability distribution function for an electron in the orbital.

When you request an orbital, you can use the cardinal number of the orbital (ordered by energy and starting with number=1) or an offset from either the highest occupied molecular orbital (HOMO) or the lowest unoccupied molecular orbital (LUMO). Offset from the HOMO are negative and from the LUMO are positive. Often these frontier orbitals are the ones of most chemical interest.

Electrostatic Potential

The results of electrostatic potential calculations can be used to predict initial attack positions of protons (or other ions) during a reaction. You can use the Contour Plot dialog box to request a plot of the contour map of the electrostatic potential of a molecular system after you done a semi-empirical or *ab initio* calculation. By definition, the electrostatic potential is calculated using the following expression:

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d\mathbf{r}'$$

The point \mathbf{r} is the position of a positive probe charge. Z_A is the nuclear charge on atom A located at position \mathbf{R}_A . The function $\rho(\mathbf{r}')$ is the electronic density. In the above equation, the first term represents the contribution of the nuclei to the electrostatic potential and the second term is the electronic contribution. Substituting the electron density expression:

$$\rho(\mathbf{r}) = \sum_{\mu\nu} P_{\mu\nu} \phi_\mu(\mathbf{r}) \phi_\nu(\mathbf{r}) \quad (89)$$

into the electrostatic potential expression above, the electrostatic potential can be rewritten as

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \sum_{\mu\nu} P_{\mu\nu} \int \frac{\phi_\mu(\mathbf{r}') \phi_\nu(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d\mathbf{r}' \quad (90)$$

The second summation is over all the orbitals of the system. This equation is used in HyperChem *ab initio* calculations to generate contour plots of electrostatic potential. If we choose the approximation whereby we neglect the effects of the diatomic differential overlap (NDDO), then the electrostatic potential can be rewritten as

$$V(\mathbf{r}) = \sum_A \left[\frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \sum_{\mu\nu}^{\text{on A}} P_{\mu\nu} \int \frac{\phi_\mu(\mathbf{r}') \phi_\nu(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d\mathbf{r}' \right] \quad (91)$$

The second summation of the above is over the orbitals of atom A. HyperChem calculates the electrostatic potential using this last expression for the semi-empirical methods.

Mixed Quantum/Classical Model

You can quickly select a portion of a molecule and then treat that portion quantum mechanically while treating the remaining portion as potential to be included as an external coulomb field in the quantum mechanical calculation. These calculations mix a quantum description (of the selected portion) with a classical (molecular mechanics) description of the point charges on the atoms of the unsettled portion. A complete merger of the two technologies (molecular mechanics and semi-empirical quantum mechanics) is not yet available (for performing molecular dynamics, for example, and having both the classical and quantum portions move); however, you can perform any quantum mechanical calculation on a selected portion of a molecule and have the remaining portion included (as a potential in the one-electron Hamiltonian matrix \mathbf{H}).

Two basic issues must be solved in order to perform such calculations.

- How to decide on or form the boundary between the classical portion and the quantum portion. (Alternatively, you may ask which atoms will be quantum atoms and which will be classical atoms?)
- How to cap the quantum calculation so that there are no dangling electrons or bonds in the quantum mechanical calculation while still preserving the desired effect of the classical portion (which is now there, only in principle!).

Choosing the Classical-Quantum Boundary

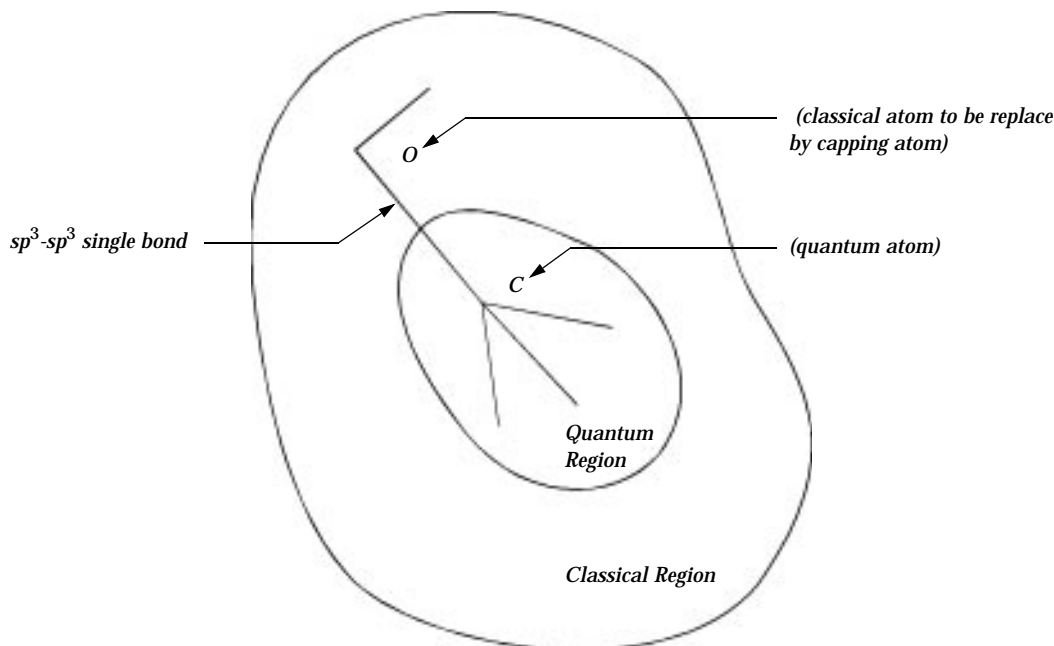
HyperChem assumes that it is easiest for you to just use subset selection to select that portion of the molecular system that is to be treated quantum mechanically. You can then extend the initial selection to form a convenient and universally acceptable boundary. Thus, you make a simple selection of atoms for the first pass at selecting the quantum mechanical portion. The selected atoms are quantum atoms and the unselected atoms are classical atoms.

If you request a semi-empirical quantum mechanical calculation now, HyperChem carries on as well as possible (as described below) in choosing how the atoms for quantum mechanical calculation is capped. If, however, an aromatic benzene ring (with delo-

calized bonds, for example), has partially quantum atoms and partially classical atoms, it may be difficult for HyperChem to create a sensible result, although it will certainly try. A special menu item, Extend to sp^3 , extends the selection outwards until it finds one of the following:

- The end of the molecule. Two atoms not part of the same connected molecule must be in separate molecules. Coming to the end of the molecule means reaching a terminal atom of the molecule such as a mono-coordinated hydrogen or fluorine, a carbonyl oxygen, etc.
- An sp^3 - sp^3 single bond where the outside atom in the bond is not a mono-coordinated terminal atom such as hydrogen or fluorine.

The menu setting results in a boundary between the classical region and the quantum region that is either intermolecular or occurs in the middle of an sp^3 - sp^3 single bond. As described below it will be easy for HyperChem to cap the quantum region if it ends this way.



Because it is desirable to break a peptide this way, some flexibility is required in the rigorous definition of sp^3 - sp^3 single bond. In particular, the dative C_{α} -N bond in the backbone of a peptide is considered to be such a bond since the definition is based on the number of neighbors — four for carbon, three for nitrogen, two for Oxygen, etc. If this were not the case, you couldn't break a protein into classical and quantum regions at all.

Capping Atoms and their Parameters

Having found a place (the sp^3 - sp^3 bond) to establish the boundary between classical atoms and quantum atoms, the next question is how to cap the quantum atoms. Let's first of all look at an illustrative example of the problem.

Consider an Alanine residue in a protein, [... C_{α} —NH—CO— C_{α} H(CH₃)—NH—CO— C_{α} ...]. If you first select, for example, the CH₃ methyl group and requested the extension to sp^3 , the selected quantum atoms would be the fragment [—NH—CO— C_{α} H(CH₃)—]. This fragment has dangling bonds on both ends and prior to performing a quantum mechanical calculation, you

wish to close them off by adding a capping (mono-coordinated) atom. The obvious choice is to add capping hydrogen atoms (H') and perform the quantum mechanical calculation on the closed-shell molecule [NHH'—CO—C_αH(H')(CH₃)].

The principal other consideration, however, is that these capping hydrogen atoms should simulate the effect of the rest of the protein that they replace, including any electronegative (electron withdrawing) or electropositive (electron donating) effects. In particular, the H' atoms should not be normal hydrogen atoms but rather (for a semi-empirical framework) be false capping hydrogen atoms that are parameterized (have their own parameters) to represent these electron withdrawing or donating effects. For example the H' on the right hand end of the fragment above (call it H^N) replaces an electronegative nitrogen and should have its own special parameters while the H' on the left hand end of the fragment above (call it H^C) replaces a relatively electroneutral carbon and should have a different set of parameters yet from the ordinary H or the capping atom H^N.

While these false hydrogen atoms would seem simple and convenient to use for the purposes described, experiments have shown that, having no π -electrons, capping hydrogen atoms leave out one principal effect of the classical atoms they replace — *hyperconjugation*. Hydrogen atoms can only pull or push around s-electrons but a Fluorine, with its p-orbitals, can also pull or push around p-electrons. The bottom line is that you cannot fully simulate the effect of the classical atoms unless you cap the quantum calculation with a false fluorine atom rather than a false hydrogen atom. If you use specially parameterized fluorine atoms, F^C, F^N, F^O, etc. to cap, then the charge distribution of the real system (a quantum calculation on the whole system) is correctly reproduced by a quantum calculation on the truncated system (selected quantum atoms plus capping atoms).

When a selection is used to distinguish a quantum region from a classical region and a subsequent semi-empirical calculation is performed on the quantum region, “phony” halogen atoms are used to cap the quantum region. These pseudo-halogen atoms are either fluorines, chlorines, bromines, or iodines depending on the row of the periodic table represented by the “connecting” atom of the classical portion being replaced by the capping atom. Parameters for pseudo-halogen atoms depend on the connecting atom and are labeled by a negative atomic number in the respective *.abp files.

The parameters for pseudo-halogen atoms have only been determined for a limited number of connecting atoms (C, N, O, Si, P and S) and only for CNDO/INDO methods. If other connecting atoms are tried, HyperChem will usually complain that the orbital exponent for that atom is zero since no parameters are available and the orbital exponent in the relevant *.abp file is zero. The parameters for these capping atoms, where known, are added to the parameter files along with parameters for normal atoms. The parameters, for example for FN, a capping false fluorine atom meant as a replacement for a nitrogen (plus any other atoms attached to the nitrogen) are indicated in the parameter file associated with atomic number -7. Atomic number +7 is used for the normal nitrogen parameters.

Other considerations (such as mixed quantum and classical forces) arise when considering the complete merger of two or more methodologies in the same molecular system, but since they are not yet available in this release of HyperChem they need not be considered here.

Note: The capping atoms are only supported in the semi-empirical quantum mechanics methods in HyperChem. If you want to use the mixed model in the *ab initio* method in HyperChem, you must select an entire molecule or molecules without any boundary atom between the selected and unselected regions and then carry out the calculation.

Supported Methods

HyperChem currently supports one first-principle method (*ab initio* theory), one independent-electron method (extended Hückel theory), and eight semi-empirical SCF methods (CNDO, INDO, MINDO/3, MNDO, AM1, PM3, ZINDO/1, and ZINDO/S). This section gives sufficient details on each method to serve as an introduction to approximate molecular orbital calculations. For further details, the original papers on each method should be consulted, as well as other research literature. References appear in the following sections.

Ab Initio Method

Ab initio methods are characterized by the introduction of an arbitrary basis set for expanding the molecular orbitals and then the explicit calculation of all required integrals involving this basis set.

Ab initio calculations can be performed at the Hartree-Fock level of approximation, equivalent to a self-consistent-field (SCF) calculation, or at a post Hartree-Fock level which includes the effects of correlation — defined to be everything that the Hartree-Fock level of approximation leaves out of a non-relativistic solution to the Schrödinger equation (within the clamped-nuclei Born-Oppenheimer approximation).

HyperChem performs *ab initio* SCF calculations generally. It also can calculate the correlation energy (to be added to the total SCF energy) by a post Hartree-Fock procedure call MP2 that does a Møller-Plesset second-order perturbation calculation. The MP2 procedure is only available for single point calculations and only produces a single number, the MP2 correlation energy, to be added to the total SCF energy at that single point configuration of the nuclei.

HyperChem's *ab initio* calculations solve the Roothaan equations (59) on page 225 without any further approximation apart from the use of a specific finite basis set. Therefore, *ab initio* calculations are generally more accurate than semi-empirical calculations. They certainly involve a more fundamental approach to solving the Schrödinger equation than do semi-empirical methods.

In an *ab initio* method, all the integrals over atomic orbital basis functions are computed and the Fock matrix of the SCF computation is formed (equation (61) on page 225) from the integrals. The Fock matrix divides into two parts: the one-electron Hamiltonian matrix, H , and the two-electron matrix, G , with the matrix elements

$$H_{\mu\nu} = \langle \mu | H^{\text{eff}} | \nu \rangle \quad (92)$$

and

$$G_{\mu\nu} = \sum_{\lambda\sigma} P_{\lambda\sigma} \left[(\mu\nu|\lambda\sigma) - \frac{1}{2}(\mu\lambda|\nu\sigma) \right] \quad (93)$$

respectively.

An *ab initio* calculation involves the calculation of the following types of integrals:

(1) Overlap integrals:

$$S_{\mu\nu} = \langle \mu | \nu \rangle \quad (94)$$

(2) Kinetic energy integrals:

$$T_{\mu\nu} = \langle \mu | \left(-\frac{1}{2} \nabla^2 \right) | \nu \rangle \quad (95)$$

(3) Nuclear-electron attraction energy integrals:

$$V_{\mu\nu} = \langle \mu | \frac{Z_A}{r_A} | \nu \rangle \quad (96)$$

(4) Electron-electron repulsion energy integrals:

$$(\mu\nu | \lambda\sigma) = \langle \mu\nu | \frac{1}{r_{12}} | \lambda\sigma \rangle \quad (97)$$

The first three types of integrals involve one or two centers. The fourth type of integral involves up to four centers.

To this point, the basic approximation is that the total wave function is a single Slater determinant and the resultant expression of the molecular orbitals is a linear combination of atomic orbital basis functions (MO-LCAO). In other words, an *ab initio* calculation can be initiated once a basis for the LCAO is chosen. Mathematically, any set of functions can be a basis for an *ab initio* calculation. However, there are two main things to be considered in the choice of the basis. First one desires to use the most efficient and accurate functions possible, so that the expansion (equation (49) on page 222), will require the fewest possible terms for an accurate representation of a molecular orbital. The second one is the speed of two-electron integral calculation.

The Schrödinger equation for a hydrogen atom has an exact solution for the wave function of the form $\exp(-\alpha r)$. These Slater Type Orbitals (STO) are good basis functions. However, it is very difficult to calculate analytically the requisite multi-center two-electron integrals using STO basis functions. In 1950, S. F. Boys [S. F. Boys, *Proc. Roy. Soc.*, A200, 542 (1950)] proposed using Gaussian functions, which are of the form $\exp(-\alpha r^2)$. With a Gaussian basis set, an MO is expanded as a linear combination of Gaussian Type

Orbitals (GTO). Each GTO is a fixed linear combination (contraction) of Gaussian functions (primitives). These contractions can be chosen, if desired, to have a GTO approximate an STO. The introduction of GTOs greatly simplifies the two-electron integral calculation, because the multi-center integrals involving GTOs can be much more easily computed than integrals involving STOs.

Normalized Primitive Gaussian Functions

A Gaussian function is of the form

$$\exp(-\alpha r_A^2)$$

where α is a constant. Boys introduced the generalized Cartesian Gaussian function,

$$x_A^l y_A^m z_A^n e^{-\alpha r_A^2}$$

for basis functions. Choosing different values of l , m , and n gives different types of Gaussian orbitals. Only the lowest principal quantum number for any symmetry is used. That is, all s orbitals are expanded in $1s$ primitive Gaussians. The normalized GTO primitives are

1s

$$\phi_{1s}^{\text{GF}}(\alpha, r_A) = \left(\frac{2\alpha}{\pi}\right)^{\frac{3}{4}} e^{-\alpha r_A^2} \quad (98)$$

2p_x

$$\phi_{2p_x}^{\text{GF}}(\alpha, r_A) = \left(\frac{128\alpha^5}{\pi^3}\right)^{\frac{1}{4}} x_A e^{-\alpha r_A^2} \quad (99)$$

2p_y

$$\phi_{2p_y}^{\text{GF}}(\alpha, r_A) = \left(\frac{128\alpha^5}{\pi^3}\right)^{\frac{1}{4}} y_A e^{-\alpha r_A^2} \quad (100)$$

2p_z

$$\phi_{2p_z}^{\text{GF}}(\alpha, r_A) = \left(\frac{128\alpha^5}{\pi^3} \right)^{\frac{1}{4}} z_A e^{-\alpha r_A^2} \quad (101)$$

$3d_{xy}$

$$\phi_{3d_{xy}}^{\text{GF}}(\alpha, r_A) = \left(\frac{2048\alpha^7}{\pi^3} \right)^{\frac{1}{4}} x_A y_A e^{-\alpha r_A^2} \quad (102)$$

etc.

Contracted Gaussian Functions

The contracted Gaussian functions are a linear combination of the primitive Gaussian functions. That is,

$$\phi_{\mu}^{\text{CGF}}(r_A) = \sum_{p=1}^L d_{p\mu} \phi_p^{\text{GF}}(\alpha_p, r_A) \quad (103)$$

where α_p and $d_{p\mu}$ are the exponents of the primitives and the contraction coefficients. The contracted basis functions may be chosen to approximate Slater functions, Hartree-Fock atomic orbitals, or any other set of functions desired. Integrals involving such basis functions reduce to the sum of integrals involving the primitive Gaussian functions. Even though many primitive integrals may need to be calculated for each basis function integral, the basis function integrals will be rapidly calculated providing that the method of computing primitive integrals is very fast.

Usually, contractions are determined from atomic SCF calculations. In these calculations one uses a relatively large basis of uncontracted Gaussians, optimizes all exponents, and determines the SCF coefficients of each of the derived atomic orbitals. The optimized exponents and SCF coefficients can then be used to derive suitable contraction exponents and contraction coefficients for a smaller basis set to be used in subsequent molecular calculations.

Minimal Basis Sets: STO-3G

A minimal basis set [W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, 51, 2657 (1969); J. B. Collins, P. V. Schleyer, J. S. Binkley, and J. A. Pople, *J. Chem. Phys.*, 64, 5142 (1976); R. F. Stewart,

J. Chem. Phys., 52, 431 (1970)] is a relatively inexpensive one and can be used for calculations on quite large molecules. It is minimal in the sense of having the smallest number of functions per atom required to describe the occupied atomic orbitals of that atom. This is not exactly true, since one usually considers 1s, 2s, and 2p, i.e., five functions, to construct a minimal basis set for Li and Be, for example, even though the 2p orbital is not occupied in these atoms. The 2sp (2s and 2p), 3sp, 4sp, 3d, ..., etc. orbitals are always lumped together as a “shell”, however. The minimal basis set thus consists of 1 function for H and He, 5 functions for Li to Ne, 9 functions for Na to Ar, 13 functions for K and Ca, 18 functions for Sc to Kr, ..., etc. Because the minimal basis set is so small, it generally can not lead to quantitatively accurate results. It does, however, contain the essentials of chemical bonding and many useful qualitative results can be obtained.

Because of the small number of functions in a minimal basis set, it is particularly important that these functions are of near optimum form. This immediately rules out a single Gaussian function. One would prefer to use Slater functions or functions that closely resemble the known shape of atomic orbitals. A significant advance in minimal basis calculations came with the development of computer programs like “Gaussian 70”, which could reproduce the results of minimal basis Slater orbital calculations using contracted Gaussian functions. The STO-NG method uses a contraction of N primitive Gaussians for each basis function, where the contraction coefficients and exponents are chosen so that the basis functions approximate Slater functions.

In the STO-NG method, the 1s, 2s, and 2p Slater functions are expanded in a set of primitive Gaussians

$$\phi_{1s}^{\text{CGF}}(\zeta = 1.0) = \sum_{i=1}^N d_{i,1s} \phi_{i,1s}^{\text{GF}}(\alpha_{i,1s}) \quad (104)$$

$$\phi_{2s}^{\text{CGF}}(\zeta = 1.0) = \sum_{i=1}^N d_{i,2s} \phi_{i,1s}^{\text{GF}}(\alpha_{i,2sp}) \quad (105)$$

$$\phi_{2p}^{\text{CGF}}(\zeta = 1.0) = \sum_{i=1}^N d_{i,2p} \phi_{i,2p}^{\text{GF}}(\alpha_{i,2sp}) \quad (106)$$

where the contraction coefficients (d's) and exponents (α 's) are to be obtained by a least-squares fit and N is the number of primitive Gaussians, $N = 1, 2, 3, \dots, 6$ corresponding to STO-1G, STO-2G, STO-3G, ..., STO-6G.

One of the unique aspects of the STO-NG method and the fitting procedure is the sharing of contraction exponents in 2sp, 3sp, ..., shells. Thus the exponents in the above three equations are constrained to be identical and the 2s and 2p fits are performed simultaneously. The reason for this constraint is that if 2s and 2p functions have the same exponents, then they have the same radial behavior, and during the radial part of the integral evaluation they can be treated as one function. That is, all integrals involving any sp shell are treated together and one radial integration is sufficient for up to 256 (4^4) separate integrals. This grouping of basis functions by shells with shared exponents leads to considerable efficiency in integral evaluation. The general STO-NG procedure uses contraction lengths up to $N = 6$. However, time spent in integral calculations increases rapidly with the length of the contraction. It has been empirically determined that a contraction of length 3 is sufficient to lead to calculated properties that reproduce essentially all the valence features of a Slater calculation, and STO-3G has become a *de facto* standard for minimal basis calculations.

Once the least-squares fits to Slater functions with orbital exponents $\zeta = 1.0$ are available, fits to Slater functions with other orbital exponents can be obtained by simply multiplying the α 's in the above three equations by ζ^2 . It remains to be determined what Slater orbital exponents ζ to use in electronic structure calculations. The two possibilities may be to use the "best atom" exponents ($\zeta = 1.0$ for H, for example) or to optimize exponents in each calculation. The "best atom" exponents might be a rather poor choice for molecular environments, and optimization of nonlinear exponents is not practical for large molecules, where the dimension of the space to be searched is very large. A compromise is to use a set of standard exponents where the average values of exponents are optimized for a set of small molecules. The recommended STO-3G exponents are

Element	ζ_{1s}	ζ_{2sp}	ζ_{3sp}
H	1.24		
He	1.69		

Element	ζ_{1s}	ζ_{2sp}	ζ_{3sp}
Li	2.69	0.80	
Be	3.68	1.15	
B	4.68	1.50	
C	5.67	1.72	
N	6.67	1.95	
O	7.66	2.25	
F	8.65	2.55	
Ne	9.64	2.88	
Na	10.61	3.48	1.75
Mg	11.59	3.90	1.70
Al	12.56	4.36	1.70
Si	13.53	4.83	1.75
P	14.50	5.31	1.90
S	15.47	5.79	2.05
Cl	16.43	6.26	2.10
Ar	17.40	6.74	2.33
...			

The Slater exponents partially listed in the table above are used for all the STO-NG basis sets. The exponents for all the atoms with atomic numbers less than and equal to 54 are available from HyperChem basis function *.BAS files.

Split-Valence Basis Sets

A minimal basis set has rather limited variational flexibility, particularly if exponents are not optimized. The first step in improving the minimal basis set is so-called split valence [J. S. Binkley, J. A. Pople, and W. J. Hehre, *J. Am. Chem. Soc.*, 102, 939 (1980); M. S. Gordon, J. S. Binkley, J. A. Pople, W. J. Pietro, and W. J. Hehre, *J. Am. Chem. Soc.*, 104, 2797 (1982); W. J. Pietro, M. M. Francl, W. J. Hehre, D. J. Defrees, J. A. Pople, and J. S. Binkley, *J. Am. Chem. Soc.*,

104, 5039 (1982); W. J. Hehre, R. Ditchfield, and J. A. Pople, *J. Chem. Phys.*, 56, 2257 (1972); P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta.*, 28, 213 (1973); M. S. Gordon, *Chem. Phys. Lett.*, 76, 163 (1980); R. Krishnan, J. S. Kinkley, R. Seeger, and J. A. Pople, *J. Chem. Phys.*, 72, 650 (1980); A. D. McLean and G. S. Chandler, *J. Chem. Phys.*, 72, 5639 (1980); T. H. Dunning and P. J. Hay, in *Modern Theoretical Chemistry*, Plenum, New York, 1976] basis set in which two basis functions are used for each valence atomic orbital. Obviously, more computational time is needed by using the split-valence technique than using the minimal basis set for the same molecular system. However, a considerable increase in computational efficiency can be achieved if the exponents of the Gaussian primitives are shared between different basis functions.

At the split-valence level, primitive exponents are shared between s and p functions for the valence shells. In particular, a series of basis sets at the split-valence level has been defined and designated K-LMG where K, L, and M are integers. For the atoms Li to Ne, such a basis consists of an s-type inner-shell function with K primitive Gaussians, an inner set of valence s- and p-type functions with L primitive Gaussians, and another outer sp set with M Gaussians. For the atoms Na to Ar, the basis set consists of an s-type inner-shell with K primitives, an sp-type inner shell functions also with K primitives, an inner set of valence s- and p-type functions with L primitive Gaussians, and another outer sp set with M Gaussians. For hydrogen and helium, only two s-type valence functions (with L and M primitives) are used. The following table lists the KLM values for split-valence basis sets

Basis Set	K	L	M
3-21G	3	2	1
4-21G	4	2	1
6-21G	6	2	1
4-31G	4	3	1
5-31G	5	3	1
6-31G	6	3	1

Thus, the 4-31G basis set consists of 2 functions for H and He, 9 functions for Li to Ne, 13 functions for Na to Ar, ..., etc. For hydrogen the contractions are

$$\phi'_{1s}(r_A) = \sum_{i=1}^3 d'_{i,1s} \phi_{i,1s}^{\text{GF}}(\alpha'_{i,1s}, r_A) \quad (107)$$

and

$$\phi''_{1s}(r_A) = \phi_{i,1s}^{\text{GF}}(\alpha''_{i,1s}, r_A) \quad (108)$$

The outer hydrogen function ϕ''_{1s} is uncontracted and the inner hydrogen function ϕ'_{1s} is a contraction of three primitive Gaussians. The split-valence basis set is not a fit to any particular functional form, but is derived by choosing the form of the contraction and then minimizing the energy of an atomic calculation by varying the contraction coefficients and exponents. The 4-31G acronym implies that the valence basis functions are contractions of three primitive Gaussians (the inner function) and one primitive Gaussian (the outer function), whereas the inner shell functions are contractions of four primitive Gaussians. Hydrogen, of course, does not have inner shells.

For the atoms Li to F, the contractions are

$$\phi_{1s}(r_A) = \sum_{i=1}^4 d_{i,1s} \phi_{i,1s}^{\text{GF}}(\alpha_{i,1s}, r_A) \quad (109)$$

$$\phi'_{2s}(r_A) = \sum_{i=1}^3 d'_{i,2s} \phi_{i,1s}^{\text{GF}}(\alpha'_{i,2sp}, r_A) \quad (110)$$

$$\phi''_{2s}(r_A) = \phi_{i,2s}^{\text{GF}}(\alpha'_{i,2sp}, r_A) \quad (111)$$

$$\phi'_{2p}(r_A) = \sum_{i=1}^3 d'_{i,2p} \phi_{i,2p}^{\text{GF}}(\alpha'_{i,2sp}, r_A) \quad (112)$$

$$\phi''_{2p}(r_A) = \phi_{i,2p}^{\text{GF}}(\alpha''_{i,2sp}, r_A) \quad (113)$$

As in the STO-LG basis, the 2s and 2p functions share the exponents for computational efficiency. The contraction coefficients d_{1s} , d_{2s}' , d_{2s}'' , d_{2p}' , and d_{2p}'' and the contraction exponents α_{1s} , α_{2sp}' , and α_{2sp}'' were explicitly varied until the energy of an atomic SCF calculation reached a minimum. Unlike the STO-NG basis,

which was obtained by a least-squares fit to known functions, or general contraction scheme based on contraction of previously determined uncontracted atomic calculations, the 4-31G basis sets were determined by choosing the specific form [equations (109) to (113)] for the contractions and then optimizing all contraction parameters. That is, the basis set was obtained by contraction first, then optimization, as opposed to optimization first, then contraction.

Since the basis set is obtained from atomic calculations, it is still desirable to scale exponents for the molecular environment. This is accomplished by defining an inner valence scale factor ζ' and an outer valence scale factor ζ'' ("double zeta") and multiplying the corresponding inner and outer α 's by the square of these factors. Only the valence shells are scaled.

The standard 4-31G scale factors are

Element	ζ'	ζ''
H	1.20	1.15
He	1.00	1.00
Li	1.03	1.12
Be	1.03	1.12
B	1.03	1.12
C	1.00	1.04
N	0.99	0.98
O	0.99	0.98
F	1.00	1.00

Polarized Basis Sets

The next step in improving a basis set could be to go to triple zeta, quadruple zeta, etc. If one goes in this direction rather than adding functions of higher angular quantum number, the basis set would not be well balanced. With a large number of s and p functions only, one finds, for example, that the equilibrium geometry of ammonia actually becomes planar. The next step beyond double zeta usually involves adding polarization functions, i.e., adding d-

type functions to the first row atoms Li-F and p-type functions to H.

To see why these are called polarization functions, consider the hydrogen atom. The exact wave function for an isolated hydrogen atom is just the 1s orbital. If the hydrogen atom is placed in a uniform electric field, however, the electron cloud is attracted to the direction of the electric field, and the charge distribution about the nucleus becomes asymmetric. It is polarized. The lowest order solution to this problem is a mixture of the original 1s orbital and a p-type function, i.e., the solution can be considered to be a hybridized orbital. A hydrogen atom in a molecule experiences a similar, but nonuniform, electric field, arising from its nonspherical environment. Adding polarization functions, e.g., p-type functions, to a basis set for H directly accommodates this effect. In a similar way, d-type functions, which are not occupied in the first and second row atoms, play the role of polarization functions for the these atoms.

Using the standard notation, a basis set with a single star (*) stands for adding a d-type function to heavy atoms (atomic numbers greater than 2) and double stars (**) stands for adding d-type functions to heavy atoms and p-type functions to light atoms (H and He). Hence, for example, 6-31G* is the basis set 6-31G plus d-type functions added to all the heavy atoms and 6-31G** is the basis set 6-31G plus d-type functions added to all the heavy atoms and p-type functions added to the light atoms (H and He). These rules apply to all the K-LMG and STO-NG basis sets except that the standard 3-21G* basis set applies d-type functions only to the atoms beyond the first row atoms: that is, there are no d-type functions added to the first row atoms. It has been empirically determined that adding polarization functions to the heavy atoms is more important than adding polarization functions to hydrogen. This is why the first star in a basis set stands for adding d-type functions to the heavy atoms.

The d-type functions used in the conventional STO-NG are Hermite Gaussians. That is, there are five 3d functions — $3d_{3z^2-r^2}$, $3d_{xz}$, $3d_{yz}$, $3d_{x^2-y^2}$, and $3d_{xy}$ (or $3d_0$, $3d_{+1}$, $3d_{-1}$, $3d_{+2}$, and $3d_{-2}$ respectively) for each d-type function. In contrast, the d-type functions used in the conventional split-valence basis sets (L-KMG) are Cartesian Gaussians. That is, there are six 3d functions — $3d_{xx}$, $3d_{yy}$, $3d_{zz}$, $3d_{xy}$, $3d_{xz}$, and $3d_{yz}$ for each d-type function. These six Cartesian Gaussians are linear combinations of the usual five 3d Her-

mit Gaussians and a 3s function ($x^2 + y^2 + z^2$). The d-type functions that are added to a basis to form a star basis are a simple set of uncontracted 3d primitive Gaussians (five Hermite Gaussians) in STO-NG basis sets but Cartesian Gaussians in the split-valence basis sets.

Calculations at the 6-31G* and 6-31G** level provide, in many cases, quantitative results considerably superior to those at the lower STO-3G and 3-21G levels. Even these basis sets, however, have deficiencies that can only be remedied by going to triple zeta (6-311G basis sets in HyperChem) or quadruple zeta, adding more than one set of polarization functions, adding f-type functions to heavy atoms and d-type functions to hydrogen, improving the basis function descriptions of inner shell electrons, etc. As technology improves, it will be possible to use more and more accurate basis sets.

Two-Electron Integrals

In order to form the Fock matrix of an *ab initio* calculation, all the core-Hamiltonian matrix elements, $H_{\mu\nu}$, and two-electron integrals ($\mu\nu|\lambda\sigma$) have to be computed. If the total number of basis functions is m , the total number of the core Hamiltonian matrix elements is

$$N_1 = \frac{1}{2}m(m+1) \quad (114)$$

after considering the symmetry of the core Hamiltonian matrix element, $H_{\mu\nu} = H_{\nu\mu}$; and the total number of the two-electron integrals is

$$N_2 = \frac{1}{8}(m^4 + 2m^3 + 3m^2 + 2m) \quad (115)$$

After considering the symmetry of the two-electron integrals, we have

$$\begin{aligned} (\mu\nu|\lambda\sigma) &= (\nu\mu|\lambda\sigma) = (\nu\mu|\sigma\lambda) = (\mu\nu|\lambda\sigma) \\ &= (\lambda\sigma|\mu\nu) = (\sigma\lambda|\mu\nu) = (\sigma\lambda|\nu\mu) = (\lambda\sigma|\nu\mu) \end{aligned} \quad (116)$$

The total number of two-electron integrals is thus approximately equal to $m^4/8$. For example, for benzene, $N_1 = 666$ and $N_2 = 222,111$ in an STO-3G basis set ($m=36$) and $N_1 = 2,346$ and $N_2 =$

2,753,031 when using a double zeta basis set such as 6-31G (m=68).

Since the total number of two-electron integrals is so large even for a small molecule like benzene, optimal algorithms for computing the two-electron integrals are a major topic in *ab initio* calculations. There are two main concerns for computing the two-electron integrals: first of all, the speed of evaluating the two-electron integrals; second, the method of storing and retrieving the two-electron integrals. J. Pople and co-workers [i.e. see M. H. Gordon and J. A. Pople, *J. Chem. Phys.* 89, 5777 (1988); P. M. W. Gill, M. H. Gordon, and J. A. Pople, *J. Phys. Chem.* 94, 5564 (1990); P. M. W. Gill, B. G. Johnson, and J. A. Pople, *Int. J. Quan. Chem.* 40, 745 (1991)] have developed a series of procedures for computing two-electron integrals.

In an SCF calculation, many iterations may be needed to achieve SCF convergence. In each iteration all the two-electron integrals are retrieved to form a Fock matrix. Fast algorithms to retrieve the two-electrons integrals are important.

Regular Integral Format

For fast access to the two-electron integrals, a four-dimensional array might be straightforward. The four indices of the four dimensional array correspond to the four basis function indices, μ , ν , λ , and σ , respectively. However, the four dimensional array may take a huge main memory or computer disk space even for a medium-size molecule. Therefore, this may not be practical.

An alternate method is to store the values and indices of two-electron integrals. The advantage is that the integrals with zero values or with a value less than a certain threshold can be ignored. However, the disadvantage is that the indices have to be stored as well as the integrals, and these indices take computer main memory or computer disk space. HyperChem uses this method when the user requests the Regular Integral Format.

HyperChem uses 16 bytes (two double-precision words) of storage for each electron repulsion integral. The first 8 bytes save the compressed four indices and the second 8 bytes store the value of the integral. Each index takes 16 bits. Thus the maximum number of basis functions is 65,535. This should satisfy all users of HyperChem for the foreseeable future.

Because of the use of two double-precision words for each integral, HyperChem needs, for example, about 44 MBytes of computer main memory and/or disk space to store the electron repulsion integrals for benzene with a double-zeta 6-31G basis set.

Raffenetti Integral Format

Raffenetti [R. C. Raffenetti, *Chem. Phys. Lett.* 20, 335(1973)] proposed another way to store the two-electron integrals in *ab initio* calculations. Raffenetti rewrote (93) on page 251 to read

$$G_{\mu\nu} = \sum_{\lambda \geq \sigma} P'_{\lambda\sigma} D_{\mu\nu,\lambda\sigma} \quad (117)$$

with the modified density matrix P'

$$P'_{\lambda\sigma} = 4P_{\lambda\sigma} \left(1 - \frac{1}{2}\delta_{\lambda\sigma} \right) \quad (118)$$

and supermatrix D

$$D_{\mu\nu,\lambda\sigma} = \left[(\mu\nu|\lambda\sigma) - \frac{1}{4}(\mu\lambda|\nu\sigma) - \frac{1}{4}(\mu\sigma|\nu\lambda) \right] \left(1 - \frac{1}{2}\delta_{[\mu\nu],[\lambda\sigma]} \right) \quad (119)$$

Obviously,

$$P'_{\lambda\sigma} = P_{\sigma\lambda} \quad (120)$$

and

$$D_{\mu\nu,\lambda\sigma} = D_{\nu\mu,\lambda\sigma} = D_{\mu\nu,\sigma\lambda} = D_{\lambda\sigma,\mu\nu} = \dots \quad (121)$$

So only the two-electron integrals with $\mu \geq \nu$, and $\lambda \geq \sigma$ and $[\mu\nu] \geq [\lambda\sigma]$ need to be computed and stored. $D_{\mu\nu,\lambda\sigma}$ only appears in $G_{\mu\nu}$, and $G_{\nu\mu}$, whereas the original two-electron integrals contribute to other matrix elements as well. So it is much easier to form the Fock matrix by using the supermatrix D and modified density matrix P' than the regular format of the two-electron integrals and standard density matrix.

The Raffenetti integral format emphasizes the speed of computing the Fock matrix.

Two-Electron Integral Cutoff

The total number of two-electron integrals is proportional to m^4 for a molecular system with m basis functions. Some of these integrals may be zero because of the symmetry, and some may be very small in magnitude. Using the regular integral format or the Raffennetti integral format, each integral value and its indices take 16 bytes and all are saved to the computer main memory or disk. All saved two-electron integrals are then used in forming the Fock matrix in every iteration. Those integrals with zero value or with a very small magnitude do not make much contribution to the Fock matrix and to the total energy. Neglecting these integrals may not affect the accuracy of *ab initio* calculations. Thus, in order to save computer main memory or disk space and speed up the calculation of the SCF procedure, a two-electron integral cutoff is introduced. HyperChem uses the two-electron integral cutoff to determine which of the two-electron integrals need to be saved. The value of 10^{-10} (Hartree) generally is good enough for most calculations. A small value is recommended for “tight” calculations and a large value for “loose” calculations.

Direct SCF Calculation

Since the first formulation of the MO-LCAO finite basis approach to molecular Hartree-Fock calculations, computer applications of the method have conventionally been implemented as a two-step process. In the first of these steps a (large) number of integrals — mostly two-electron integrals — are calculated and stored on external storage. The second step then consists of the iterative solution of the Roothaan equations, where the integrals from the first step are read once for every iteration.

In any scheme for performing *ab initio* calculations, the limitations of accuracy, as well as to the size of the system that can be studied are set by the two-electron integrals. Their number is of the order of $m^4 / 8$, where m is the number of basis functions; roughly proportional to the size of the system studied. If only integrals whose magnitude exceeds a certain threshold are considered, the size dependence is asymptotically reduced to $m^2 \log m$ [J. Almlöf, K. Faegri Jr., and K. Korsell, *J. Comp. Chem.* 3, 385 (1982)]. However, in practical applications that threshold must be tightened as large systems are considered, in order to reduce the accumulation of errors. Significant deviation from the m^4 dependence is therefore

only seen for extended systems, and a calculation on a molecule of chemically interesting size may easily require 10^7 to 10^9 integrals even for rather modest basis sets. Such large *ab initio* calculations may not be practical on a small- or medium-size computer.

Direct SCF calculations [J. Almlof, K. Faegri Jr., and K. Korsell, *J. Comp. Chem.* 3, 385 (1982)] offer a solution to this problem by eliminating the storage of two-electron integrals. This can, however, only be done at the expense of having to recompute integrals for every iteration.

With the current impressive CPU and main memory capacity of relatively inexpensive desktop PC's, non-direct SCF *ab initio* calculations involving 300-400 basis functions can be practical. However, to run these kinds of calculation, 20 GBytes of hard disk space might be needed. Such big disk space is unlikely to be available on desktop PCs. A direct SCF calculation can eliminate the need for large disk storage.

Initial Guess of MO Coefficients

In any SCF method, an initial estimate of the MO coefficients is necessary before starting the SCF iterations. Normally, the initial guess to the MO coefficients is obtained by solving the Hartree-Fock Roothaan equations with replacement of the Fock matrix by the core Hamiltonian. The core Hamiltonian gives a reasonable good initial guess in most cases. In some cases, however, the core Hamiltonian gives a wrong order for the energy levels or the initial guess MO coefficients are far from the actual MO coefficients. HyperChem provides alternative methods for generating an initial guess of the MO coefficients. These alternative methods are:

Projected Hückel

HyperChem performs an empirical Hückel calculation to produce the MO coefficients for a minimal basis set and then projects these coefficients to the real basis set used in an *ab initio* calculation. The projected Hückel guess can be applied to molecular systems with an atomic number less than or equal to 54 (Xe).

Projected CNDO/INDO

A projected CNDO/INDO guess uses the computed coefficients from a minimum basis set CNDO/INDO calculation and then

projects these MO coefficients to the real basis set used in an *ab initio* calculation. The projected CNDO/INDO guess can be applied to molecular systems with atomic number less than or equal to 18 (Ar).

Mixed Model

Selection is used for many purposes in HyperChem, normally in a select-operate mode. When a quantum mechanical calculation is requested, either semi-empirical or *ab initio*, selection serves to separate the system into a classical region and a quantum mechanical region (the selected region). HyperChem treats the unselected region of any molecular system as a classical perturbation for the quantum mechanical selected region. The charges in the unselected region form a background of electrostatic potential and perturb the properties of the selected quantum mechanical region. The interaction of the charges in the classical region with the quantum mechanical region are treated correctly by including them in the one-electron core Hamiltonian for the quantum region. The contribution of the charges in the classical region, to the core Hamiltonian, is treated in the following way:

$$\Delta H_{\mu\nu} = \sum_B \langle \mu | \frac{Q_B}{R_{1B}} | \nu \rangle \quad (122)$$

where the sum runs over all the atoms, B, in the unselected region. R_{1B} is the distance between the nucleus of B and the electron, and Q_B is the net charge (the nuclear charge minus the electron charge) on atom B.

Ghost-Atoms

Atoms with an atomic number that is sometimes treated as if it were zero are known as ghost atoms. That is, a ghost atom is non-interacting and has effectively no nucleus or electrons. HyperChem defines a ghost atom in exactly the same way as a regular atom, and any basis set can be applied to a ghost atom. Under most situations ghost-atoms is just the name for a set of atoms (a named selection) and they act as any other atom. When performing an *ab initio* calculation, however, HyperChem may treat ghost atoms differently than regular atoms. A ghost atom is represented by a basis set, but does not have any nuclei attached to it, and

therefore can be regarded as a point in space upon which orbitals can be centered. The concept of ghost atoms can be very useful in avoiding the basis set superposition error (BSSE) when describing a so called “basis set deficient” systems, i.e. systems with relatively large number of electrons represented by relatively poor basis sets. Some long range interactions (i.e. complexes, hydrogen bonding) can be poorly represented without the use of a ghost atom concept. Also ghost atoms provide a convenient way to specify some arbitrary point in molecular space at which one wishes to place basis functions.

In the current version of HyperChem, this option is only available for Single Point calculation.

Extended Hückel Theory

Extended Hückel theory (EHT) is principally attributed to the work of Roald Hoffmann and his collaborators at Cornell University although other groups have certainly contributed to the development. EHT is normally used just as a rapid method for computing molecular orbitals, to investigate the orbital structure of molecules. The energies produced have to be somewhat suspect. For example, optimizing a molecule, i.e., minimizing the energy to predict the structure of the molecule, cannot give satisfactory results and is disallowed in HyperChem.

Since no iterations are involved, it is faster than the semi-empirical SCF methods and no convergence difficulties arise.

Basic Method

Since EHT is an independent-electron method, it is defined by giving formulas for each of the $H_{\mu\nu}$ matrix elements of the effective one-electron Hamiltonian \mathcal{H}^{eff} , described above. Once the matrix \mathbf{H} is available, the molecular orbitals ψ_i and their orbital energies ϵ_i are just solutions of a standard eigenvalue problem $\mathbf{H}\mathbf{C} = \mathbf{S}\mathbf{C}\epsilon$ where \mathbf{C} describes the MO-LCAO coefficients of the molecular orbitals in the atomic orbital basis set:

$$\psi_i = \sum_{\nu} C_{\nu i} \phi_{\nu} \quad (123)$$

and ϵ is a diagonal matrix of the orbital energies. The method thus requires:

- Specification of the atomic orbital basis set $\{\phi_{\mu}\}$.
- Computation of the overlap integrals $S_{\mu\nu}$ in the atomic orbital basis set.
- Specification of the EHT Hamiltonian matrix elements $H_{\mu\nu}$ in the atomic orbital basis set.

Valence Atomic Orbitals

Most simple empirical or semi-empirical molecular orbital methods, including all of those used in HyperChem, neglect inner shell orbitals and electrons and use a *minimal basis set of valence Slater orbitals*.

Thus for H and He, the basis set consists of one orbital, a 1s atomic orbital. For atoms Li to Ne the 2 inner-shell electrons are combined with the nucleus and the basis set consists of 4 orbitals, the 2s, 2p_x, 2p_y, and 2p_z atomic orbitals. This means, for example, that carbon has a nucleus with an effective positive charge of (6-2)=4, not the usual 6. For atoms Na to Al, the 10 inner shell electrons are combined with the nucleus and the basis set consists of the 4 orbitals, the 3s, 3p_x, 3p_y, and 3p_z atomic orbitals. For atoms Si to Cl, there is the question whether to include the 3d orbitals into the basic set as they are close in energy to the 3s and 3p orbitals, but are unoccupied. The standard option of EHT in HyperChem includes the d-orbitals so that the basis set for Si to Cl consists of 9 orbitals, 3s, 3p_x, 3p_y, 3p_z, 3d_{z²}, 3d_{xz}, 3d_{yz}, 3d_{xy}, and 3d_{x²-y²}. An option in the EHT Option dialog box neglects the 3d orbitals to speed up calculations. The standard parameter set, however, is derived assuming 3d orbitals are used.

So called Hydrogenic atomic orbitals (exact solutions for the hydrogen atom) have radial nodes (values of the distance r where the orbital's value goes to zero) that make them somewhat inconvenient for computation. Results are not sensitive to these nodes and most simple calculations use Slater atomic orbitals of the form

$$\phi_{\nu}(x, y, z) = \phi_{\nu}(r, \theta, \varphi) = N_{n,l,m} r^{n-1} e^{-\zeta r} Y_{l,m}(\theta, \varphi) \quad (124)$$

where $N_{n,l,m}$ is a normalization constant, ζ is the orbital exponent and Y is an angular function distinguishing s(l=0) from p(l=1) from d(l=2), etc. A 3p_x orbital, for example, has identical angular behavior to a 2p_x orbital but differs in its radial function

by an extra power of r and its orbital exponent ζ . The orbital exponents are usually common between ns and np orbitals but different for nd . The default orbital exponents of the first three row elements used by HyperChem are shared by s and p orbitals and are

Element	Zeta (s and p)	Zeta (d)
H	1.3	
Li	0.650	
Be	0.975	
B	1.3	
C	1.625	
N	1.950	
O	2.275	
F	2.425	
Na	0.733	
Mg	0.950	
Al	1.167	
Si	1.383	1.383
P	1.600	1.4
S	1.817	1.5
Cl	2.033	2.033

Hamiltonian Matrix Elements

The diagonal matrix elements $H_{\mu\mu}$, for an atomic orbital ϕ_{μ} , can be shown to bear a very close association with the energy needed to ionize (remove) an electron from the orbital. Valence state ionization energies (VSIEs) can be determined from experiment and extended Hückel theory equates $H_{\mu\mu}$ to the corresponding VSIE, with opposite sign:

$$H_{\mu\mu} = -\text{VSIE} \quad (125)$$

The VSIE values of the first three row elements used by HyperChem are shown in the following table.

ELEMENT	S-VSIE	P-VSIE	D-VSIE
H	13.6		
Li	5.4	3.5	
Be	10.0	6.0	
B	15.2	8.5	
C	21.4	11.4	
N	26.0	13.4	
O	32.3	14.8	
F	40.0	18.1	
Na	5.1	3.0	
Mg	9.0	4.5	
Al	12.3	6.5	
Si	17.3	9.2	6.0
P	18.6	14.0	7.0
S	20.0	13.3	8.0
Cl	30.0	15.0	9.0

The off-diagonal elements of Extended Hückel theory, $H_{\mu\nu}$ ($\mu \neq \nu$) represent the effects of bonding between the atoms and are assumed to be proportional to the overlap, $H_{\mu\nu} \sim S_{\mu\nu}$. An approximation for differential overlap referred to as the Mulliken approximation

$$\phi_{\mu} \phi_{\nu} = S_{\mu\nu} \frac{(\phi_{\mu}^2 + \phi_{\nu}^2)}{2} \quad (126)$$

can be used to estimate the off-diagonal elements

$$H_{\mu\nu} = k S_{\mu\nu} \frac{(H_{\mu\mu} + H_{\nu\nu})}{2} \quad (127)$$

The Hückel constant k has been inserted here as one more adjustable parameter. Note that the integrated form of equation (126) is exact.

Choosing a Hückel Constant

The constant k can be adjusted to give best agreement with experiment. It is found that a good value to use is somewhat larger than would be indicated by the Mulliken approximation and a very standard value used by many groups is:

$$k = 1.75 \quad (128)$$

Alternatively, a slight modification to this formula makes k a function of the specific orbital pair, $k_{\mu\nu}$, rather than identical for each matrix element $H_{\mu\nu}$:

$$k_{\mu\nu} = k + \delta^2 + \delta^4(1 - k) \quad (129)$$

where

$$\delta = (H_{\mu\mu} - H_{\nu\nu}) / (H_{\mu\mu} + H_{\nu\nu}) \quad (130)$$

The derivation of this result introduces a generalization of the Mulliken approximation:

$$\phi_{\mu}\phi_{\nu} = 1/2S_{\mu\nu}((1 + \delta)\phi_{\mu}^2 + (1 - \delta)\phi_{\nu}^2) \quad (131)$$

where the weighting is based on a measure of the relative diffuseness, δ , of ϕ_{μ} and ϕ_{ν} . HyperChem allows you to use a simple constant k or a diffuseness weighted constant $k_{\mu\nu}$.

Mixed Model

In the Extended Hückel approximation, the charges in the unselected part are treated like classical point charges. The correction of these classical charges to the diagonal elements of the Hamiltonian matrix may be written as:

$$\Delta H_{\mu\mu} = -a \sum_j \frac{Q_j}{R_{ij}}$$

and the off-diagonal elements of the Hamiltonian matrix are computed based on the corrected diagonal elements. In this equation, a is a scale factor for the classical-quantum interaction, μ is the μ th atomic orbital belonging to atom i , Q_j is a pure charge on atom j in the classical region, R_{ij} is the distance between atom i in the selected region and atom j in the unselected region, and the sum is over all atoms in the unselected region.

CNDO

HyperChem implements the CNDO method based upon a complete neglect of differential overlap approximation. Specifically, HyperChem implements the CNDO/2 scheme developed by Pople, Segal, and Santry [J. A. Pople, D. P. Santry, and G. A. Segal, *J. Chem. Phys.*, 43, S129 (1965); J. A. Pople and G. A. Segal, *J. Chem. Phys.*, 43, S136 (1965); J. A. Pople and G. A. Segal, *J. Chem. Phys.*, 44, 3289 (1966)]. The method is the simplest of the zero differential overlap (ZDO) methods and generally thought to be the least accurate. The CNDO/1 method, as originally developed, was quickly modified and re-parameterized to CNDO/2, which is the method that has remained in common use for many years.

The CNDO equations

The form of the CNDO/2 equations for the Fock matrix comes from the basic approximation $\phi_\mu \phi_\nu = \delta_{\mu\nu} \phi_\mu \phi_\mu$. This reduces the general two-electron integral $(mn|ls)$ to $(mm|ll)$. However, in order that this approximation have rotational invariance (a calculation must give the same result if a molecule is rotated in the molecular coordinate system) it is necessary to make the further approximation that this last integral is independent of the specific orbital ϕ_μ or ϕ_λ but dependent only on the atom A or atom B that the orbital resides on

$$(\mu\nu|\lambda\sigma) = \delta_{\mu\nu} \delta_{\lambda\sigma} \gamma^{AB} \quad (132)$$

where γ^{AB} is the average electrostatic repulsion between an electron on atom A (in any orbital) and an electron on atom B (in any

orbital). These Coulomb integrals are fundamental to many semi-empirical methods. Sometimes they are computed (using spherical ns atomic orbitals for the mathematical functions) and sometimes they are parameterized to experimental results. In CNDO/2 they are computed.

The elements of the CNDO/2 Fock matrix (for the RHF case) thus become

$$F_{\mu\mu} = H_{\mu\mu} + \left(P_{AA} - \frac{1}{2} P_{\mu\mu} \right) \gamma^{AA} + \sum_{B \neq A} P_{BB} \gamma^{AB} \quad (133)$$

$$F_{\mu\nu} = H_{\mu\nu} - \frac{1}{2} P_{\mu\nu} \gamma^{AB} \quad (134)$$

In a ZDO computation where the overlap matrix is assumed to be the unit matrix, the diagonal elements of the density matrix become occupancy numbers for the atomic orbitals. Thus $P_{\mu\mu}$ is the effective number of electrons occupying atomic orbital ϕ_{μ} . The sum of these numbers over all orbitals on a given atom is the total number of electrons, P_{AA} residing on that atom, in this case atom A. The net atomic charge is then the charge of the nucleus (with collapsed inner shell electrons) Z_A minus P_{AA}

$$q_A = Z_A - P_{AA} = Z_A - \sum_{\mu}^A P_{\mu\mu} \quad (135)$$

It remains to specify the elements of the one-electron core Hamiltonian, $H_{\mu\nu}$, containing the kinetic energy and nuclear attraction integrals.

The diagonal elements of the core Hamiltonian simply represent the energy of an electron in an atomic orbital of the corresponding atom, $U_{\mu\mu}$, plus the attraction of an electron in that atomic orbital (on atom A) for the other nuclei (atoms B),

$$H_{\mu\mu} = U_{\mu\mu} - \sum_{B \neq A} V_{AB} \quad (136)$$

The off-diagonal elements represent the dominant effects of bonding and are set to be proportional to the overlap by a parameter dependent on the two atoms involved in the overlap,

$$H_{\mu\nu} = \beta_{AB}^O S_{\mu\nu} \quad (137)$$

One center overlaps are all zero so that the above describes only two center contributions.

It was found that computed bond lengths were much too short in CNDO/1 because of poor balance between the attractive V_{AB} terms and the repulsive γ^{AB} terms. Good theoretical justification can be made for a further simplification that approximates the nuclear attraction terms V_{AB} as follows,

$$V_{AB} = Z_B \gamma^{AB} \quad (138)$$

This approximation leads to the CNDO/2 scheme. It remains to explore the values of $U_{\mu\mu}$ which are closely related to valence state ionization energies, as in Extended Hückel theory. In the CNDO/1 scheme they were set to just that. The CNDO/2 scheme considers the electron affinity (the process of adding an electron to orbital ϕ_μ) as well as the ionization potential (subtracting an electron) and develops the following expression for $U_{\mu\mu}$

$$U_{\mu\mu} = -\frac{1}{2}(I_\mu + A_\mu) - \left(Z_A - \frac{1}{2}\right) \gamma^{AA} \quad (139)$$

where I_μ is the ionization potential of an electron in atomic orbital ϕ_μ , A_μ is the electron affinity of the same orbital (determined by adding an electron to the ionized atom) and the average of the two is a measure of the chemical concept, *electronegativity*.

The final expressions for the (UHF) Fock matrices are

$$F_{\mu\mu}^\alpha = -\frac{1}{2}(I_\mu + A_\mu) \quad (140)$$

$$+ \left[(P_{AA} - Z_A) - \left(P_{\mu\mu}^\alpha - \frac{1}{2} \right) \right] \gamma^{AA} + \sum_{B \neq A} (P_{BB} - Z_B) \gamma^{AB}$$

$$F_{\mu\nu}^\alpha = \beta_{AB}^0 S_{\mu\nu} - P_{\mu\nu}^\alpha \gamma^{AB} \quad (141)$$

The RHF form of these equations simply substitutes $\mathbf{P}^T = 1/2 \mathbf{P}^\alpha = 1/2 \mathbf{P}^\beta$

The CNDO parameters are discussed below.

Expectation Values

You would normally expect to make the same zero differential overlap (ZDO) approximation in computing expectation values as in deriving the form for the Fock matrices. However, the original authors of the CNDO method found that when considering the dipole moment such a strict ZDO approximation reduces the dipole moment to just the classical value computed from the point charges given by equation (135) on page 274. It is expected, however, that one-center (s, p_x), (s, p_y), or (s, p_z) hybridization terms are significant contributors to the dipole moment and these terms were included by the original CNDO authors. HyperChem continues to include these hybridization terms when computing dipole moments.

Mixed Model (CNDO and INDO)

In the CNDO and INDO level of approximation, the interaction of the charges between the quantum mechanical region and the classical region is treated semi-empirically. The charges appearing in the classical region affects the charge distribution and the energy level of the quantum mechanical region. The contribution of the charges (including the electronic charges and the nuclear charges) in the classical region to the core Hamiltonian is treated in the following way:

$$\Delta H_{\mu\mu} = \sum_B (Z_B - Q_B) \gamma_{AB}$$

$\Delta H_{\mu\mu}$ corrects the core Hamiltonian element, $H_{\mu\mu}$, and

$$\Delta E_N = \sum_{(A, B)} \left(\frac{Z_A Z_B}{R_{AB}} - Z_A Q_B \gamma_{AB} \right)$$

corrects the nuclear-nuclear interaction energy. In these two equations, A is the index for an atom in the quantum region and B for an atom in the classical region, Z_A , is the nuclear charge of atom A with a number of the valence electrons, Q_B is the electronic charge, R_{AB} is the distance between atom A and atom B, and γ_{AB} is the Coulomb interaction of two electrons located on atom A and atom B, respectively:

$$\gamma_{AB} = (\text{nsns} | \text{n}' \text{s}' \text{n}' \text{s})$$

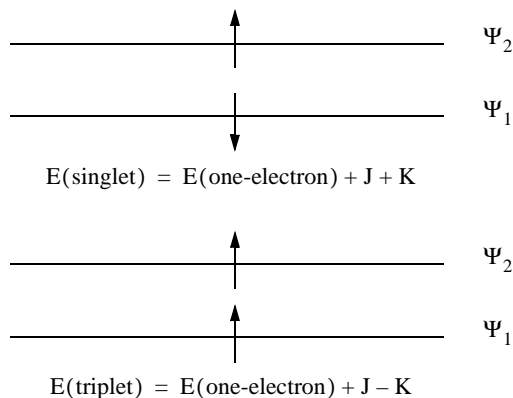
a Coulomb integral of the Slater orbitals. Therefore, in order to run a mixed model at the CNDO and INDO approximation level, HyperChem needs the Slater exponents of s-orbitals for the atoms in the classical region and limits the elements in the classical region to be in the range of H through Xe.

INDO

Exchange Phenomena

The difference between CNDO and INDO is best understood in relation to the phenomenon of exchange, which we briefly describe here.

Consider first of all the problem of two electrons, one occupying orbital ψ_1 and the other occupying a different orbital ψ_2 . The two electrons can have their electron spins parallel or anti-parallel, as shown below. The parallel arrangement leads to a triplet state with total spin $S=1$ and the anti-parallel arrangement leads to a singlet state with total spin $S=0$. The total energy of the two states includes the kinetic energy of the electrons, the attraction of the electrons for any fixed nuclei (these two contributions sum to give the one-electron energy contributions) and electron-electron interactions. In each of the two cases there is a *Coulomb* interaction $J = (\psi_1\psi_1 | \psi_2\psi_2)$ between the two electrons. The difference in energy between the two states, with the triplet having the lower energy, comes from a special quantum mechanical effect called *electron exchange*. Since electrons are all identical, they can be exchanged without changing any observable. That electrons have individual spins, $s=1/2$, results in the quantum mechanical effect that the triplet (parallel spin) arrangement has a lower energy than the singlet (anti-parallel spin) associated with the *exchange* interaction $K = (\psi_1\psi_2 | \psi_1\psi_2)$. The CNDO procedure basically neglects most of these exchange effects leading to a poor treatment of the differences between different spin states of molecules. The INDO procedure restores the major exchange interactions neglected in CNDO theory.



Differences Between INDO and CNDO

The INDO (Intermediate Neglect of Differential Overlap) differs from CNDO in the treatment of one-center exchange integrals. The CNDO (Complete Neglect of Differential Overlap) treatment retains only the two-electron integrals $(\mu\mu|\nu\nu) = \gamma_{\mu\nu}$. The $\gamma_{\mu\nu}$ are atomic Coulomb integrals approximated in CNDO by γ^{AB} . In order to take at least minimal account of exchange phenomena, the INDO procedure restores integrals based on *monatomic differential overlap*. That is, it retains, in addition to the CNDO terms, all integrals $(\mu\nu|\lambda\sigma)$, where the atomic orbitals ϕ_μ , ϕ_ν , ϕ_λ , and ϕ_σ are on the same atom A. In practice, this amounts to adding all one-center exchange integrals $(\mu\nu|\mu\nu)$ as well as distinguishing between different one-center coulomb integrals γ^{AA} .

The one-center exchange integrals that INDO adds to the CNDO scheme can be related to the Slater-Condon parameters F^0 , G^1 , and F^2 used to describe atomic spectra. In particular, for a set of s, p_x , p_y , p_z atomic orbitals, all the one-center integrals are given as:

$$\begin{aligned}
 (ss|ss) &= (ss|xx) = F^0 = \gamma^{AA} \\
 (sx|sx) &= \frac{1}{3}G^1 \\
 (xy|xy) &= \frac{3}{25}F^2
 \end{aligned} \tag{142}$$

$$\langle xx|xx \rangle = F^0 + \frac{4}{25}F^2$$

$$\langle xx|yy \rangle = F^0 - \frac{2}{25}F^2$$

There are similar expressions for symmetry related integrals ($ss|yy$), etc. For direct comparison with CNDO, F^0 is computed as in CNDO. The other INDO parameters, G^1 , and F^2 , are generally obtained [J. I. Slater, *Quantum Theory of Atomic Structure*, McGraw-Hill Book Company, Vol. 1, New York, 1960.] from fits to experimental atomic energy levels, although other sources for these Slater-Condon parameters are available. The parameter file CINDO.ABP contains the values of G^1 and F^2 (columns 9 and 10) in addition to the CNDO parameters.

Spin Interactions in INDO

The advantages of INDO over CNDO involve situations where the spin state and other aspects of electron spin are particularly important. For example, in the diatomic molecule NH, the last two electrons go into a degenerate p-orbital centered solely on the Nitrogen. Two well-defined spectroscopic states, $^3S^-$ and 1D , result. Since the p-orbital is strictly one-center, CNDO results in these two states having exactly the same energy. The INDO method correctly makes the triplet state lower in energy in association with the exchange interaction included in INDO.

A second common example of the utility of INDO over CNDO is the methyl radical CH_3 . This planar molecule is a free radical with an unpaired electron occupying a p-orbital centered on the carbon. The p-orbital is purely a p-orbital with a node in the plane of the molecule; CNDO results in zero spin density at the positions of the carbon and hydrogen nuclei. Electron Spin Resonance (ESR) spectra measure quantities proportional to the spin density at the nucleus and show that it is non-zero (negative) at the position of the hydrogen nucleus. An INDO calculation allows the spin of the unpaired electron to affect the spin distribution in the s-orbitals (because of one-center exchange interactions) and correctly results in negative spin density at the position of the hydrogen nucleus. Obtaining this result requires, in addition to INDO, the use of unrestricted Hartree-Fock (UHF) wave functions, which allow different spatial distributions for electrons of different spins.

While INDO calculations have more parameters and are somewhat more complex than CNDO calculations, they require essentially no extra computation time and in most situations they are superior to CNDO calculations.

MINDO/3

MINDO/3 stands for Modified Intermediate Neglect of Differential Overlap, *version 3*; it is a modification of the INDO method. The method was proposed and developed by M. J. S. Dewar and co-workers at the University of Texas at Austin [N. C. Baird and M. J. S. Dewar, *J. Chem. Phys.*, 50, 1262(1969); M. J. S. Dewar and E. Has-selbach, *J. Am. Chem. Soc.*, 92, 590(1970); M. J. S. Dewar and D. H. Lo, *J. Am. Chem. Soc.*, 94, 5296(1972); R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, 97, 1285(1975); 97, 1302(1975); 97, 1307(1975); 97, 1311(1975)].

Using the same nomenclature as for the INDO approximation, the elements of the MINDO/3 UHF Fock matrix are described below. When ϕ_μ and ϕ_ν are on different centers the off-diagonal elements are

$$F_{\mu\nu}^\alpha = H_{\mu\nu} - P_{\mu\nu}^\alpha(\mu\mu|\nu\nu) \quad (143)$$

(μ on A, ν on B, $A \neq B$)

and when f_m and f_n are on the same center, the off-diagonal elements are

$$F_{\mu\nu}^\alpha = (2P_{\mu\nu}^{\alpha+\beta} - P_{\mu\nu}^\alpha)(\mu\nu|\mu\nu) - P_{\mu\nu}^\alpha(\mu\mu|\nu\nu) \quad (144)$$

(μ on A, ν on A, $\mu \neq \nu$)

The diagonal elements of the Fock matrix are

$$F_{\mu\mu}^\alpha = H_{\mu\mu} + \sum_{\nu}^A (P_{\nu\nu}^{\alpha+\beta}(\mu\mu|\nu\nu) - P_{\nu\nu}^\alpha(\mu\nu|\mu\nu)) \quad (145)$$

$$+ \sum_B \gamma^{AB} \sum_A P_{\lambda\lambda}^{\alpha+\beta} \quad (146)$$

where $\mathbf{P}^T \equiv \mathbf{P}^{\alpha+\beta} \equiv \mathbf{P}^\alpha + \mathbf{P}^\beta$. By replacing the superscripts α and β by β and α , respectively, in the above three equations, you can easily get three similar equations for the Fock matrix elements for beta orbitals. Similar expressions to the above for Fock matrix elements of restricted Hartree-Fock (RHF) calculations can be generated by simply replacing \mathbf{P}^α (or \mathbf{P}^β) by $1/2 \mathbf{P}^T$ in the above equations.

The two-center two-electron, one-center two-electron, two-center one-electron, one-center one-electron, and core-core repulsion integrals involved in the above equations are discussed below.

Two-Center Two-Electron Integrals

All non-zero integrals over atomic orbitals on the two centers are set equal, as in CNDO/INDO, to an averaged γ^{AB} . Thus, $(s_A s_A | s_B s_B) = (s_A s_A | p_B p_B) = (p_A p_A | p_B p_B) = \gamma^{AB}$. The two-center Coulomb integrals, rather than being calculated from first principles using s orbitals as in CNDO/INDO, are approximated by an Ohno-Klopman [K. Ohno, *Theor. Chim. Acta*, 2, 219 (1964); G. Klopman, *J. Amer. Chem. Soc.*, 86, 4550 (1964); 87, 3300 (1965)] relation as follows:

$$\gamma^{AB} = \frac{1}{\left(R_{AB}^2 + \frac{1}{2} \left[\frac{1}{A_A} + \frac{1}{A_B} \right]^2\right)^{1/2}} \quad (147)$$

where A_A and A_B are the averages of the appropriate one center two-electron integrals.

One-Center One-Electron Integral $H_{\mu\mu}$

The one-center one-electron integral $H_{\mu\mu}$ represents the energy that an electron in an atomic orbital ϕ_μ would have if all other valence electrons were removed to infinity. This is calculated by adding to the one-electron energy of the atomic orbital in the fully ionized atom the potential due to all the other nuclei in the system. The one-electron energy is obtained parametrically, and is given by the symbol $U_{\mu\mu}$. $H_{\mu\mu}$ is thus derived from the fundamental equation, identical to that of CNDO/INDO,

$$H_{\mu\mu} = U_{\mu\mu} - \sum_{B \neq A} V_{AB} \quad (148)$$

The core-electron integral, V_{AB} , as in CNDO/INDO, is then equated to the corresponding two-electron integral:

$$V_{AB} = Z_B \gamma^{AB}$$

The one-center integrals, $U_{\mu\mu}$, are computed according to techniques originally developed by Oleari et. al. [L. Oleari, L. DiSipio, and G. De Michelis, *Mol. Phys.*, 10, 97 (1966)].

Two-Center One-Electron Integral $H_{\mu\nu}$ (Resonance Integral)

The two-center one-electron integral $H_{\mu\nu}$, sometimes called the resonance integral, is approximated in MINDO/3 by using the overlap integral, $S_{\mu\nu}$, in a related but slightly different manner to CNDO/INDO as

$$H_{\mu\nu} = S_{\mu\nu} \beta_{AB} (I_\mu + I_\nu) \quad (149)$$

where β_{AB} is a adjustable parameter dependent on the specific element pair (unlike CNDO/INDO where it ends up as an average over the two elements involved), and I_μ and I_ν are the ionization potentials of the atomic orbitals μ and ν on atoms A and B respectively.

One-Center Two-Electron Integral

The one-center two-electron integrals used in MINDO/3 are derived from an analysis of atomic spectra [see, e.g., N. C. Baird and M. J. S. Dewar, *J. Chem. Phys.* 50, 1262(1969)]. Following Pople et al. [J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.*, 47, 2026(1967)], the one-center two-electron integrals are written in terms of the Slater-Condon F^k and G^k parameters exactly as in equation (111) on page 230 for INDO. MINDO/3 uses the values quoted by Pople et al. for G^1 and F^2 , and calculates F^0 for each atom.

Core-Core Repulsion Integrals

From simple electrostatics the core-core repulsion (as used, for example, in CNDO/INDO) is:

$$E_N(A, B) = \frac{Z_A Z_B}{R_{AB}} \quad (150)$$

where Z_A and Z_B are the core charges (nuclear point charges minus inner shell electrons). Since, electron-electron and electron-core integrals do not immediately collapse to the form c/R_{AB} (R_{AB} is the distance of atom A and atom B, c is a constant) for distances beyond the van de Waals radii, there would be a net repulsion between two neutral atoms or molecules. To correct for this, core-core repulsion is approximated by:

$$E_N(A, B) = Z_A Z_B \gamma^{AB} \quad (151)$$

In addition to this term, account must be taken of the decreasing screening of the nucleus by the electrons as the interatomic distance becomes very small. At very small distances the core-core term should approach the classical form. To account for this, an additional term is added to the basic core-core repulsion integral in MINDO/3 to give:

$$E_N(A, B) = Z_A Z_B \left[\gamma^{AB} + \left(\frac{1}{R_{AB}} - \gamma^{AB} \right) \exp(-\alpha_{AB} R_{AB}) \right] \quad (152)$$

Here α_{AB} is a diatomic parameter. In the case of N-H and O-H interactions only, this expression is replaced by:

$$E_N(A, B) = Z_A Z_B \left[\gamma^{AB} + \left(\frac{1}{R_{AB}} - \gamma^{AB} \right) \alpha_{AB} \exp(-R_{AB}) \right] \quad (153)$$

The MINDO/3 parameters appearing in the above equations are discussed later in the parameter section.

Mixed Model

The basic idea of mixed model in MINDO/3 is the same as that used for CNDO and INDO and corrects γ_{AB} , which appears in the core Hamiltonian. Because the algorithm in calculating the Coulomb interaction in MINDO/3 is different from that used in CNDO and INDO, the procedure to correct γ_{AB} is also different from that in CNDO and INDO.

The core Hamiltonian, $H_{\mu\mu}$ correction due to the interaction of charges in the quantum region and classical region is

$$\Delta H_{\mu\mu} = -\sum_B (Z_B - Q_B) \gamma_{AB}$$

and to the interaction energy of the nuclei in the quantum region and the charges in the classical region, E_N , is

$$\Delta E_N = \sum_{(A,B)} \left((Z_A Z_B) \left[\gamma_{AB} + \left(\frac{1}{R_{AB}} - \gamma_{AB} \right) \exp(-\alpha_{AB} R_{AB}) \right] - Z_A Q_B \gamma_{AB} \right)$$

The sum A is over all the atoms in the quantum region and B is over all the atoms in the classical region. The two-electron and two-center Coulomb integral, γ_{AB} , is computed in MINDO/3 by

$$\gamma_{AB} = \frac{1}{\left[R_{AB}^2 + \frac{1}{4} \left(\frac{1}{A_A} + \frac{1}{A_B} \right)^2 \right]^{1/2}}$$

where R_{AB} is the distance between atom A and atom B . A_A and A_B are the averaged one-center, two-electron integral. Therefore, to run the mixed model at the MINDO/3 of approximation, HyperChem requires not only all the parameters for the atoms in the quantum mechanical region, but also the parameters for the pseudo-halogen atoms for the boundary atoms, if any, and some parameters for the atoms in the classical region. The parameters for the atoms in the classical region are A , the averaged one-center two-electron integral and α_{AB} , the bond parameters.

MNDO

MNDO is a Modified Neglect of Diatomic Overlap method based on the neglect of diatomic differential overlap (NDDO) approximation. The method was proposed and developed by M. J. S. Dewar and co-workers at the University of Texas at Austin [e.g. see M. J. S. Dewar and M. L. McKee, *J. Am. Chem. Soc.*, 99, 5231(1977); M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 99, 4899(1977); M. J. S. Dewar and H. S. Rzepa, *J. Am. Chem. Soc.*, 100, 58(1978); L. P. Davis, R. M. Guidry, J. R. Williams, M. J. S. Dewar, and H. S. Rzepa, *J. Comp. Chem.* 2, 433(1981)].

The elements of the MNDO Fock matrix based on the neglect of diatomic differential overlap approximation are described below. When ϕ_μ and ϕ_ν are on different centers the off-diagonal elements of the Fock matrix are:

$$F_{\mu\nu}^\alpha = H_{\mu\nu} - \sum_{\lambda \in A} \sum_{\sigma \in B} P_{\lambda\sigma}^\alpha (\mu\lambda|\nu\sigma) \quad (154)$$

(μ on A, ν on B, $A \neq B$)

and when ϕ_μ and ϕ_ν are different atomic orbitals but on the same center then the off-diagonal elements of the Fock matrix are:

$$F_{\mu\nu}^\alpha = H_{\mu\nu} + P_{\mu\nu}^\alpha [3(\mu\nu|\mu\nu) - (\mu\mu|\nu\nu)] + \sum_{\lambda \in B} \sum_{\sigma \in B} P_{\lambda\sigma}^{\alpha+\beta} (\mu\nu|\lambda\sigma) \quad (155)$$

(μ on A, ν on A, $\mu \neq \nu$)

The diagonal elements of the Fock matrix are:

$$F_{\mu\mu}^\alpha = H_{\mu\mu} + \sum_{\nu \in A} [P_{\nu\nu}^{\alpha+\beta} (\mu\mu|\nu\nu) - P_{\nu\nu}^\alpha (\mu\nu|\mu\nu)] + \sum_{\lambda \in B} \sum_{\sigma \in B} P_{\lambda\sigma}^{\alpha+\beta} (\mu\mu|\lambda\sigma) \quad (156)$$

where $\mathbf{P}^T \equiv \mathbf{P}^{\alpha+\beta} \equiv \mathbf{P}^\alpha + \mathbf{P}^\beta$. By replacing the superscripts α and β by β and α , respectively, in the above three equations, you can easily get three similar equations for the Fock matrix elements for beta orbitals. Similar expressions to the above for Fock matrix elements of restricted Hartree-Fock (RHF) calculations can be generated by simply replacing \mathbf{P}^α (or \mathbf{P}^β) by $-1/2 \mathbf{P}^T$ in the above equations.

The terms involved in the above equations are described below.

Two-Center Two-Electron Integrals

The MNDO method has 22 unique two-center two-electron integrals for each pair of heavy (non-hydrogen) atoms in their local atomic frame. They are:

$$\begin{array}{lll}
 (ss|ss) & (ss|p_{\pi}p_{\pi}) & (ss|p_{\sigma}p_{\sigma}) \\
 (p_{\pi}p_{\pi}|ss) & (p_{\sigma}p_{\sigma}|ss) & (p_{\pi}p_{\pi}|p_{\pi}p_{\pi}) \\
 (p_{\pi}p_{\pi}|p'_{\pi}p'_{\pi}) & (p_{\pi}p_{\pi}|p_{\sigma}p_{\sigma}) & (p_{\sigma}p_{\sigma}|p_{\pi}p_{\pi}) \\
 (p_{\sigma}p_{\sigma}|p_{\sigma}p_{\sigma}) & (sp_{\sigma}|ss) & (sp_{\sigma}|p_{\pi}p_{\pi}) \\
 (sp_{\sigma}|p_{\sigma}p_{\sigma}) & (ss|sp_{\sigma}) & (p_{\pi}p_{\pi}|sp_{\sigma}) \\
 (p_{\sigma}p_{\sigma}|sp_{\sigma}) & (sp_{\pi}|sp_{\pi}) & (sp_{\sigma}|sp_{\sigma}) \\
 (sp_{\pi}|p_{\pi}p_{\pi}) & (p_{\pi}p_{\pi}|sp_{\pi}) & (p_{\pi}p_{\sigma}|p_{\pi}p_{\sigma}) \\
 (p_{\pi}p'_{\pi}|p_{\pi}p'_{\pi}) & &
 \end{array}$$

With the exception of integral 22, $(p_{\pi}p_{\pi}|p_{\pi}p_{\pi})$, all the integrals can be computed *a priori* without loss of rotational invariance. That is, no integral depends on the value of another integral, except for this last one. It can, however, be shown that

$$(p_{\pi}p'_{\pi}|p_{\pi}p'_{\pi}) = \frac{1}{2}[(p_{\pi}p_{\pi}|p_{\pi}p_{\pi}) - (p_{\pi}p_{\pi}|p'_{\pi}p'_{\pi})] \quad (157)$$

The use of this formula for integral 22 gives rotational invariance.

The two-center two-electron repulsion integrals $(\mu\nu|\lambda\sigma)$ represents the energy of interaction between the charge distributions $\phi_{\mu}\phi_{\nu}$ at atom A and $\phi_{\lambda}\phi_{\sigma}$ at atom B. Classically, they are equal to the sum over all interactions between the multipole moments M_{lm} of the two charge contributions, where the subscripts l and m specify the order and orientation of the multipole. MNDO uses the classical model in calculating these two-center two-electron interactions.

The electron density distributions are approximated by a series of point charges. There are four possible types of contributions, i.e.

- Monopole (1 charge): unit negative charge centered on the nucleus.

- Dipole (2 charges): $+1/2$ charge located at position (x, y, z) and $-1/2$ charge located at position $(-x, -y, -z)$.
- Linear quadrupole (3 charges): $+1/2$ charge located at nucleus and $-1/2$ charge located at positions (x, y, z) and $(-x, -y, -z)$.
- Square quadrupole (4 charges) — four charges of magnitude $+1/4, -1/4, +1/4,$ and $-1/4$ forming a square centered on the nucleus.

The following types of multipole distributions are used to represent the four types of atomic orbital products.

Atomic orbitals	Multipole distribution	Number of charges
$ ss\rangle$	Monopole	1
$ sp\rangle$	Dipole	2
$ pp\rangle$	Monopole plus linear quadrupole	4
$ pp'\rangle$	Square quadrupole	4

Each two-electron integral is the sum of all the terms arising from the charge distribution representative of the first pair of atomic orbitals interacting with the charge distribution representative of the second pair of atomic orbitals. Thus in the simplest case, the $(ss|ss)$ interaction is represented by the repulsion of two monopoles, while a $(p_\pi p_\pi | p'_\pi p'_\pi)$, a much more complicated interaction, is represented by 16 separate terms, arising from the four charges representing the monopole and linear quadrupole on one center interacting with the equivalent set on the second center.

Because the repulsion interaction energy of two point charges is inversely proportional to the distance separating the two charges, Dewar and co-workers, for example, represent the $(ss|ss)$ two-center two-electron integral by:

$$(ss|ss) = \frac{1}{\left((R + c_A + c_B)^2 + \frac{1}{4} \left(\frac{1}{A_A} + \frac{1}{A_B} \right)^2 \right)^{1/2}} \quad (158)$$

where A_A and A_B are parameters to be defined below and c_A and c_B are distances of the multipole charges from their respective nuclei

A and B (a simple function of the atomic orbital type). In the case of an sp product, this is a vector of length D_1 atomic units pointing along p axis,

$$D_1 = \frac{(2n+1)(4\zeta_s\zeta_p)^{n+1/2}}{3^{1/2}(\zeta_s + \zeta_p)^{2n+2}} \quad (159)$$

where ζ_s and ζ_p are the orbital exponents and n is the principal quantum number, equal to 2 for atoms in the first long row. The corresponding distances of the charges from the nucleus for the linear and square quadrupoles are $2D_2$ and $\sqrt{2}D_2$, respectively, where

$$D_2 = \left(\frac{4n^2 + 6n + 2}{20}\right)^{1/2} \frac{1}{\zeta_p} \quad (160)$$

There are some boundary conditions which can be used to fix parameters A_A and A_B . For example, when the distance between nucleus A and nucleus B approaches zero, i.e., $R_{AB} = 0.0$, the value of the two-electron two-center integral should approach that of the corresponding monocentric integral. The MNDO nomenclature for these monocentric integrals is,

$$\begin{aligned} G_{ss} &= (ss|ss) \\ G_{sp} &= (ss|pp) \\ H_{sp} &= (sp|sp) \\ G_{pp} &= (pp|pp) \\ G_{p2} &= (pp|p'p') \\ H_{pp} &= (pp'|pp') \end{aligned} \quad (161)$$

Three cases can be identified:

- A monopole-monopole interaction, where the integral should converge to G_{ss}
- A dipole-dipole interaction, where the integral should converge to H_{sp}
- A quadrupole-quadrupole interaction, where the integral should converge to $H_{pp} = 1/2 (G_{pp} - G_{p2})$

Using the above asymptotic forms of the two-center two-electron integrals, the parameters A_A and A_B can be derived. Certainly, parameter A_A is different for different orbitals even though they reside on the same atom. Dewar used AM to represent the parameter A obtained via G_{ss} , AD to represent the parameter A obtained via H_{sp} , and AQ to represent the parameter A obtained from H_{pp} .

Therefore, the two-center two-electron integral $(ss | ss)$ can be written as:

$$(ss|ss) = \frac{1}{\left(R_{AB}^2 + \frac{1}{2}\left(\frac{1}{AM_A} + \frac{1}{AM_B}\right)^2\right)^{1/2}} \quad (162)$$

Equivalently, $(ss | p_\pi p_\pi)$ can be represented as

$$\begin{aligned} (ss|p_\pi p_\pi) = & \frac{1}{\left(R_{AB}^2 + \frac{1}{2}\left(\frac{1}{AM_A} + \frac{1}{AM_B}\right)^2\right)^{1/2}} \\ & + \frac{1/2}{\left(R_{AB}^2 + (2D_2^B)^2 + \frac{1}{2}\left(\frac{1}{AM_A} + \frac{1}{AQ_B}\right)^2\right)^{1/2}} \\ & - \frac{1/4}{\left(R_{AB}^2 + \frac{1}{4}\left(\frac{1}{AM_A} + \frac{1}{AQ_B}\right)^2\right)^{1/2}} \end{aligned} \quad (163)$$

This last integral is the interaction of a monopole with the sum of a monopole and a linear quadrupole. This gives rise to a total of four terms. However, since the interaction of the monopole with each of two negative charges of the dipole are the same, only three terms remain. The remaining integrals are developed by similar manipulations.

One-Center One-Electron Integral $H_{\mu\mu}$

In the MNDO method, the one-center one-electron integral, $H_{\mu\mu}$, is given by:

$$H_{\mu\mu} = U_{\mu\mu} - \sum_{B \neq A} V_{AB} \quad (164)$$

with V_{AB} approximated in a similar way to before:

$$V_{AB} = Z_B(\mu\mu|ss)$$

where $(\mu\mu|ss)$ is the MNDO generalization of the CNDO/INDO and MINDO/3 two-electron integral γ^{AB} .

Two-Center One-Electron Integral $H_{\mu\nu}$

In the MNDO method the resonance integral, $H_{\mu\nu}$, is proportional to the overlap integral, $S_{\mu\nu}$:

$$H_{\mu\nu} = S_{\mu\nu} \frac{(\beta_\mu + \beta_\nu)}{2} \quad (165)$$

where β_μ and β_ν are adjustable parameters characteristic of atomic orbitals ϕ_μ on atom A and ϕ_ν on atom B. For a given first-row or second-row element, there are at most two different β parameters, i.e., β_s^A for the s-orbital and β_p^A for the p orbital of atom A. This differs from MINDO/3 where N^2 beta parameters are required compared to the $O(N)$ beta parameters needed here.

One-Center Two-Electron Integrals

The one-center two-electron integrals in the MNDO method are derived from experimental data on isolated atoms. Most were obtained from Oleari's work [L. Oleari, L. DiSipio, and G. DeMichellis, *Mol. Phys.*, 10, 97(1977)], but a few were obtained by Dewar using fits to molecular properties.

For each atom there are a maximum of five one-center two-electron integrals, that is $(ss|ss)$, $(ss|pp)$, $(sp|sp)$, $(pp|pp)$, and $(pp|p'p')$, where p and p' are two different p-type atomic orbitals. It has been shown that the extra one-center two-electron integral, $(pp'|pp')$, is related to two of other integrals by

$$(pp'|pp') = \frac{1}{2}[(pp|pp) - (pp|p'p')] \quad (166)$$

If the five independent one-center two-electron integrals are expressed by symbols such as G_{ss} , G_{sp} , defined above, then the Fock matrix element contributions from the one-center two-electron integrals are:

$$F_{ss}^{\alpha} \leftarrow P_{ss}^{\beta} G_{ss} + (P_{px}^{\alpha+\beta} + P_{py}^{\alpha+\beta} + P_{pz}^{\alpha+\beta}) G_{sp} - (P_{px}^{\alpha} + P_{py}^{\alpha} + P_{pz}^{\alpha}) H_{sp} \quad (167)$$

$$F_{sp}^{\alpha} \leftarrow P_{sp}^{\alpha+\beta} H_{sp} - P_{sp}^{\alpha} (H_{sp} + G_{sp}) \quad (168)$$

$$F_{pp}^{\alpha} \leftarrow P_{ss}^{\alpha+\beta} G_{sp} - P_{ss}^{\alpha} H_{sp} + P_{pp}^{\beta} G_{pp} + (P_{p'p'}^{\alpha+\beta} + P_{p''p''}^{\alpha+\beta}) G_{p2} - \frac{1}{2} (P_{p'p'}^{\alpha} + P_{p''p''}^{\alpha}) (G_{pp} - G_{p2}) \quad (169)$$

$$F_{pp'}^{\alpha} \leftarrow P_{pp'}^{\alpha+\beta} (G_{pp} - G_{p2}) - \frac{1}{2} P_{pp'}^{\alpha} (G_{pp} + G_{p2}) \quad (170)$$

where $\mathbf{P}^T \equiv \mathbf{P}^{\alpha+\beta} \equiv \mathbf{P}^{\alpha} + \mathbf{P}^{\beta}$. By replacing the superscripts α and β by β and α , respectively, in the above three equations, you can easily get three similar equations for the Fock matrix elements for beta orbitals. Similar expressions to the above for Fock matrix elements of restricted Hartree-Fock (RHF) calculations can be generated by simply replacing \mathbf{P}^{α} (or \mathbf{P}^{β}) by $1/2 \mathbf{P}^T$ in the above equations.

Core-Core Repulsion Integrals

In practice the MNDO approximation to the screening effect is similar to that of MINDO/3 but has a different functional form:

$$E_N(A, B) = Z_A Z_B (s_A s_A | s_B s_B) \times [1 + \exp(-\alpha_A R_{AB}) + \exp(-\alpha_B R_{AB})] \quad (171)$$

The core-core repulsion integrals are different for O-H and N-H interactions. They are expressed as:

$$E_N(A, H) = Z_A Z_H (s_A s_A | s_H s_H) \times \left(1 + \frac{\exp(-\alpha_A R_{AH})}{R_{AH}} + \exp(-\alpha_H R_{AH}) \right) \quad (172)$$

where a is an adjustable atomic parameter. The numerical values of the a parameter are the same for each element.

Mixed Model (MNDO, AM1, and PM3)

The mixed models used in MNDO, AM1, and PM3, are identical, because all of these three methods are derived based on NDDO. The core Hamiltonian correction due to the interaction of the charges between the quantum mechanical region and the classical region is

$$\Delta H_{\mu\nu} = -\sum_B (Z_B - Q_B) \gamma_{\mu\nu}^{AB}$$

for both μ and ν are on atom A , and $\gamma_{\mu\nu}^{AB}$ is

$$\gamma_{AB} = (\mu_A \nu_A | s_B s_B)$$

and calculated by the MNDO method. And the interaction energy between the nuclei in the quantum mechanical region and the charges (including the nuclear charges and the electronic charges) is

$$\Delta E_N = \sum_{(A,B)} \{ Z_A Z_B (s_A s_A | s_B s_B) \left[1 + \exp(-\alpha_A R_{AB}) + \frac{\exp(-\alpha_A R_{AB})}{R_{AB}} \right] - Z_A Q_B (s_A s_A | s_B s_B) \}$$

with

$$(s_A s_A | s_B s_B) = \frac{1}{\left[R_{AB}^2 + \frac{1}{2} \left(\frac{1}{AM_A} + \frac{1}{AM_B} \right)^2 \right]^{1/2}}$$

where AM are the monopole-monopole interaction parameters.

AM1 and PM3

AM1 (Austin Model 1) is a modified MNDO method proposed and developed by M. J. S. Dewar and co-workers at the University of Texas at Austin [see, e.g., M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 107, 3902(1985); M. J. S. Dewar and K. M. Dieter, *J. Am. Chem. Soc.*, 108, 8075(1986); J. J. P. Stewart, *J. Comp. Aided Mol. Design*, 4, 1(1990)].

PM3, developed by James J.P. Stewart, is a reparameterization of AM1, which is based on the neglect of diatomic differential overlap (NDDO) approximation. NDDO retains all one-center differential overlap terms when Coulomb and exchange integrals are computed. PM3 differs from AM1 only in the values of the parameters. The parameters for PM3 were derived by comparing a much larger number and wider variety of experimental versus computed molecular properties. Typically, nonbonded interactions are less repulsive in PM3 than in AM1. PM3 is primarily used for organic molecules, but is also parameterized for many main group elements.

While MINDO/3 has proved very effective in studies of a wide variety of hydrocarbons [M. J. S. Dewar and H. S. Rzepa, *J. Am. Chem. Soc.*, 99, 7432(1977)], problems arise in the case of molecules containing heteroatoms because of the neglect of one-center differential overlap in the INDO approximation on which MINDO/3 based. The problems are avoided in MNDO but at the expense of other weaknesses [M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 99, 4899(1977); 99, 4907(1977)]. In particular MNDO fails to reproduce hydrogen bonds correctly, gives energies that are too positive for crowded molecules (e.g. neopentane) and too negative for ones containing four-membered rings, and gives activation energies that tend to be too large. Dewar and co-workers found that the reason is because MNDO overestimates the repulsions between atoms at their Van der Waals distance. Hence they modified the core-core repulsion for N-H and O-H interactions to:

$$E_N(A, H) = Z_A Z_H (s_A s_A | s_H s_H) \times \left(1 + \frac{\exp(-\alpha_A R_{AH})}{R_{AH}} + \exp(-\alpha_H R_{AH}) \right) + \left(\frac{Z_A Z_H}{R_{AH}} \right) \times \left(\sum_k a_{kA} \exp[-b_{kA} (R_{AH} - c_{kA})^2] + \sum_k a_{kH} \exp[-b_{kH} (R_{AH} - c_{kH})^2] \right) \quad (173)$$

and for all other interactions to:

$$E_N(A, B) = Z_A Z_B (s_A s_A | s_B s_B) \left[1 + \exp(-\alpha_A R_{AB}) + \exp(-\alpha_B R_{AB}) \right] + \left(\frac{Z_A Z_B}{R_{AB}} \right) \quad (174)$$

$$\left(\sum_k a_{kA} \exp[-b_{kA}(R_{AB} - c_{kA})^2] + \sum_k a_{kB} \exp[-b_{kB}(R_{AB} - c_{kB})^2] \right)$$

Comparing the core-core repulsion of the above two equations with those in the MNDO method, it can be seen that the only difference is in the last term. The extra terms in the AM1 core-core repulsion define spherical Gaussian functions — the a , b , and c are adjustable parameters. AM1 has between two and four Gaussian functions per atom.

These are the only differences between the MNDO and AM1 functional form. Dewar's group regenerated AM1 parameters for the elements H, B, C, N, O, F, Al, Si, P, S, Cl, Zn, Ge, Br, and Sn and found that the main gains in AM1 over MNDO were the ability to reproduce hydrogen bonds and the promise of better activation energies for reactions. AM1 does not significantly change the computation time compared with MNDO.

ZINDO/1

ZINDO/1 is based on a modified version of the intermediate neglect of differential overlap (INDO), which was developed by Michael Zerner of the Quantum Theory Project at the University of Florida. Zerner's original INDO/1 used the Slater orbital exponents with a distance dependence for the first row transition metals only. (See *Theoret. Chim. Acta (Berl.)* **53**, 21-54 (1979).) However, in HyperChem constant orbital exponents are used for all the available elements, as recommended by Anderson, Edwards, and Zerner, *Inorg. Chem.* **25**, 2728-2732, 1986.

As with the other semi-empirical methods, HyperChem's implementation of ZINDO/1 is restricted to spin multiplicities up to a quartet state. ZINDO/1 lets you calculate the energy states in molecules containing transition metals.

HyperChem's implementation of ZINDO/1 has been tested using parameters suggested by references to work done by Zerner on first row transition metals.

The basic equations of ZINDO/1 are the same as those in INDO, except for $U_{\mu\nu}$. Instead of using the electronegativity in INDO, ZINDO/1 uses the ionization potential for computing $U_{\mu\nu}$.

Overlap Weighting Factors

The developers of ZINDO found that the parameters required to reproduce orbital energy orderings and UV spectra are different from those required to reproduce accurate structures by geometry optimization. They introduced a new pair of parameters, called the *overlap weighting factors*, to account for this. These parameters are provided in HyperChem in the Semi-empirical Options dialog box. Their effect is to modify the *resonance integrals* for the off-diagonal elements of the Fock matrix.

In semi-empirical formulations, resonance integrals account for sigma and pi bonding patterns in molecules. These one-electron two-center integrals represent the kinetic energy and electron-nuclear attraction energy associated with a charge distribution that lies between two atoms (overlap distribution). The actual magnitude of the resonance integral is proportional to the overlap integral $S_{\mu\nu}$. There are two general types of atomic orbital overlap: sigma-sigma and pi-pi. Sigma-pi overlap is generally absent due to orthogonality conditions. Adjusting the weights provides a mechanism to adjust the relative contributions of sigma versus pi bonding.

For geometry optimizations and comparison of total energies (which should be carried out with ZINDO/1, not ZINDO/S), both overlap weighting factors (Sigma-Sigma and Pi-Pi) should be set to 1 in the Semi-empirical Options dialog box.

If you use ZINDO/S for spectroscopic investigations and orbital energies, the default values are 1.267 for Sigma-Sigma (Ridley, J.E. and Zerner, M.C. *Theor. Chim. Acta* 42:223, 1976) and 0.640 for Pi-Pi (Bacon, A.D. and Zerner, M.C. *Theor. Chim. Acta* 53:21, 1979). However, several different values for the Pi-Pi overlap weighting factor have been used in the literature. For UV spectra and orbital eigenvalues of organic molecules, 0.585 is commonly used (Del Bene, J. and Jaffe, H.H. *J. Chem. Phys.* 48:1807, 1968; *ibid.*, 4050). For transition-metal complexes, 0.640 has been recommended. If you want to change the number that appears in the Semi-Empirical Options dialog box you could include a script command that sets the value explicitly in your chem.scr initialization script.

Mixed Model

The mixed model used in ZINDO/1 is identical to that used in CNDO and INDO if there is no d-orbital involved in the quantum

mechanical calculation. Once the system involves transition metals, the mixed model is slightly more complex. HyperChem treats the charges in the classical region as the following way:

$$\Delta H_{\mu\mu} = \sum_B (Z_B - Q_B) \gamma_{\mu\mu ss}^{AB}$$

corrects the core Hamiltonian element $H_{\mu\mu}$, and

$$\Delta E_N = \sum_{(A, B)} \left(\frac{Z_A Z_B}{R_{AB}} - Z_A Q_B \gamma_{ss ss}^{AB} \right)$$

corrects the interaction energy between the quantum mechanical nuclei and classical charges. Because the Slater exponent for *s* orbital may be different from the Slater exponent for *d* orbital,

$\gamma_{ss ss}^{AB}$ may not be equal to $\gamma_{dd ss}^{AB}$. To keep the rotational invariance,

four *s* type Slater orbitals are used in calculating $\gamma_{dd ss}^{AB}$ with *d* orbital

Slater exponent for the *s* type Slater orbitals on atom *A* and *s* orbital Slater exponent for the *s* type Slater orbitals on atom *B*.

ZINDO/S

ZINDO/S is an modified INDO method parameterized to reproduce UV visible spectroscopic transitions when used with the CI singles methods. It was developed in the research group of Michael Zerner of the Quantum Theory Project at the University of Florida. As with the other semi-empirical methods, HyperChem's implementation of ZINDO/S is restricted to spin multiplicities of up to a quartet state. Higher spin systems may not be done using HyperChem.

The algorithms in ZINDO/S are almost the same as those in ZINDO/1, except of the one-center two-electron integral, F^0 .

ZINDO/S uses empirical value of F^0 instead of using *ab initio* value in terms of the Slater orbitals.

Mixed Model

ZINDO/S is different from ZINDO/1 because they use different algorithms in computing the Coulomb integrals. Hence the two equations used in the mixed model in ZINDO/1 are also employed

in ZINDO/S. But the Coulomb integrals are computed by the following way:

$$\gamma_{ss}^{AB} = \frac{f_r}{\frac{2f_r}{\gamma_{ss}^A + \gamma_{ss}^B} + R_{AB}}$$

and

$$\gamma_{dd}^{AB} = \frac{f_r}{\frac{2f_r}{\gamma_{ss}^A + \gamma_{ss}^B} + R_{AB}}$$

where f_r is a constant and equal to 1.2 and γ_{ss}^A and γ_{dd}^A are two-electron one-center Coulomb integrals and they are semi-empirical parameters required by the ZINDO/S model.

Chapter 13

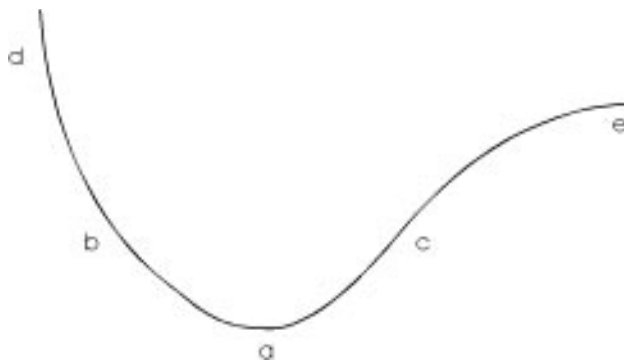
Computational Options

HyperChem provides calculations that explore molecular potential energy surfaces. Indeed, most of computational chemistry relates in one way or another to molecular potential energy surfaces, the topography of the surface and motion on the surface.

Single Points on a Potential Energy Surface

An N -atom molecular system may be described by $3N$ Cartesian coordinates. Six independent coordinates (five for linear molecules, three for a single atom) describe translation and rotation of the system as a whole. The remaining coordinates describe the molecular configuration and the internal structure. Whether you use molecular mechanics, quantum mechanics, or a specific computational method (AMBER, CNDO, etc.), you can ask for the energy of the system at a specified configuration. This is called a single point calculation.

For a diatomic molecule, for example, there is only one internal coordinate and the energy as a function of configuration (internuclear distance) will look something like the following:



A single point calculation at the points b, c, d, or e will give a higher energy, E , than a single point calculation near the minimum at a.

In addition, a single point calculation yields information about the net forces on each atom. If (X_A, Y_A, Z_A) are the Cartesian coordinates of an atom A, then the gradient (force) on atom A has the components, $(\partial E/\partial X_A, \partial E/\partial Y_A, \partial E/\partial Z_A)$. The gradient at position b is positive for one atom and negative for the other atom in the direction of increasing the bond length. The gradient is large at d compared to the gradient at b, which is large compared to the gradient at points near the equilibrium distance a or near the dissociation limit e. Note that the gradient is not only zero at a minimum but at any extreme (maximum, transition state, etc.).

For multi-dimensional potential energy surfaces a convenient measure of the gradient vector is the root-mean-square (RMS) gradient described by

RMS Gradient =

$$(3N)^{-1} \left[\sum_A \left(\left(\frac{\partial E}{\partial X_A} \right)^2 + \left(\frac{\partial E}{\partial Y_A} \right)^2 + \left(\frac{\partial E}{\partial Z_A} \right)^2 \right) \right]^{1/2} \quad (175)$$

For a molecular mechanics calculation the energy and the gradient are essentially the only quantities available from a single point calculation. An analysis of the components of this molecular mechanics energy is placed in the log file for further detail. In the case of MM+, a much more complete description of the individual

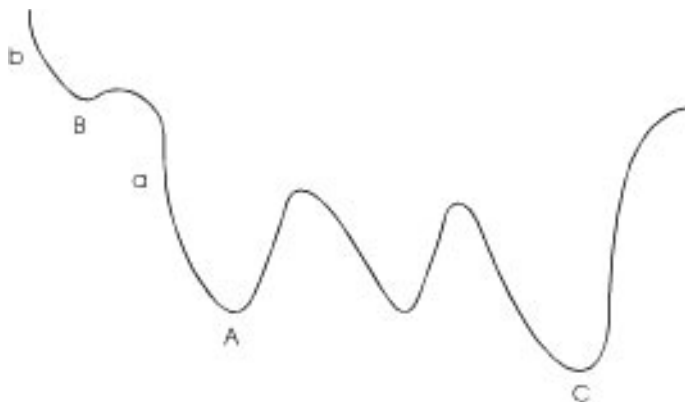
contributions to the energy, including individual stretch energies, bending energies, etc., is placed in the log file along with the system dipole moment, if bond dipoles are available.

For a quantum mechanical calculation, the single point calculation leads to a wave function for the molecular system and considerably more information than just the energy and gradient are available. In principle, any expectation value might be computed. You can get plots of the individual orbitals, the total (or spin) electron density and the electrostatic field around the molecule. You can see the orbital energies in the status line when you plot an orbital. Finally, the log file contains additional information including the dipole moment of the molecule. The level of detail may be controlled by the `PrintLevel` entry in the `chem.ini` file.

Local Minima on a Potential Energy Surface

While you might be interested in knowing the energy or gradient at any arbitrary point on a potential surface, you might be more interested in classifying the extrema of the potential surface. For a simple potential surface as illustrated above, there are two significant points on the surface, the global minimum and the dissociation limit (two isolated atoms). The first describes a stable configuration of this set of atoms and the second is an important configuration if one is studying chemical reactions. Both are desirable configurations to be obtained from an exploration of the potential surface. In this simple case, the dissociation limit can be known beforehand. In more complicated cases it is important to be able to discover configurations that represent dissociation into chemical products. The subject of chemical reactions (one of the two extrema shown above) is described below. Here we are more interested in the possibility of multiple minima on the same potential surface.

A HyperChem optimizer attempts to find extrema on a potential surface. That is, it finds points where all the components of the gradient vector go to zero. For the simple surface above, an optimizer would easily find the stable equilibrium configuration of the diatomic molecule, the only minimum on the surface. It would do this by starting at some initial guess, say point *c*, and iterating until it found point *a*. In more complicated cases, however, the potential surface is not so simple and might be qualitatively represented as something like the following.



This surface has multiple minima (four) with one global minimum. Starting at a is likely to lead to A, while starting at b could lead to B or to A depending on the shallowness of B, the step size, etc. Neither are likely to lead to the global minimum C. This general issue of optimizers leading to local minima rather than global minima is inherent in most procedures. The amount of effort to insure that a minimum is a global minimum is impractical in most problems with many degrees of freedom.

Unconstrained Geometry Optimization

HyperChem has a set of optimizers available to explore potential surfaces. These differ in their generality, convergence properties and computational requirements. One must be somewhat pragmatic about optimization and switch optimizers or restart an optimizer when it encounters specific problems.

A particular problem with many optimizers relates to planar molecules. HyperChem directs optimization to proceed initially along directions associated with the force on an atom. If the starting point for an optimization is rigorously planar there may be no initial forces out of the plane, and optimization will lead only to the optimum planar form, which may or may not be a relevant structure. If this is the case, a slight nudge of any atom perpendicular to the plane will give a non-planar starting point and will lead to a lower energy non-planar structure.

HyperChem includes only unconstrained optimization. That is, given the coordinates $\{ X_A, Y_A, Z_A \}$ of a set of atoms A (the independent variables), it attempts to find a minimum in the energy E

(the objective function) as a function of the coordinates with no constraints on the value of these coordinates. In the process, there is no guarantee that a minimum is obtained rather than a transition state, etc. It is only guaranteed that the first derivatives have all gone to zero. The proper characterization of all extrema requires second derivatives which are not yet available in HyperChem.

HyperChem does not use constrained optimization but it is possible to restrain molecular mechanics and quantum mechanics calculations by adding extra restraining forces.

Optimization Methods

Unconstrained optimization methods [W. H. Press, et. al., *Numerical Recipes: The Art of Scientific Computing*, Cambridge University Press, 1986, Chapter 10] can use values of only the objective function, or of first derivatives of the objective function, second derivatives of the objective function, etc. HyperChem uses first derivative information and, in the Block Diagonal Newton-Raphson case, second derivatives for one atom at a time. HyperChem does not use optimizers that compute the full set of second derivatives (the Hessian) because it is impractical to store the Hessian for macromolecules with thousands of atoms. A future release may make explicit-Hessian methods available for smaller molecules but at this release only methods that store the first derivative information, or the second derivatives of a single atom, are used.

Steepest Descent

Steepest Descent is the simplest method of optimization. The direction of steepest descent, \mathbf{g} , is just the negative of the gradient vector:

$$\mathbf{g} = -\nabla E = -\left(\frac{\partial E}{\partial X_1}, \frac{\partial E}{\partial Y_1}, \frac{\partial E}{\partial Z_1}, \frac{\partial E}{\partial X_2}, \frac{\partial E}{\partial Y_2}, \dots\right) \quad (176)$$

HyperChem uses the steepest descent by steps method. New points are found by:

$$\mathbf{x}_{i+1} = \mathbf{x}_i + \lambda_i \frac{\mathbf{g}_i}{|\mathbf{g}_i|} \quad (177)$$

where the step size λ_i is increased by a factor of 1.2 for the next step if the energy at \mathbf{x}_{i+1} is lower than at \mathbf{x}_i , or decreased by a half if the energy has risen.

The steepest descent by steps method may provide a reasonably good method to begin an optimization when the starting point is far from the minimum. However, it converges slowly near the minimum and it is principally recommended only to initiate optimization when the starting point is particularly bad.

The principal difficulty with steepest descent is that the successive directions of search, $\mathbf{g}_i, \mathbf{g}_{i+1}, \dots$ are not conjugate directions.

Searching along the successive directions of steepest descent might, for example, keep skipping back and forth *across* a long narrow valley. A conjugate direction would be *along* the long narrow valley. Conjugate gradient methods are a considerable improvement over steepest descent methods and involve search down conjugate directions rather than steepest descent directions.

Conjugate Gradient Methods

If you iterate in the steepest descent method, you are recomputing the first derivatives all the time but not essentially looking at how these first derivatives are changing. A better approach would be to use the information on a history of first derivatives to implicitly (or, explicitly, if the Hessian could be stored) gather second derivative information. The basis of conjugate gradient methods is that the history of first derivatives allows a more intelligent search direction than just the direction of steepest descent. These methods search in conjugate gradient directions \mathbf{h}_i rather than simple steepest descent directions \mathbf{g}_i .

Another difference from steepest descent is that a one-dimensional minimization is performed in each search direction. A line minimization is made along a direction \mathbf{h}_i until a minimum energy is found at a new point $i+1$; then the search direction is updated and a search down the new direction \mathbf{h}_{i+1} is made. This is repeated until convergence is obtained. The line minimization method takes increasing steps along the search direction until a minimum in that direction is bracketed. It then interpolates to the minimum of the cubic polynomial fit to the energy and its directional derivative at the bracketing points.

If a surface is quadratic it can be characterized by its Hessian matrix \mathbf{A} of second derivatives of the energy with respect to the Cartesian coordinates of the atoms A, B, ..., i.e. $A_{ij} = \partial^2 E / \partial X_A \partial Y_B$, etc. The conjugate directions are defined as a set of $3N$ search directions having the property that for a quadratic surface a successive search down $3N$ conjugate directions leads to the exact minimum. The conjugate directions are defined by:

$$\mathbf{h}_i \cdot \mathbf{A} \cdot \mathbf{h}_j = 0 \quad (178)$$

Conjugate Gradient methods compute the conjugate directions \mathbf{h}_i by iterative computation involving the gradient \mathbf{g}_i without recourse to computation of second derivatives. The steps in a conjugate gradient minimization are:

1. A starting point is defined and the initial conjugate direction is chosen to be the steepest descent direction, $\mathbf{h}_0 = \mathbf{g}_0$.
2. A line minimization is performed along the conjugate direction \mathbf{h}_i until a minimum is found that defines the next point, where the gradient is re-evaluated as \mathbf{g}_{i+1} . If the RMS gradient is below the convergence threshold the procedure is terminated, otherwise:
3. The conjugate direction is updated according to the formula $\mathbf{h}_{i+1} = \mathbf{g}_{i+1} + \gamma_{i+1} \mathbf{h}_i$ where the coefficient γ_{i+1} is computed from the new and old gradients \mathbf{g}_{i+1} and \mathbf{g}_i . Two slightly different procedures for computing this coefficient are used in HyperChem and the two procedures are referred to as the Fletcher-Reeves method and the Polak-Ribiere method.
4. A return to step 2 is made with the new conjugate direction.

Fletcher-Reeves

This procedure computes the coefficient γ_{i+1} as:

$$\gamma_{i+1} = \frac{\mathbf{g}_{i+1} \cdot \mathbf{g}_{i+1}}{\mathbf{g}_i \cdot \mathbf{g}_i} \quad (179)$$

The conjugate direction is reset to the steepest descent direction every $3N$ search directions or cycles, or if the energy rises between cycles.

Polak-Ribiere

This procedure computes the coefficient \mathbf{g}_{i+1} as:

$$\gamma_{i+1} = \frac{(\mathbf{g}_{i+1} - \mathbf{g}_i) \cdot \mathbf{g}_{i+1}}{\mathbf{g}_i \cdot \mathbf{g}_i} \quad (180)$$

For quadratic functions this is identical to the Fletcher-Reeves formula but there is some evidence that the Polak-Ribiere may be somewhat superior to the Fletcher-Reeves procedure for non-quadratic functions. It is not reset to the steepest descent direction unless the energy has risen between cycles.

Newton-Raphson Methods

The full Newton-Raphson method computes the full Hessian \mathbf{A} of second derivatives and then computes a new guess at the $3N$ coordinate vector \mathbf{x} , according to

$$\mathbf{x}_{i+1} = \mathbf{x}_i + \mathbf{A}^{-1} \cdot \mathbf{g}_i \quad (181)$$

Numerous optimization methods aim at approximating the Hessian (or its inverse) in various ways.

Block Diagonal Newton-Raphson

The block diagonal Newton-Raphson method is an option for MM+ minimizations only. This method derives from Allinger's original MM2 program. It retains diagonal blocks of the Hessian associated with individual atoms and neglects off-diagonal blocks coupling the minimization of two different atoms.

Pragmatically, the procedure considers only one atom at a time, computing the 3×3 Hessian matrix associated with that atom and the 3 components of the gradient for that atom and then inverts the 3×3 matrix and obtains new coordinates for the atom according to the Newton-Raphson formula above. It then goes on to the next atom and moves it in the same way, using first and second derivatives for the second atom that include any previous motion of atoms.

The procedure uses second derivative information and can be quite efficient compared to conjugate gradient methods. However, the neglect of coupling in the Hessian matrix can lead to situations where oscillation is possible. Conjugate gradient methods,

although perhaps slower in reaching a minimum, implicitly involve the full Hessian.

Transition Structures on a Potential Energy Surface

As indicated earlier, potential energy surfaces are usually quite complex, with more than one minimum on the surface. In the illustration above, the potential surface had four minima that were discussed in the geometry optimization section. Between the energy minima there are three transition structures, located at the local maximum energy values along the reaction coordinate path. HyperChem has two methods to locate the transition energy structures: eigenvector following and synchronous transit.

Exploring reaction mechanisms is a major challenge for chemical theory. The geometries of reactants and products may generally be obtained using wide range of spectroscopic methods. The same techniques provide little if any information about connecting pathways. Activation energies, *i.e.*, energies of transition structures relative to reactants, can also be experimentally determined in most cases. Geometries of transition structures, local energy maxima along such reaction pathways, usually can only be hypothesized from theory. Computational methods can also be applied to characterize short-lived reactive intermediates, which correspond to shallow local minima on the potential energy surface. Such reactive intermediates frequently can be determined experimentally, but detailed information about their geometries is usually very difficult to obtain.

Theory can be used to examine any arrangement of atoms in a molecule. A reaction potential surface can be explored to any desired degree, using the same computational methods as for geometry optimization of reactants and products. In theory, it is possible to determine whether or not a given structure corresponds to a local minimum (stable intermediate) or a saddle point (transition structure). Favored reaction pathways can then be obtained as those involving progression from reactants to products over the lowest-energy transition structures.

The success of simple theoretical models in determining the properties of stable molecules may not carry over into reaction pathways. Therefore, *ab initio* calculations with larger basis sets may be more successful in locating transition structures than semi-empirical methods, or even methods using minimal or small basis sets.

Nevertheless, this area is one of the richest fields for chemical theory, with great potential to deepen our understanding of the way chemical reactions occur.

Transition States Search Methods

In HyperChem, two different methods for the location of transition structures are available. Both are the combinations of separate algorithms for the maximum energy search and quasi-Newton methods. The first method is the eigenvector-following method, and the second is the synchronous transit method.

Eigenvector Following Method

HyperChem uses the eigenvector following method described in Baker, J., *J. Comput. Chem.*, **7**, 385-395 (1986), where the details of the procedures can be found.

The eigenvector following algorithm comprises several consecutive steps. First is needed to make an initial guess X of the position of the transition state. The gradient vector \mathbf{g} and the Hessian matrix \mathbf{H} at the initial point are then calculated (or estimated). If analytical second derivatives are available in the calculational method, the exact Hessian can be calculated. For the other wave functions, the Hessian can be estimated by stepping through each variable and doing a finite-difference calculation on the gradient. The second step involves the diagonalization of the Hessian and determination of the local surface characteristics, *i.e.*, the number of negative eigenvalues. Then \mathbf{g} is transformed into the local Hessian modes $\mathbf{F}=\mathbf{Ug}$.

The next step depends on the structure of the Hessian. If the Hessian has the wrong number of negative eigenvalues (more than one) then the next step would be P-RFO step, which involves separation of positive and negative hessian eigenvalues, that gives two matrix equations. If the mode following has been switched on, then eigenvector followed will be saved. The subsequent steps will determine which Hessian mode has the greatest overlap with the eigenvector followed on the previous cycle, and save and follow this mode.

The next step will determine optimization convergence. If the criteria are satisfied, HyperChem will stop at this point, having found the position of the transition state. If convergence criteria are not

satisfied, it will calculate the energy and gradient vector at the new point, provided that maximum number of steps has not been exceeded.

Synchronous Transit Method

HyperChem uses the synchronous transit method described in Peng, C., and Schlegel, H.B., *Israel Journal of Chemistry*, **33**, 449-454 (1993), and the details of the method can be found there.

The synchronous transit method is combined with quasi-Newton methods to find transition states. Quasi-Newton methods are very robust and efficient in finding energy minima. Based solely on local information, there is no unique way of moving uphill from either reactants or products to reach a specific reaction state, since all directions away from a minimum go uphill.

HyperChem has two synchronous transit methods implemented. The linear synchronous transit method (LST) searches for a maximum along a linear path between reactants and products. It may happen that this method will end up with a structure having two or more negative eigenvalues. The quadratic synchronous transit method (QST) is an improvement of LST approach and searches for a maximum along a parabola connecting reactants and products, and for a minimum in all directions perpendicular to the parabola.

Let \mathbf{X} , \mathbf{R} and \mathbf{P} be the coordinates of the current point, the reactants, and products. (Note that it is necessary to evaluate the geometries of the reactants and products using the same method or the same basis set as the one used here to calculate the transition structure). In the linear synchronous transit approach, \mathbf{X} is on a path that is a linear interpolation between \mathbf{R} and \mathbf{P} . The quadratic synchronous transit method uses a curved path through \mathbf{X} , \mathbf{R} and \mathbf{P} . In both cases, a maximum is found along the path. The tangent to the synchronous transit path (LST or QST) is used to guide the optimization to the quadratic region of the transition state. Then the tangent to the path is used to choose the best eigenvector for the ascent direction and the quasi-Newton method is used to complete the optimization. It is also possible to use an eigenvector-following step to complete optimization.

Molecular Dynamics on a Potential Energy Surface

HyperChem uses molecular mechanics or quantum mechanics to compute a potential energy surface. This surface is the energy of a molecular system as a function of the 3N Cartesian coordinates of the N atoms comprising the molecular system. Having obtained such a surface or having a method to determine the energy and its derivatives at any point on the surface, you are in a position to investigate many chemical phenomena.

Reality suggests that a quantum dynamics rather than classical dynamics computation on the surface would be desirable, but much of chemistry is expected to be explainable with classical mechanics only, having derived a potential energy surface with quantum mechanics. This is because we are now only interested in the motion of atoms rather than electrons. Since atoms are much heavier than electrons it is possible to treat their motion classically. Quantum scattering approaches for small systems are available now, but most chemical phenomena is still treated by a classical approach. A chemical reaction or interaction is a classical trajectory on a potential surface. Such treatments leave out phenomena such as tunneling but are still the state of the art in much of computational chemistry.

Temperature

Classical mechanics involves studying motion (trajectories) on the potential surface where the classical kinetic energy equates to the temperature. The relationship is that the average kinetic energy of the N atoms, $\frac{1}{2} N^{-1} \sum_A m_A (v_{xA}^2 + v_{yA}^2 + v_{zA}^2)$ is equated to $\frac{3}{2} kT$, where m_A is the mass of the A^{th} atom, v_{xA} is the x-component of the velocity of the A^{th} atom, k is the Boltzmann constant and T is the temperature. When the number of degrees of freedom in the microscopic system is small, the relationship between the average velocity and the macroscopic temperature may be dubious unless many different configurations of the microscopic system are considered. For example, to study a reaction at a specific temperature requires using a Boltzmann distribution of initial conditions for the reacting (or non-reacting) trajectory.

Statistical Averaging

Statistical mechanics states that the macroscopic values of certain quantities, like the energy, can be obtained by ensemble averaging over a very large number of possible states of the microscopic system. In many realms of chemistry, these statistical averages are what computational chemistry requires for a direct comparison with experiment. A fundamental principle of statistical mechanics, the Ergodic Hypothesis, states that it is possible to replace an ensemble average by a time average over the trajectory of the microscopic system. Molecular dynamics thus allows you to compute a time average over a trajectory that, in principle, represents a macroscopic average value. These time averages are fundamental to the use of molecular dynamics.

Background

This section describes a minimal theoretical background so you can understand the process of creating a classical molecular dynamics trajectory and use it to obtain a visual or statistical result.

Newton's Equations of Motion

A classical molecular dynamics trajectory is simply a set of atoms with initial conditions consisting of the $3N$ Cartesian coordinates of N atoms A (X_A , Y_A , Z_A) and the $3N$ Cartesian velocities (\mathbf{v}_{xA} , \mathbf{v}_{yA} , \mathbf{v}_{zA}) evolving according to Newton's equation of motion:

$$\mathbf{a}_{xA} = d\mathbf{v}_{xA}/dt = (m_A)^{-1}\mathbf{F}_{xA} = (m_A)^{-1}\partial E/\partial X_A \quad (182)$$

where \mathbf{a}_{xA} is the acceleration in the X direction of atom A , and \mathbf{F}_{xA} is the total force in the X direction on atom A arising from all the other atoms.

Leap-frog Algorithm

The leap-frog algorithm uses the simplest central difference formula for a derivative

$$\frac{df}{dt} = \frac{f(t + \Delta t) - f(t - \Delta t)}{2\Delta t} \quad (183)$$

as the basis for a simple iterative scheme to integrate Newton's equations of motion. If $\mathbf{v}_{-1/2}$ is a first guess at a velocity (for the time $t_0 - 1/2\Delta t$) and \mathbf{x}_0 is a position at time t_0 , then by computing first a new velocity, then a new coordinate, then a new velocity, etc., we can integrate as follows:

$$\mathbf{v}_{\frac{1}{2}} = \mathbf{v}_{-\frac{1}{2}} + \mathbf{a}_0\Delta t \quad (184)$$

$$\mathbf{x}_1 = \mathbf{x}_0 + \mathbf{v}_{1/2}\Delta t \quad (185)$$

$$\mathbf{v}_{3/2} = \mathbf{v}_{1/2} + \mathbf{a}_1\Delta t \quad (186)$$

$$\mathbf{x}_2 = \mathbf{x}_1 + \mathbf{v}_{3/2}\Delta t \quad (187)$$

The new coordinates (\mathbf{x}) and accelerations (\mathbf{a}) are computed at integral times and the velocities (\mathbf{v}) at half integral times. The time step Δt entered by the user is the time between evaluations of \mathbf{a} , i.e., $\Delta t = t_1 - t_0$. The temperatures reported at integral times are the averages of the values on either side, determined from $\mathbf{v}_{i+1/2}$ and $\mathbf{v}_{i-1/2}$

Statistical Mechanical Averages

Statistical mechanical averages in a molecular dynamics run are obtained by simply averaging an energetic or structural value over time steps. Thus if the values $\{x_i, i\}$ are being computed in a trajectory, the statistical mechanical average is just

$$\langle x \rangle = \frac{1}{N} \sum_{i=1}^N x_i \quad (188)$$

For purposes of exploring fluctuations and determining the convergence of these statistical averages the root mean square (RMS) deviation in x is also computed:

$$D_x = [\langle x^2 \rangle - \langle x \rangle^2]^{1/2} \quad (189)$$

Random Velocities or Restart Velocities

As described previously, the Leap-frog algorithm for molecular dynamics requires an initial configuration for the atoms and an initial set of velocity vectors $\mathbf{v}_{-1/2}$. These initial velocities can come

from two sources; the status of the HyperChem molecular dynamics Restart check box determines the source of these velocities.

If Restart is not checked then the velocities are randomly assigned in a way that leads to a Maxwell-Boltzmann distribution of velocities. That is, a random number generator assigns velocities according to a Gaussian probability distribution. The velocities are then scaled so that the total kinetic energy is exactly $3/2$ kT where T is the specified starting temperature. After a short period of simulation the velocities evolve into a Maxwell-Boltzmann distribution.

If Restart is checked then the velocities are the existing assigned velocities derived from a previous molecular dynamics simulation or included in the HIN file when it was first read in. You can thus restart a trajectory at exactly the point it was terminated by using the Restart check box.

The Restart check box can be used in conjunction with the explicit editing of a HIN file to assign completely user-specified initial velocities. This may be useful in classical trajectory analysis of chemical reactions where the initial velocities and directions of the reactants are varied to statistically determine the probability of reaction occurring, or not, in the process of calculating a rate constant.

The Basic Phases of a Trajectory

A given molecular dynamics trajectory can be divided into three sequentially-ordered phases:

- Heating
- Running
- Cooling

Any one of these is optional. The running phase is often thought of as first an equilibration phase and then an averaging phase, although HyperChem does not specifically distinguish these two.

The heating phase is used to take a molecular system smoothly from lower temperatures, indicative of a static initial (possibly optimized) structure, to the temperature T at which it is desired to perform the molecular dynamics simulation. The run phase then constitutes a simulation at temperature T. If the heating has been done carefully, it may be possible to skip the equilibration phase

and start collecting statistics immediately. If the heating has been done rapidly, then it may be necessary to run the simulation for an extended period of time to equilibrate the sample fully prior to collecting statistics. The cooling phase is simply to enable simulated annealing as discussed below. Proper heating and equilibration are appropriate to the use of molecular dynamics in studying equilibrium statistical mechanical properties but may not be relevant for certain non-equilibrium studies.

The Fundamental Time Step

Molecular dynamics involves the integration of Newton's equations of motion. To perform this integration, a discrete time step, Δt , must be used. A large value of this fundamental time step will result in inaccurate integration, and a small value will waste computer resources taking very small steps. The appropriate value of the time step is related to the frequency of the motions involved, which are in turn related to the value of force constants and atomic masses. Large force constants and small masses imply high frequency motion and need small time steps to preserve integration accuracy. If too large a time step is used, it is possible to have a basic instability in the equations that results in a molecule blowing apart, i.e. in the molecular coordinates becoming too large, inappropriate, etc.

The time step should be at least an order of magnitude lower than the shortest period of internal motion. If hydrogens are present in a system near room temperature a value of 0.5 femtoseconds (0.0005 ps) is usually appropriate.

Heating and Cooling

If the heating time t_h or cooling time t_c are non-zero, or if the run time t_r is non-zero and constant temperature is selected, velocities are adjusted (rescaled) during the molecular dynamics run to change the temperature of the system.

In the heating phase (assuming t_h is non-zero), the velocities are periodically rescaled to change the system temperature from the initial temperature T_1 to the simulation temperature T_2 in increments of the temperature step ΔT . The heating period for rescaling the velocities, P_h , is defined by:

$$P_h = \frac{t_h}{\Delta t} \times \frac{\Delta T}{|T_2 - T_1|} \quad (190)$$

where Δt is the integration time step. Thus every P_h steps in the heating phase, the current velocities $\mathbf{v}_{i+1/2}$ are rescaled to give velocities $\mathbf{v}'_{i+1/2}$ with the desired temperature T_d :

$$\mathbf{v}'_{i+1/2} = \sqrt{\frac{T_d}{T_{i+1/2}}} \times \mathbf{v}_{i+1/2} \quad (191)$$

where i is the step number and $T_{i+1/2}$ is the temperature corresponding to the velocities $\mathbf{v}_{i+1/2}$ (rather than the temperature reported for step i that is the average of $T_{i-1/2}$ and $T_{i+1/2}$). The scaled velocities $\mathbf{v}'_{i+1/2}$ are used to compute the next set of atomic coordinates. The desired temperature T_d is incremented from T_1 to T_2 in increments of the temperature step ΔT (for the final heat phase rescaling at t_h , T_d is set to T_2). Note that the heating phase may actually be used to cool the system if T_1 is greater than T_2 .

In the cooling phase (assuming t_c is non-zero), the velocities are periodically rescaled to change the system temperature from the run temperature T_2 to the final temperature T_3 in increments of the temperature step ΔT . The cooling period for rescaling the velocities, P_c , is defined by:

$$P_c = \frac{t_c}{\Delta t} \times \frac{\Delta T}{|T_2 - T_3|} \quad (192)$$

where Δt is the integration time step. Thus every P_c steps in the cooling phase the current velocities $\mathbf{v}_{i+1/2}$ are rescaled to give velocities $\mathbf{v}'_{i+1/2}$ with the desired temperature T_d as in the heating phase, except that the desired temperature T_d is changed from T_2 to T_3 , again in increments of the temperature step ΔT (for the final cooling phase, rescaling at $t_h + t_r + t_c$, T_d is set to T_3). Note that the cooling phase may actually be used to heat the system if T_3 is greater than T_2 .

When using the heating and cooling features of HyperChem it should be remembered that it is accomplished through rescaling of the velocities, so if the velocities are zero no temperature can occur. This happens, for example, if you start with an exactly optimized structure and heat from a starting temperature T_1 of zero, or use the restart option when velocities are all zero.

It is also desirable to let the system equilibrate somewhat at each value of T_d . This may be accomplished by increasing the rescaling periods P_h and P_c through a longer cooling time or larger temperature step, though the larger the temperature step, the greater the perturbation to the system when rescaling. A compromise value of ΔT needs to be chosen that allows sufficient equilibration at each temperature but does not unduly perturb the system when rescaling.

Equilibration at a Temperature T

When using molecular dynamics to study equilibrium properties like enthalpy (the average energy), etc., you want the average over a trajectory to be equivalent to an ensemble average. This means the system must be in equilibrium; the initial conditions have been forgotten and you are sampling from a set of phase space configurations representative of the macroscopic equilibrium state. You should not begin sampling for the purpose of collecting statistical averages until this equilibration is performed. The lack of any long term drift is one indication of possible equilibration. To achieve equilibration to a temperature T, it may be necessary to rescale velocities through the use of the constant temperature bath algorithm, (the use of a heating phase with a small temperature step and overall temperature change such as one degree or less) or by re-initializing periodically. Equilibration requires the temperature to fluctuate about the requisite value T.

Naturally, the study of non-equilibrium properties involves different criteria although the equilibrium state and evolution towards the equilibrium state may be important.

Collecting Data

Subsequent to equilibration, averages over the trajectory can be accumulated to describe statistical mechanical properties. For example, to calculate an average bond length, the bond should first be selected, prior to collecting molecular dynamics data or playing back snapshots, and made a named selection with the Select/Name Selection menu item. Then, the named selection should be placed in the Average only or Avg. & graph column of the Molecular Dynamics Averages dialog box invoked by the Averages button of the Molecular Dynamics Options dialog box. A molecular dynamics simulation will then average the bond length. The average may be viewed after the sampling by re-opening the

Molecular Dynamics Averages dialog box and selecting the desired property, so that it is outlined, in the Average only or Avg. & graph column. If a graph was requested, the average appearing here is equivalent to the average over the simulation or playback period.

In deciding the convergence of these averages, the RMS deviation of a value from its average (i.e., Δx) may be a very useful indicator.

Free Dynamics or Constant Temperature Dynamics

If the Constant temperature option has not been selected, HyperChem's molecular dynamics uses constant volume and constant total energy corresponding to a microcanonical ensemble. The temperature then becomes something to be calculated rather than specified (it is used, however, to specify the initial kinetic energy). This is free dynamics. The total energy remains constant but there is a free flow of energy back and forth between the potential energy and the kinetic energy (the temperature). If, initially, the system is far from equilibrium (high potential energy), potential energy is converted to kinetic energy as the trajectory evolves and the temperature rises significantly from the initial temperature. If a molecular dynamics simulation is stopped and started again without the Restart box being checked, a re-equilibration of velocities will be performed and such excess energy purged. The temperature always fluctuates, however, rather than remaining constant, and may continue to drift as the trajectory evolves.

Berendsen *et al.* [H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. di Nola, and J. R. Haak, *J. Chem. Phys.* 81, 3684 (1984)] have described a simple scheme for constant temperature simulations that is implemented in HyperChem. You can use this constant temperature scheme by checking the constant temperature check box and specifying a bath relaxation constant τ . This relaxation constant must be equal to or bigger than the dynamics step size Δt . If it is equal to the step size, the temperature will be kept as close to constant as possible. This occurs, essentially, by rescaling the velocities used to update positions to correspond exactly to the specified initial temperature. For larger values of the relaxation constant, the temperature is kept approximately constant by superimposing a first-order relaxation process on the simulation. That is:

$$\frac{dT}{dt} = \frac{(T_d - T)}{\tau} \quad (193)$$

where T_d is the specified desired temperature. This is accomplished by scaling the velocities every time step during the running phase by

$$v'_{i+1/2} = \sqrt{\left(\frac{T_d}{T_{i+1/2}} - 1\right) \times \frac{\Delta t}{\tau} + 1} \times v_{i+1/2} \quad (194)$$

If the relaxation constant is large there is little effect on a trajectory apart from the long term drift towards fluctuation about T_d , and the reduction of cumulative numerical roundoff error.

Data, Averaging, Snapshot, and Screen Refresh Periods

HyperChem includes a number of time periods associated with a trajectory. These include the basic time step in the integration of Newton's equations plus various multiples of this associated with collecting data, the forming of statistical averages, etc. The fundamental time period is $\Delta t_1 \equiv \Delta t$, the integration *time step* set in the Molecular Dynamics dialog box.

The Data Collection Period

HyperChem runs the molecular dynamics trajectory, averaging and analyzing a trajectory and creating the Cartesian coordinates and velocities. The period for reporting these coordinates and velocities is the data collection period Δt_2 . It is a multiple of the basic time step, $\Delta t_2 = n_2 \Delta t_1$, and is also referred to as a data step. The value n_2 is set in the Molecular Dynamics options dialog box.

The Statistical Averaging Period

You can average and plot various energetic and structural quantities and save the instantaneous values in a file (in comma separated value, or CSV format). The period for such activity is called the Average/graph period Δt_3 . The quantities to be averaged are thus collected at times t_0 , $t_0 + \Delta t_3$, $t_0 + 2\Delta t_3$, etc. The Average/graph period is specified in the Averages dialog box by n_3 data steps, i.e. as a multiple of the data collection period, $\Delta t_3 = n_3 \Delta t_2$.

The Snapshot Collection Period

HyperChem can store a file of snapshots of a trajectory for subsequent analysis. The period for doing so is referred to as the Snap-

shot period Δt_4 . The snapshots are made at times t_0 , $t_0 + \Delta t_4$, $t_0 + 2\Delta t_4$, etc. The Snapshot period is specified in the Snapshot dialog box by n_4 data steps, i.e. as a multiple of the data collection period, $\Delta t_4 = n_4 \Delta t_2$.

The Screen Refresh Period

HyperChem updates the screen during a trajectory at regular intervals so you can visualize the trajectory. Since this screen update may slow down a trajectory if it occurs too frequently, you can specify the duration of the Screen Refresh period Δt_5 . The screen updates at times t_0 , $t_0 + \Delta t_5$, $t_0 + 2\Delta t_5$, etc. The Screen Refresh period is specified in the Molecular Dynamics options dialog box by n_5 data steps, i.e. as a multiple of the data collection period, $\Delta t_5 = n_5 \Delta t_2$.

Averaging Energetic and Structural Data

Statistical mechanical averaging is a fundamental aspect of molecular dynamics. While there may be many reasons for wanting to generate a molecular dynamics trajectory, using it to obtain statistical mechanics averages may be the most common. In the microcanonical ensemble of constant volume and number of particles, the appropriate equilibrium macroscopic average of some variable $x(\mathbf{r})$ depending on the configuration \mathbf{r} of the particles is given by,

$$\langle x \rangle = \left(\frac{1}{Z} \right) \int x(\mathbf{r}) \exp\left(-\frac{V(\mathbf{r})}{kT}\right) d\mathbf{r} \quad (195)$$

where Z is the partition function and $\exp[-V(\mathbf{r})/kT]$ is the Boltzmann factor associated with the potential energy of the configuration \mathbf{r} . By the nature of the ergodic hypothesis, any equilibrium value computed this way can also be computed by a time average from a molecular dynamics trajectory. That is:

$$\langle x \rangle = \frac{1}{N} \sum_{i=1}^N x_i = \frac{1}{N} \sum_{i=1}^N x(\mathbf{r}_i, t_i) \quad (196)$$

where the x_i are the values of x at time step i . In addition to equilibrium values, it is possible to compute dynamic values, like correlation functions, from the molecular dynamics approach. Although HyperChem includes no specific facility for such

dynamic properties, the values stored in the *.csv file or the snapshots of the trajectory in a *.csv file can be used off-line to compute correlation functions.

Averaging Energetic Values

You can request the computation of average values by clicking the Averages button in the Molecular Dynamics Options dialog box to display the Molecular Dynamics Averages dialog box. The energetic quantities that can be averaged appear in the left Selection column. When you select one or more of these energetic quantities (EKIN, EPOT, etc.) and click Add, the quantity moves to the Average Only column on the right. You can move quantities back to the left column by selecting them and clicking Del. Quantities residing in the Average Only column are not plotted but are written to a CSV file and averaged over the molecular dynamics trajectory. If you return to this dialog box after generating the trajectory and select one of the quantities so that the outline appears around it in the Average Only column, the average value over the last trajectory is displayed at the bottom of the column next to the word "Value".

Quantities, which are selected from the Averages Only column and added to the Avg. & graph column, will be written out and averaged, as described above, but will also be plotted on the molecular dynamics graph. To inspect the computed average value, select the quantity so that the outline appears around it and the average is displayed beside Value.

HyperChem allows the computation and display of the potential energy (EPOT), the kinetic energy (EKIN), or the total energy $ETOT = EPOT + EKIN$. The temperature (TEMP) can also be chosen for averaging or plotting but is simply related to EKIN by $EKIN = 3/2 Nk TEMP$.

For free dynamics where the constant temperature check box in the Molecular Dynamics dialog box is not checked, the total energy ETOT should remain constant. A fluctuation of the total energy about its average value of about 1 part in 10^4 is normally considered acceptable. A larger fluctuation, or a drift in the total energy, is symptomatic of an unphysical phase space trajectory, and generally indicates that the time step is too large. In free dynamics, however, the individual kinetic and potential energy contributions to this total energy will fluctuate.

For constant temperature dynamics where the constant temperature check box in the Molecular Dynamics Options dialog box is checked, the energy will not remain constant but will fluctuate as energy is exchanged with the bath. The temperature, depending on the value set for the relaxation constant, will approach constancy.

In addition to the energy quantities E_{KIN} , etc., it is possible to average and plot their standard deviations $D E_{KIN}$, etc. as described below.

Averaging Named Selections

In addition to averaging and plotting energetic values associated with a trajectory, it is possible to average or plot structural quantities. The structural quantities that can be averaged are those that represent 2, 3, or 4-atom structural variables. Monitoring such a value represents a study of diffusion. A 2-atom structural quantity is a distance between atoms; any bonded or nonbonded interatomic distance can be monitored. A 3-atom structural quantity is an angle, and a 4-atom structural quantity is a dihedral angle.

To average or plot a structural quantity, the structural quantity must first be selected and named by the normal process for creating named selections (select the atoms and then use the menu item Select/Name Selection to give the selected atoms a name). From then on the Molecular Dynamics Averages dialog box will show these named selections as possible candidates to be averaged or plotted in addition to energetic quantities described above.

To average a torsion, select the four atoms of the torsion, name the torsion "tor," for example, and then select "tor" as the quantity to be averaged from the Molecular Dynamics Averages dialog box.

Deviations from the Average

In addition to being able to plot simple instantaneous values of a quantity x along a trajectory and reporting the average, $\langle x \rangle$, HyperChem can also report information about the deviation of x from its average value. These RMS deviations may have particular significance in statistical mechanics or just represent the process of convergence of the trajectory values.

If a request for a deviation in a quantity x is made, the instantaneous values that are plotted represent:

$$Dx = [\langle x^2 \rangle_i - \langle x \rangle_i^2]^{1/2} \quad (197)$$

The i subscripts emphasize that the averaging is only up to the current step in the trajectory, not necessarily over the whole trajectory:

$$\langle x \rangle_i = \frac{1}{i} \sum_{j=1}^i x_j \quad (198)$$

The single average value that is reported for this quantity in the Molecular Dynamics averages dialog box is the limit reached by the plotted values at $i=N$, i.e. the RMS value of x :

$$[\langle x^2 \rangle - \langle x \rangle^2]^{1/2} = \langle (x - \langle x \rangle)^2 \rangle = \lim_{i \rightarrow N} Dx \quad (199)$$

In summary, for x , the average value is the average of the plotted values; for Dx the average value is the final value of the plotted values.

The CSV File

When a molecular dynamics average is requested over a trajectory, certain quantities can be plotted as previously described. It is desirable, however, to allow the user to collect a full set of appropriate data values for possible custom use. Since HyperChem is not a full plotting package, it cannot allow you every desired plot. Therefore, HyperChem collects the basic data used for averaging and plotting into a comma-separated-values file, with the extension *.csv*, for general use in other applications. For example, the values can be readily brought into Microsoft Excel and plotted and manipulated in innumerable ways using the convenient plotting and statistical analysis features of Excel.

For every quantity you request to average, a column of the CSV file contains the N values of x_i . These are exactly the values that are plotted, and can be used to create further custom averages. For example, if you were interested in NMR, you might wish to average $\langle r^{-3} \rangle$ for certain internuclear distances r . The instantaneous values of r could be placed in the *chem.csv* file and a spreadsheet program such as Microsoft Excel be used to generate and plot values of r^{-3} and its average over various regions of the trajectory.

Plotting Instantaneous Values Along the Trajectory

Molecular dynamics is essentially a study of the evolution in time of energetic and structural molecular data. The data is often best represented as a graph of a molecular quantity as a function of time. The values to be plotted can be any quantity x that is being averaged over the trajectory, or the standard deviation, Dx . You can create as many as four simultaneous graphs at once.

While you can follow the progress of a trajectory, you cannot get publication quality graphs from HyperChem. You can, however, use the information in the CSV file with other programs for creating graphs for publication.

Obtaining and Understanding MD Graphs

The graph associated with choosing an x is just the sequence of values of x_i as a function of i . The values of i run from $i=0$ to $i=N$ where N is the total number of time steps requested, i.e. the total run time in picoseconds divided by the time increment Δt . The graph appears in a fixed-size window with the total graph (determined by the value of N) scaled to fit the window, if necessary. The plot lines appear only after enough points (the number of points is set by the chem.ini setting DynamicsGraphOnset) have been created to establish an initial vertical scale for the graph. The graph then fills all of the vertical space apart from a single pixel. The vertical scale factor is kept constant unless you explicitly request a rescaling by clicking on the rescale button (or performing the equivalent by pressing the space bar). If no rescaling is performed the plot may go off scale and not be seen until a rescale is performed.

As many as four plots are possible with colors red, green, blue and black. Each plot is scaled independent of the others and the colored labels identify the minimum and maximum of the plot and the name of the quantity being plotted. In addition to the values of x , the RMS deviation in x (Dx) can be plotted. The plot of Dx converges to the RMS deviation of x at the end of the run and represents the current value of the RMS deviation at any point in the plot.

You can request a plot by selecting a quantity from the Averages Only column of the Molecular Dynamics Averages dialog box and passing it to the right (to the Avg. & graph column) by clicking the Add button. Only four quantities can be plotted as indicated by their presence in this last column of the dialog box. A molecular

dynamics run with any quantity in the Avg. & graph column automatically pops up the Molecular Dynamics Results window to show requested plots. This window is of fixed size and cannot be resized, but can be moved or iconized to place it out of the way. It can always be made visible again by double-clicking on the icon. In addition to the plots and their labels, the window contains two buttons, one (Rescale) for rescaling the plot and one (Done) for deciding that plots are to be discontinued. Discontinuing the plotting of values does not terminate the trajectory. If new values are to be plotted, the trajectory must be terminated (by selecting Cancel from the Menu bar or by pressing the `[Esc]` key) and restarted using the restart check box in the Molecular Dynamics Options dialog box. Restarting the trajectory results in no discontinuity in the trajectory but does initiate averaging from scratch. If complete continuity is desired it may be necessary to save the CSV file prior to restart and concatenate individual CSV files.

Placing Graphs into Other Documents

Since the Molecular Dynamics Results window containing plots is a true window, an image of it alone can be captured into the clipboard or a file using Top-level in the File/Preferences/Setup Image dialog box. This captured image, in addition to showing the molecular dynamics plots, shows the Restart and Done buttons, etc. If you only want the plots, you can erase the details of the box with a paint program, such as Microsoft Windows Paintbrush which comes with Microsoft Windows.

Collecting Trajectory for Subsequent Playback

Particularly in the past, molecular dynamics has been batch-oriented where the trajectory is calculated as a one-shot operation requiring large amounts of computer time over a period of months with the trajectory being stored on tape or disk. The trajectory was then analyzed, perhaps many times, in much shorter time frames by reading the trajectory tape. HyperChem, which utilizes faster computers, uses more real-time, interactive molecular dynamics trajectories and averages, allowing a degree of experimentation not possible with a batch approach. Nevertheless, computing a trajectory, particularly for large molecules, can be a very lengthy process; therefore, HyperChem can compute a trajectory for storage and later playback for analysis, visualization, etc.

The molecular dynamics analyzes time steps, also called snapshots (coordinates and velocities), for display, averaging, and plotting (possibly from other applications). In the present release of HyperChem, two particular sources are relevant (the DDE interface allows the possibility of other generators of snapshots as well). The first source are time steps that are computed, displayed, and averaged. This is the normal real-time use of HyperChem molecular dynamics.

The second source of time steps is individual snapshots stored in a snapshot file (*.*snp*) on disk and analyzed later. The limiting rate is determined by disk access times. Thus HyperChem, in addition to the real-time operation of molecular dynamics, allows the playback of molecular dynamics from previously created trajectories (snapshot files). A given snapshot file can be played back over and over again with different aspects of the trajectory being investigated each time. For a large molecule the trajectory might be created overnight, for example, and then analyzed interactively, playing back particular parts of the trajectory, analyzing different structural changes, etc. If you request frequent display of the time steps of a trajectory, the playback speed is limited by the display update time rather than disk speed.

Creating a Snapshot (SNP) file

To create a set of snapshots of any molecular dynamics run, press the Snapshot button of the Molecular Dynamics Options dialog box to bring up the Molecular Dynamics Snapshots dialog box for naming a snapshot file. A snapshot file contains snapshots of the coordinates and velocities of a molecular system along the trajectory. The dialog box allows you to name the file and decide at what frequency to take snapshots. For example, choosing the snapshot period to be two data steps implies that only every other time step is stored in the snapshot file.

These snapshots, created for playback purpose (or for third-party purposes), consist of two components. The first is simply a HIN file that contains the starting configuration for the molecular dynamics run. The name of the snapshot becomes the name of the HIN file. The second component is the actual snapshots of the coordinates (velocities) stored in a SNP file. A snapshot stored as XXX will have a file, xxx.hin, containing the molecular system's starting configuration and a file, xxx.snp, containing the energies, coordinates and velocities of subsequent configurations. The snap-

shot HIN file contains an entry (for example, dynamics c:\hyper\xxx.snp) indicating that there exists a corresponding SNP file. When you read the HIN file it warns you that editing the molecule will invalidate the attached SNP file.

The format of the binary snapshot file is described in the Reference Manual.

Reading a (HIN, SNP) File for Playback

To playback a trajectory that has been stored in a snapshot file you must first read the appropriate HIN file unless you have already saved snapshots with the current system. When reading the HIN file a warning will be issued that the attached SNP file is only valid if the molecular system in the HIN file is not edited in any way. That is, the attached *.snp trajectory applies only to the molecular system as it is currently constituted. Any editing of the molecular system such as deleting an atom, etc. will gray the playback option, making it inaccessible. It is possible, however, to change the view of the system, define new named selections, etc. as long as its atomic information is not altered. You need not decide what structural features you are interested in at the time of creation of the trajectory; you could, for example, name a new torsion angle and average that torsion angle only at playback time, with no need for the torsion to be defined before the snapshot creation.

To playback a trajectory rather than create one, you simply check the playback check box in the Molecular Dynamics Options dialog box. The check box is not available if no SNP file exists (all options of the dialog box that are not relevant to playback are also grayed and show the parameters used in the original creation of the snapshot). Clicking on the Snapshots button brings up a dialog box to set parameters for the playback. In all other regards the molecular dynamics run from playback is identical to a real-time run. Averaging, graphing and visualization of the evolving molecular system can be performed in the same way at playback time as at creation time. Real-time interactive exploration at the creation of a trajectory is appropriate when the trajectory is computed quickly. Exploration at playback time is appropriate when the trajectory is computed slowly instead.

Global Minima on a Potential Energy Surface

The HyperChem optimization algorithms only guarantee that the minimum obtained is a local minimum. The global minimum of the potential energy surface is a desirable point to know but can be impractical to find when there are large numbers of degrees of freedom (large numbers of atoms). Many techniques are available, however, for exploring the surface and finding additional minima. Knowing that one of these additional minima is the global minimum is not easy, however. You could obviously try to find additional minima by using different starting points for a minimization. As shown in the diagram earlier, a potential surface can be very convoluted and different starting points will lead to different minima.

HyperChem has a facility for a more systematic approach to the global minimum than just choosing random starting points. This facility is associated with the idea of simulated annealing.

Simulated Annealing

The basic concept of simulated annealing is to use the temperature and kinetic energy to get over energy barriers between a particular region with a local minimum and a generally lower energy region where the global minimum might exist. The pragmatic procedure involves heating the system to an artificially high temperature, letting molecular dynamics move the system to a more favorable potential energy region, and then letting the system gradually cool down to seek out the lowest energy without getting stuck in shallow local minima. Simulated annealing is described more extensively in the *Practical Guide*.

Simple Reactions on a Potential Energy Surface

The theory of chemical reactions has many facets including elaborate quantum mechanical scattering approaches that treat the kinetic energy of atoms by proper wave mechanical methods. These approaches to chemical reaction theory go far beyond the capabilities of a product like HyperChem as many of the ideas are yet to have wide-spread practical implementations.

Fortunately, the theory of chemical reactions need not always require such sophistication. Indeed, since nuclei (atoms) are much heavier than electrons you can use classical mechanics to under-

stand many chemical reactions. That is, as long as the potential energy surface is computed quantum mechanically, a classical mechanical treatment of motion on this potential surface can provide an adequate treatment of many chemical reactions. This approach is referred to as classical trajectory analysis and is the methodology for HyperChem's molecular dynamics with a potential surface that allows molecules to come apart, i.e., to react. In most molecular mechanics potential surfaces, the potential is such that it describes molecules only near their equilibrium geometry but does not describe dissociation or movement into totally new regions of the potential surface that equate to a chemical reaction occurring. Quantum mechanically calculated surfaces such as those available in HyperChem allow such reactions to be described. Basically HyperChem performs molecular dynamics but allows bonds to break and reform.

Trajectory Analysis

The $F + H - H \rightarrow F-H + H$ reaction is a common example of a reaction easily studied by classical trajectory analysis. The potential surface we are interested in is that for FH_2 . This potential surface may have many extrema. One of them corresponds to an isolated Fluorine atom and a stable H_2 molecule; these are the reactants. Another extremum of the surface corresponds to an isolated hydrogen atom and the stable $H-F$ molecule; these are the products. Depending on how the potential surface was obtained there may or may not be an extremum corresponding to stable H_2F , but at the least you would expect an extremum corresponding to the transition state of the reaction being considered.

The reaction in question can be studied by exploring molecular dynamics on the potential energy surface paying particular attention to trajectories that lead from a region of the potential surface characterizing reactants to a region of the potential surface characterizing products. In the simplest scenario you start with H_2 and an isolated F atom but then shoot the F atom at the H_2 and watch the molecular dynamics trajectory to see what happens. If the trajectory leads to a region of the potential surface representing products, a score for *reaction* is tallied. If the trajectory terminates in a region of the potential surface that still corresponds to $F + H_2$, then a score for *non-reaction* is tallied. By giving the F atom a distribution of initial positions, velocities, and directions corresponding to experimental conditions, and performing the experiment over

and over again, you can calculate the probability that the end result of a trajectory is *react over non-react*, and hence calculate a reaction rate constant. HyperChem includes no particular facilities for setting up these Boltzmann distributions of initial conditions but does allow the exploration of any one particular initial condition. A script or third-party software package interfaced to HyperChem via DDE could, in principle, do a full trajectory analysis by looping over initial conditions and keeping score.

Setting Initial Coordinates and Velocities

To study a particular classical trajectory you must set the initial coordinates and velocities. In the above case of $F + H_2$ you might position an H_2 molecule at the center of the screen, oriented any way you chose, and then place the F atom in the left part of the screen approximately on line with the H_2 molecule. This positioning might be done manually, or by setting the coordinates to specified values, using interactive translation of selected atoms or by actually editing the HIN file. The initial velocities of the two H atoms would probably best be set to values sampled from an isolated H_2 molecule trajectory at the temperature T of the experiment. The velocity of the F atom might then be set to have only a large positive x value, say a few hundred Ångstroms/picosecond so as to come in to the center of the screen from the left and collide with the H_2 molecule causing a reaction or possibly bouncing off without reaction. A variety of these initial conditions correspond to the experimental situation.

Coordinates of atoms can be set by normal translation or rotation of HyperChem molecules. To set initial velocities, however, it is necessary to edit the HIN file explicitly. The unit of velocity in the HIN file is Ångstroms/picosecond. A `react.hin` file and a script `react.scr` are included with HyperChem to illustrate one simple reacting trajectory. In order to have these initial velocities used in a trajectory the Restart check box of the Molecular Dynamics Options dialog box must be checked. If it is not, the initial velocities in the HIN file will be ignored and a re-equilibration to the temperature T of the Molecular Dynamics Options dialog box will occur. This destroys any imposed initial conditions on the molecular dynamics trajectory.

Temperature Considerations

A trajectory analysis of a chemical reaction is less ambiguous if free dynamics is used and constant temperature algorithm is turned off. If Restart is correctly checked, then the temperature setting in the Molecular Dynamics Options dialog box becomes irrelevant. It is used only to determine an initial set of velocities when free dynamics is used. If the velocities come from the HIN file instead (Restart) then the temperature is related only to the average kinetic energy from the velocities in the HIN file. In a proper trajectory analysis the initial velocities are sampled according to the temperature of the experimental situation being simulated.

If the constant temperature algorithm is used in a trajectory analysis, then the initial conditions are constantly being modified according to the simulation of the constant temperature bath and the relaxation of the molecular system to that bath temperature. The effect of such a bath on a trajectory analysis is less studied than for the simulation of equilibrium behavior.

RHF/UHF Considerations

As discussed earlier, the RHF scheme may not be appropriate to the situation where open shells are present or bonds are breaking. In this case, a UHF scheme may be the only sensible computational approach. This becomes particularly relevant here in conjunction with chemical reactions where we need to correctly describe molecular dissociation. This can be easily illustrated with the H₂ molecule. At equilibrium distances the UHF and RHF methods give the same answer; the UHF different-orbitals-for-different-spins solution degenerates into the RHF solution. However, at long bond lengths a branch point occurs and the UHF becomes a lower energy solution. As dissociation occurs, the UHF solution converges to a correct description of two isolated H atoms whereas the RHF solution goes to the wrong limit, indicative that a closed shell is an improper description of isolated hydrogen atoms. Thus, if the whole potential surface is to be described correctly, a UHF solution must be used. HyperChem cannot detect that the UHF solution is now lower in energy than the RHF solution and switch to the UHF solution; the UHF solution must be used throughout. HyperChem kicks the UHF solution off the metastable RHF initial guess and is always able to obtain the UHF solution (when it is lower than the RHF one) although, in principle, the RHF solution is also a solution to the UHF equations.

UV Visible Spectroscopy

In HyperChem, you can now compute the energy difference between the ground electronic state and the first few excited electronic states of a molecular system by using the *ab initio* method or any of the semi-empirical methods except for the Extended Hückel. To generate a UV-vis spectrum, you must perform a singly excited CI method with the *ab initio* method or semi-empirical method you choose.

Use the Electronic Spectrum dialog box to display and analyze the UV-vis spectrum produced by a singly excited CI calculation. This dialog box is available only after you do a single point CI semi-empirical calculation. Electronic Spectrum is then activated on the Compute menu.

By definition, the transition frequency, ν , of the UV spectrum is given by

$$\nu = \frac{E_f - E_i}{h} \quad (200)$$

and the oscillator strength is given by

$$f_{i \rightarrow f} = \left(\frac{8\pi^2 m}{3e^2 h^2} \right) (E_f - E_i) |d_{fi}|^2 \quad (201)$$

for the transition $i \rightarrow f$, where i is the initial state and f is the final state and d_{fi} is the transition dipole moment, and h is the Planck constant. Here only the dipole moment transition is considered and all the higher orders of transitions are ignored because of the small probability of the higher order transitions. The oscillator strength is a dimensionless value.

The energies, E_i and E_f of the initial and final states of transitions in equations (178) and (179) are determined by the CI eigenvalues and the transition dipole moment d_{fi} is obtained by using the CI eigenvectors, that is,

$$d_{fi} = \langle \Phi_f | \sum_k r_k | \Phi_i \rangle \quad (202)$$

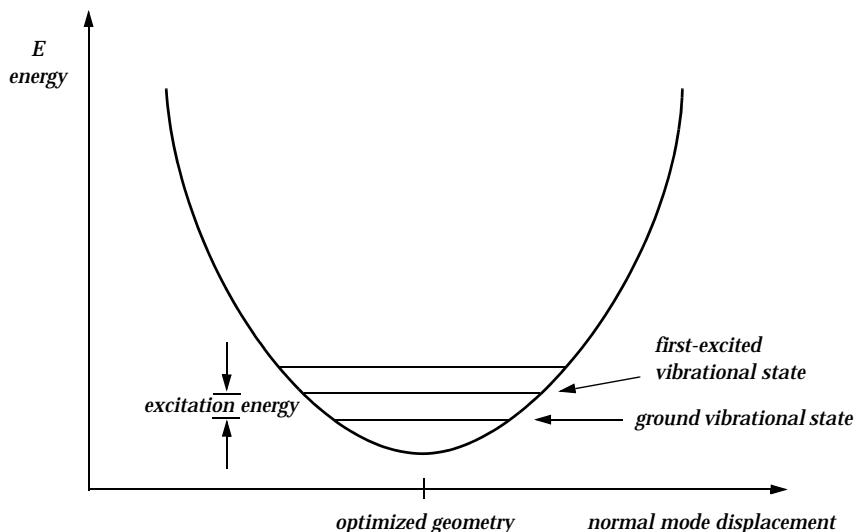
where k is the sum over all the electrons.

Vibrational Analysis and IR Spectroscopy

Vibrational Calculation

You can now use HyperChem to calculate vibration using *ab initio* methods and any of the semi-empirical methods except for Extended Hückel.

The following illustration shows the potential energy surface for vibrational motion along one normal mode:



HyperChem computes the Hessian using numerical second derivative of the total energy with respect to the nuclear positions based on the analytically calculated first derivatives in *ab initio* methods and any of the semi-empirical methods, except the Extended Hückel. Vibration calculations in HyperChem using an *ab initio* method may take much longer than calculations using the semi-empirical methods.

HyperChem performs a vibrational analysis at the molecular geometry shown in the HyperChem workspace, without any automatic pre-optimization. HyperChem may thus give unreasonable results when you perform vibrational analysis calculations with an unoptimized molecular system, particularly for one far from optimized. Because the molecular system is not at a stationary point, neither at a local minimum nor at a local maximum, the vibra-

tional analysis may give strange results including negative vibrational frequencies. Except in very specialized cases, you should always do a geometry optimization before a vibrational analysis.

Normal Coordinate Analysis

HyperChem models the vibrations of a molecule as a set of N point masses (the nuclei of the atoms) with each vibrating about its equilibrium (optimized) position. The equilibrium positions are determined by solving the electronic Schrödinger equation.

Defining mass-weighted Cartesian displacement coordinates q_i ,

$$q_i = m_i^{1/2}(x_i - x_i^e) \quad (203)$$

then the classical kinetic energy, T , of vibration about the equilibrium positions is

$$T = \frac{1}{2} \sum_{i=1}^{3N} \left(\frac{dq_i}{dt} \right)^2 \quad (204)$$

The potential energy of vibration is a function of the coordinates, x_1, \dots, x_N ; hence it is a function of the mass-weighted coordinates, q_1, \dots, q_{3N} . For a molecule, the vibrational potential energy, U , is given by the sum of the electronic energy and the nuclear repulsion energy:

$$U = U(q_1, \dots, q_{3N}) \quad (205)$$

The vibrational potential may be expanded in a Taylor series about the equilibrium positions of the atoms.

$$U = U_e + \sum_{i=1}^{3N} \left(\frac{\partial U}{\partial q_i} \right)_e q_i + \frac{1}{2} \sum_{i=1}^{3N} \sum_{j=1}^{3N} \left(\frac{\partial^2 U}{\partial q_i \partial q_j} \right)_e q_i q_j + \dots \quad (206)$$

At the equilibrium geometry of the molecule, U is a minimum and the gradient vanishes

$$\left(\frac{\partial U}{\partial q_i} \right)_e = 0 \quad (207)$$

If the vibrations are small (e.g., low temperatures, rigid bonding framework), the higher order terms can be neglected. Thus the potential energy simplifies to

$$U = U_e + \sum_{i=1}^{3N} u_{ij} q_i q_j \quad (208)$$

where u_{ij} is given by

$$u_{ij} = \left(\frac{\partial^2 U}{\partial q_i \partial q_j} \right)_e \quad (209)$$

The classical-mechanical problem for the vibrational motion may now be solved using Newton's second law. The force on the x component of the i^{th} atom is

$$F_{i,x} = m \frac{d^2 x_i}{dt^2} = - \frac{\partial U}{\partial x_i} \quad (210)$$

Transforming to mass-weighted coordinates, equation (210) can be rewritten into a set of $3N$ simultaneous linear differential equations

$$\frac{d^2 q_i}{dt^2} + \frac{\partial U}{\partial q_i} = 0 \quad (211)$$

Each differential equation contains all the coordinates q_i since $\frac{\partial U}{\partial q_i}$ is expressed as a single summation over the q_j 's.

$$\frac{\partial U}{\partial q_i} = \sum_{j=1}^{3N} u_{ij} q_j \quad (212)$$

Substituting equation (212) into equation (211), it becomes

$$\frac{d^2 q_i}{dt^2} + \sum_{j=1}^{3N} u_{ij} q_j = 0 \quad (213)$$

for $i = 1, 2, \dots, 3N$.

Equations (213) are a system of $3N$ simultaneous linear differential equations in the $3N$ unknowns q_j . It can be transformed to a

matrix form, if the mass-weighted coordinates, q_i , are rewritten into

$$q_i = A_i \sin(\lambda^{1/2} t + b) \quad (214)$$

for $i = 1, 2, \dots, 3N$, where λ and b are constants. Then the matrix form of equation (213) is

$$\mathbf{U}\mathbf{L} = \mathbf{L}\mathbf{\Lambda} \quad (215)$$

where matrix \mathbf{U} is the mass-weighted Hessian with matrix element u_{ij} defined in equation (209), \mathbf{L} and $\mathbf{\Lambda}$ are eigenvectors and eigenvalues, respectively.

The eigenvalues and eigenvectors of the mass-weighted force matrix can be obtained by diagonalizing equation (215). Then each eigenvalue corresponds to its normal coordinates, Q_k

$$Q_k = \sum_{i=1}^{3N} l_{ki} q_i \quad (216)$$

Because \mathbf{U} is a unitary transformation matrix, equation (216) can be written in the form

$$q_i = \sum_k l_{ki} Q_k \quad (217)$$

Using normal coordinates Q_k , equation (213) can be rewritten to

$$\frac{d^2 Q_k}{dt^2} + \lambda_k Q_k = 0 \quad (218)$$

with $k = 1, 2, \dots, 3N$. The general solutions of these equations are

$$Q_k = B_k \sin(\lambda_k^{1/2} t + \beta_k) \quad (219)$$

with $k = 1, 2, \dots, 3N$.

Motion along each normal coordinate is described by each atom vibrating in phase with one another with the same frequency. The vibration frequency, ν , is related to the eigenvalues, λ , by

$$\nu = \frac{\lambda_i^{1/2}}{2\pi} \quad (220)$$

Notice that although the energies and forces are evaluated quantum mechanically in HyperChem, the vibrational analysis has been purely classical.

Infrared Absorption

The mechanism of infrared (IR) light absorption is conceptually similar to that of UV visible light absorption. In both cases, the oscillating electric dipole of the light beam induces a mirror image oscillating electric dipole in the molecule (transition dipole). Energy (photons) may be exchanged between the molecule and the light beam if the frequency of the light closely corresponds to an energy gap between levels of the molecule.

The connection between transition energy ΔE and frequency ν is given by Einstein's classic formula

$$\Delta E = h\nu \quad (221)$$

where h is the Planck constant. UV visible frequencies ($\sim 10^{15}$ cycles per second) correspond to gaps between different electronic energy levels, whereas IR frequencies ($\sim 10^{12}$ cycles per second) correspond to gaps between vibrational energy levels. Thus, each line in a UV-visible spectrum corresponds to an excitation of electrons from one electronic state to another. Analogously, each line in an IR spectrum represents an excitation of nuclei from one vibrational state to another.

The frequency of electronic motion in a molecule (classically speaking, the number of orbits per second) is similar to that of UV-visible light, and the frequency of vibrational motion is similar to that of IR light. When IR light passes through a molecule, the electrons see an essentially constant electric field rather than an oscillating dipole. Similarly, when UV-visible light passes through a molecule, the nuclei see an essentially constant electric field rather than an oscillating dipole. In both cases, no mechanism exists for the absorption of light due to the frequency mismatch between the light and the molecule. In other words, IR light cannot polarize electrons and UV-visible light cannot polarize nuclei.

When IR radiation passes through a molecule, the nuclei move so as to create a molecular dipole that is synchronized with that of

the light. To a first approximation, each normal mode of vibration interacts independently with IR light.

A normal mode can absorb IR light if the molecular dipole moment changes during the course of a normal vibration. For example, the symmetric stretch in CO₂ does not entail a changing dipole moment, whereas the asymmetric stretch and bend do induce a changing dipole moment. CO₂ absorbs IR light at frequencies corresponding to the asymmetric stretch and bend because the IR light is “shaking” the atoms of the molecule along the asymmetric stretch and bending coordinates.

Quantitatively, we may express how “shakeable” a given normal mode will be under the influence of IR light, by examining the magnitude of its induced dipoles.

$$\mu = \mu_0 + (d\mu/dq)_0 q + (d^2\mu/dq^2)_0 q^2 + \dots \quad (222)$$

Keeping only the linear term, the transition dipole moment is given by

$$\langle \mu_{fi} \rangle = \int \Psi_f^{\text{vib}} (d\mu/dq)_0 \Psi_i^{\text{vib}} dq \quad (223)$$

Since we assume that all higher derivatives are essentially zero, $d\mu/dq = \text{constant}$. Therefore, it may be taken out of the integral sign as follows:

$$\langle \mu_{fi} \rangle = (d\mu/dq)_0 \int \Psi_f^{\text{vib}} q \Psi_i^{\text{vib}} dq \quad (224)$$

Qualitatively, the selection rule for IR absorption for a given mode is that the symmetry of $q \Psi_i^{\text{vib}}$ must be the same as $q \Psi_f^{\text{vib}}$. Quantitatively, the transition dipole moment is proportional to the dipole derivative with respect to a given normal mode $d\mu/dq$.

Generally, IR oscillator strengths (absorption intensities) are on the order of 10^{-4} of those of UV visible lines.

The integrated infrared band intensity for the k^{th} fundamental is defined [W. B. Person and K. C. Kim, *J. Chem. Phys.* 69, 1764 (1978)] as

$$A_k = \frac{1}{CL} \int_{\text{band}} \left(\ln \frac{I_0}{I} \right) d\nu \quad (225)$$

where C is concentration (in moles liter⁻¹), L is optical path length (in cm), ν is wavenumber in cm⁻¹, and I_0 and I , respectively, are the intensities of incident and transmitted light. Assuming electric and mechanical harmonicity, A_k may be approximated by

$$A_k = \frac{\pi N_A g_k}{3000c^2} \left| \frac{\partial \mu}{\partial Q_k} \right|^2 \quad (226)$$

where N_A is the Avogadro number (mol⁻¹), c is the light velocity (cm s⁻¹), g_k is the degeneracy factor, and $\partial \mu / \partial Q_k$ is the dipole-moment derivative with respect to the k^{th} normal coordinate Q_k .

In equation (225), a natural logarithm is used. Another definition [B. A. Hess, Jr., L. J. Schaad, P. Carsky, and R. Zahradnik, *Chem. Rev.* 86, 709 (1986)] uses a common logarithm in equation (225), that is,

$$A_k = \frac{1}{CL} \int_{\text{band}} \left(\log \frac{I_0}{I} \right) d\nu \quad (227)$$

So, the integrated infrared band intensity for the k^{th} fundamental is defined as

$$A_k = \frac{\pi N_A g_k}{3000 \ln(10) c^2} \left| \frac{\partial \mu}{\partial Q_k} \right|^2 \quad (228)$$

In HyperChem, equation (226) is used for calculating the integrated infrared band intensities for the *ab initio* method and equation (228) is employed for all the semi-empirical methods. All IR lines correspond to transitions from the ground vibrational state to an excited vibrational state that has one additional quantum deposited in a given vibrational mode.

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Index

- * and ** in basis set name, 261
- '***' atom type, 205
- 10–12 potential, 26
- 1–4 electrostatic interactions, 104
- 1–4 interactions, 182, 195
- 1–4 van der Waals interactions, 104
- 4-31G scale factors, table, 260
- 6–12 function, 26
- 6–12 potential, 176

A

- ab initio method, 251 to 268
- ab initio quantum mechanics, 31
- absolute energy, 22
- absorption, infrared, 336
- acceleration, convergence, 48, 112, 230
- acceptance ratio, 98
- accuracy
 - atomic charges, 137
 - dipole moments, 134
 - heats of formation, 130
 - proton affinities, 132
 - rotational barriers, 133
 - UV-visible spectra, 147
 - vibrational frequencies, 144
- Activation energies, 307
- activation energy, 17, 133
- affinities, proton, 132
- All Atom force fields, 28
- all atoms, 170, 189, 193
- alpha electrons, 37
- alpha spins, 44
- AM1, 119, 128, 150, 239, 292 to 294

- AMBER, 101, 106, 168, 188
- angle bending, 174, 185, 189, 194, 211
- angle bending, sextic, 185
- anharmonicity, 144
- annealing time, molecular dynamics, 89
- annealing, simulated, 79, 327
- annealing, trajectory, 313
- anti-parallel spins, 277
- architecture, HyperChem, 155
- asterisk in basis set name, 261
- atom types, 168, 169
- atom types, new or changed, 172
- atom velocities, 73
- atomic charges, 137, 184
- atomic mass, 170
- atoms, fixed, 83
- atoms, unknown type, 205
- Aufbau principle, 41, 49
- Austin Model 1 *See* AM1
- averages, molecular dynamics results, 85
- averaging, dynamics data, 319
- averaging, dynamics, deviations, 321

B

- back end, 155
- barrier, rotational, 133
- barriers, potential, 82
- barriers, reaction, 32
- basis functions, non-nuclear, 116
- basis set, 43
- basis set superposition effects, 116
- basis set superposition error (BSSE), 268
- basis set, minimal, 254

basis set, split-valence, table of KLM values, 258
 basis sets
 references, 110
 selection, 109
 basis sets, references, 216
 basis sets, split-valence, 257
 bath relaxation constant, 72
 beta electrons, 37
 beta spins, 44
 bibliography, computational chemistry, 2
 binding energy, 130
 BIO^+ , 101, 168, 193
 biradicals, 45
 black box — not, 157
 block diagonal method, 60
 block diagonal Newton-Raphson
 optimization, 306
 Boltzmann distribution, 19, 91, 310
 bond angle bending, 175
 bond angles, 23
 bond breaking, 46
 bond breaking/formation, simulation, 90
 bond dipoles, 103, 184
 bond dissociation, 37
 bond formation and breaking, 22
 bond stretch, 174
 bond stretching, 175, 183, 189, 193, 209
 bond-centered orbitals, 267
 bonded neighbors, 169
 bonding interactions, 174
 bonds, 23
 Born-Oppenheimer approximation, 11, 32, 161
 boundary conditions, periodic, theory, 201
 breaking bonds, simulation, 90
 Brillouin's Theorem, 39
 BSSE, 116, 268
 butadiene, modeling, 210

C

calculation types, 16
 calculations, mixed mode, 246
 canonical ensemble, 72
 capping atoms, 246, 248 to 250
 Cartesian Gaussians, 261
 charge density, 134
 charge, formal, 169
 charge-charge interaction, 192
 charges, atomic, 137, 184
 charges, point, 103
 CHARMM, 101, 106, 193
 chem.rul, 170
 chemical environment, 169
 chemical equilibrium, 131
 chemical reactions, 32, 327 to 330
 chemical reactivity, 138
 CI, 233, 235
 clamped-nuclei approximation, 161
 classical mechanics, 165
 classical perturbation, 267
 classical trajectory analysis, 328
 closed-shell singlet ground states, 38
 CNDO, 119, 127, 149, 239, 242, 273 to 277
 CNDO mixed model, 276
 comma-separated values file, 322
 Complete Neglect of Differential Overlap
 (CNDO), 239
 computational modules, 155
 Configuration Interaction (CI), 37, 233, 235
 conformational searching, 78, 87
 conjugate gradient, 59
 conjugate gradient optimization, 122, 304
 conservation, energy, 71, 123
 constant energy, 86
 constant temperature, 72, 87
 constant temperature/energy, 77
 contour plots, 243
 contracted Gaussian functions, 253, 254
 convergence, 229
 convergence acceleration, 48, 112
 convergence criteria, 60
 convergence limit, 112
 convergence, SCF, 47
 cooling time, molecular dynamics, 89
 cooling, dynamics, 73
 cooling, trajectory, 313
 core Hamiltonian MO coefficients, 266
 core orbitals, 43
 correlation energy, 38
 coulomb field, external, 246
 covalent radii, 209
 CSV file, 322

cubic stretch, 168, 183
cutoff, two-electron integral, 265
cutoffs, nonbonded, 64, 104, 181
cutoffs, nonbonded potential, 29
cycles, optimization, 60

D

d orbitals, ab initio, 115
d Orbitals, Hückel method, 118
DBF files, parameters, 197
default force field, 206
default MM+ force field, 204
default orbital exponents, table, 270
default scheme, 182
degenerate state, 39
density, charge, 134
density, electron, 52
density, spin, 52
dielectric constant, 27, 84, 180
dielectric constant, distance dependent, 180
dielectric functions, 103
dielectric permittivity, 180
diffusion constant, solvent, 91
dihedral angle, 187, 189, 194
dihedral angle rotation, 174
dihedral angles, 175, 211
dihedral potential, 25
dihedrals, improper, 176
DIIS convergence accelerator, 112, 230
dipole moment, 52, 134, 240, 276
dipole, oscillating electric, 336
dipole, transition, 336
dipole-dipole interactions, 179
dipoles, bond, 103, 184
Direct Inversion in the Iterative Subspace (DIIS), 48, 230
direct SCF calculation, 115, 265
dispersion forces, 174
dissociation, bond, 37, 46
distribution function, 96
docking molecules, 83
double zeta, 260
doublet, 111, 218, 232
doublet open-shell ground states, 38
Dreiding force field, 206

d-type functions, number, 261
dynamics data, averages, 316
dynamics results file, 322
dynamics sampling interval, 80
dynamics, molecular, 69
dynamics, periods, 73
dynamics, quenched, 78

E

EHT, 148, 268 to 273
eigenvector following, 66, 122, 308
electron density, 52, 241
electron lone pairs, 191
electron spin resonance (ESR), 243
electron-electron repulsion, 252
electronic density, 121
electronic spectra, 39
electronic spectroscopy, 235
electronic spectrum, 125
electronic states, 232
electrons, alpha and beta, 37
electrostatic interactions, 103, 174, 179, 190, 192, 196, 213
electrostatic potential, 27, 53, 121, 135, 244 to 245
energy barriers, 82
energy conservation, 71, 123
energy, activation, 17, 133
energy, binding, 130
energy, constant, 77, 86
ensemble averaging, 91
ensemble averaging, dynamics, 311
ensemble, isokinetic vs. isothermal, 72
enthalpies, 22
enthalpy of formation, 130
environment, chemical, 169
equilibration time, molecular dynamics, 88
equilibration, molecular dynamics, 74
equilibration, trajectory, 313
equilibrium properties, 19
equilibrium, chemical, 131
Ergodic Hypothesis, 311
ESR, 243
exchange integrals, one-center, 278
exchange phenomena, 277

exchange repulsion, 37, 174
excited singlet states, 38
excited state, 232
Exclusion Principle, Pauli, 34
Extend to sp³, 246
Extended Hückel method, 34, 125
Extended Hückel method, options, 117
Extended Hückel Theory (EHT), 148, 219, 268
to 273
external coulomb field, 246

F

file, CSV, 322
file, dynamics results, 322
files, snapshot, 325 to 326
fixed atoms, 83
Fletcher-Reeves, 59
Fletcher-Reeves optimization, 305
force constants, units, 183
force field options, set up, 199
force field parameters, 168
force field selection, 101
force fields, 21
force fields, distinguishing features, 101
force fields, limitations, 167
formal charge, 169
formation, heat of, 130
forming bonds, simulation, 90
free radicals, 232
frequency, dynamics sampling, 80
friction coefficient, solvent, 91
front end, 155
Frontier molecular orbitals, 141
Frontier Orbital theory, 140
Frontier orbitals, 42
frozen atoms, 83

G

Gaussian basis set, 252
Gaussian functions, 252
Gaussian Type Orbitals (GTO), 43, 252
Gaussians, Cartesian, 261
Gaussians, Hermite, 261

geminal interactions, 174
geometric restraints, 81
geometry optimizations, 16, 57, 132
geometry, molecular, 41
ghost-atoms, 116, 267
global minima, 327
global minimum, 301
gradient, RMS, 60
graphical user interface, 155
ground state, 232
GTO, 43, 252
GTO primitives, 253

H

half-electron excited singlet states, 38
half-electron method, 233
half-electron technique, 46
Hamiltonian, 162, 217
electronic, 163
exact, 162
nuclear, 163
Hamiltonian matrix elements, 270
hard nucleophiles and electrophiles, 140
harmonic approximation, 144
harmonic frequencies, 124
harmonic oscillator, 22
harmonic potential, 24
Hartree-Fock, 37, 224
Hartree-Fock approximation, 126, 251
heat of formation, 130
heating time, molecular dynamics, 88
heating, dynamics, 73
heating, trajectory, 313
Hermite Gaussians, 261
Hessian, 65, 308
Hessian matrix, 124
HOMO, 141, 221
Hooke's law, 22
Hückel constant, 117, 272
hybridization, 169, 207
hydrogen bond potential, 26
hydrogen bonding, 174, 179, 191
hydrogen bonding term, 196
HyperChem architecture, 155

hyperconjugation, mixed mode
calculations, 249
HyperMM+, HyperNewton, HyperEHT,
HyperNDO, HyperGauss, 156

I

improper dihedrals, 176, 190, 194
independent-electron approximation, 219
independent-electron method, 268
INDO, 119, 127, 149, 239, 242, 277 to 280
INDO mixed model, 276
infrared absorption, 336
Infrared frequencies, characteristic, 144
infrared spectroscopy, 143
infrared spectrum, negative frequencies, 144
initial conditions, dynamics, 310
initial guess, MO coefficients, 115, 266
integral cutoff, two-electron, 113, 265
integral format
 Raffenetti, 264
 regular, 263
interactions, bonding, 174
interactions, electrostatic, 174
interactions, nonbonding, 174
Intermediate Neglect of Differential Overlap
(INDO), 239
intermediates, 32
intermediates, potential, 131
intermediates, reactive, 307
interval, dynamics sampling, 80
ionic reactivity, 140
ionization energy, 134
ionization potential, 41
isokinetic energy ensemble, 72
isosurfaces, 243
isothermal ensemble, 72
iteration limit, 112

K

kinetic energy integrals, 252
KLM values, table, split-valence basis set, 258
Klopman-Salem equation, 139
Koopmans' theorem, 134

L

lambda, 67
Langevin dynamics, 18, 91
LCAO, 34, 222
LCAO-MO, 42
leap-frog algorithm, 70, 311
Lennard-Jones function, 26
Lennard-Jones potential, 176, 187
linear combination of atomic orbitals, 34
Linear Combination of Atomic Orbitals-
 Molecular Orbital, 42
local minima, 301
London dispersion forces, 39
lone pairs, 191
lowest state, 232
LUMO, 141, 221

M

mass, atomic, 170
mechanisms, reaction, 131
Metropolis method, 96
microcanonical ensemble, 72
microstate CI, 39
Microstate CI Method, 39
microstates, 234
MINDO/3, 119, 127, 149, 239, 242, 280 to
 284
minima, global, 327
minima, local, 301
minimal basis set, 254
minimizations, geometry, 57
minimum, global, 301
mixed mode calculations, 246, 267
mixed model, CNDO and INDO, 276
mixed model, MINDO/3, 283
mixed model, MNDO, AM1, and PM3, 292
MM+, 101, 168, 182
MM2, 106, 182
MM2(1977), 102
MNDO, 119, 128, 150, 239, 284 to 292
MO coefficients, initial guess, 115, 266
Modified Intermediate Neglect of Differential
 Overlap *See* MINDO/3

modifying parameters, 197
MO-LCAO approximation, 221
molecular dynamics, 18, 69, 123, 310 to 326
Molecular dynamics calculations, 85
molecular dynamics equilibration, 74
molecular geometry, 41
molecular mechanics, 21, 167
molecular mechanics, type selection, 101
molecular orbitals, 121
Møller-Plesset second-order perturbation
(MP2), 40, 113, 236 to 238, 251
Monte Carlo, 19, 91
Morse function, 24
MP2, 113, 251
MP2 Correlation Energy, 236 to 238
Mulliken approximation, 271
Mulliken atomic charges, 137
multiplicity, 218, 232
multiplicity, spin, 44, 111

N

NDDO, 128, 239
NDO, 34, 238 to 239
NDO methods, 126
NDO methods, options, 118
negative frequencies, 144
Neglect of Diatomic Differential Overlap
(NDDO), 128, 239
Neglect of Differential Overlap (NDO), 34,
126, 238 to 239
neighbors, bonded, 169
Newton-Raphson, 60
Newton-Raphson optimization, 306
next lowest state, 232
NOE data, 82
nonbonded cutoffs, 64, 104
non-bonded interactions, 26
nonbonded interactions, 174
nonbonded potential, 29
non-nuclear basis functions, 267
normal coordinate analysis, 333
normal modes, vibration, 124
notation, basis sets, 261
Nuclear Overhauser Effect (NOE), 82
nuclear-electron attraction, 252

number of d orbitals, 115

O

occupancy, orbital, 41
one-center exchange integrals, 278
OPLS, 101, 106, 168, 191
optimization cycles, 60
optimization methods, 303 to 307
optimization termination, 61
optimizations, structural, 57, 132
options, force field, set up, 199
Orbital Criterion, 39
orbital energy diagrams, 220
orbital exponents, default, table, 270
orbital occupancy, 41
orbital plots, 243
oscillating electric dipole, 336
out-of-plane bending, 186
out-of-plane bends, 211
overlap integrals, 252
overlap weighting factors, ZINDO, 295

P

parallel spins, 277
parameter sets, 196
parameter sets, compiling, 199
parameter sets, new, 198
parameters, changed molecular
mechanics, 173
parameters, default, 182
parameters, force field, 168
parameters, missing, 205
parameters, modifying, 197
parameters, wild-card approach, 205
Pauli Exclusion Principle, 34
period, dynamics averaging, 318
period, dynamics data collection, 318
period, dynamics sampling, 80
period, dynamics screen refresh, 319
period, dynamics snapshot, 318
periodic boundary conditions, 62, 200
periodic boundary conditions, theory, 201
permittivity, dielectric, 180

perturbation, classical, 267
perturbation, Møller-Plesset, 40
phase space, 96
phases, trajectory, 313
planar molecules, 302
PM3, 119, 128, 150, 239, 292 to 294
point charges, 103, 246
Polak-Ribiere, 59
Polak-Ribiere optimization, 306
polarizability, 179
polarization functions, 260
polarized basis sets, 260
Pople-Nesbet equations, 227
potential
 angle, 23
 electrostatic, 27, 53
 harmonic, 24
 Morse, 24
 non-bonded, 26
 nonbonded, 29
 torsional, 25
potential energy surfaces, 11, 12, 158
potential intermediates, 131
potential switching function, 29
potential, electrostatic, 135
potential, shifting, 30
primitives, GTO, 253
products, reaction, 139
Projected CNDO/INDO MO coefficients, 266
Projected Hückel MO coefficients, 266
proton affinities, 132
pseudo-halogens, 248 to 250

Q

quadratic stretch, 168, 183
quadruple zeta, 260
quantum mechanics
 ab initio, 31
 semi-empirical, 31
quartet, 232
quasi-Newton, 309
quenched dynamics, 78

R

radicals, free, 232
Raffenetti integral format, 114, 264
random velocities, 312
Rayleigh-Schrödinger many-body perturbation (RSPT), 40, 236
reaction barriers, 32
reaction coordinate, 14, 32, 139
reaction coordinate parameter (lambda), 67
Reaction Map, 67
reaction mechanisms, 131, 307
reaction products, 139
reactions, chemical, 327 to 330
reactivity, chemical, 138
reactivity, ionic, 140
relaxation constant, bath, 72
repulsion, exchange, 174
resonance integrals, 295
restart velocities, 312
restraints, structural, 81
restraints, theory, 203
Restricted Hartree-Fock (RHF), 37, 112, 230 to 234
Restricted Open-shell Hartree-Fock (ROHF), 112
RHF, 37, 44, 112, 227, 230 to 234
RHF half-electron technique, 46
RMS Gradient, 300
RMS gradient, 60
ROHF, 112
Roothaan equations, 225, 251
root-mean-square gradient, 60
rotational barriers, 133
RSPT, 40, 236
rules, atom typing, 170
running, trajectory, 313

S

saddle point, 65
saddle points, 17, 32
sampling interval, 80
SCF, 38, 224
SCF calculation, direct, 265

SCF convergence, 47
SCF Technique, 43
Schrödinger equation, 11, 164, 217
second order optimizer, 60
Self-Consistent Field (SCF), 38, 224, 251
semi-empirical method, selection, 128, 148
semi-empirical quantum mechanics, 31
sextic angle bending, 185
shifted function, 104
shifting function, 181
shifting potential, 30
simulated annealing, 79, 327
single point calculation, 16, 51, 299
single point calculations, 121
singlet, 111, 218, 232
singlet ground states, 38
singlet molecules, 37
singlet-triplet splittings, 39
singly excited CI, 39
Slater Type Orbitals (STO), 43, 252
Slater-Condon parameters, 278
snapshot files, 325 to 326
snapshot, dynamics period, 318
soft electrophiles and nucleophiles, 141
solute temperature, 75
solute-solute interactions, 62
solvation, 62
solvent effects, 62, 200
solvent friction and diffusion, 91
solvent temperature, 75
spin couplings, 39
spin density, 52, 121, 243
spin interactions, 279
spin multiplicity, 44, 111
spin pairing, 226
spin state, 218, 232
spins, parallel or anti-parallel, 277
spins, unpaired, 37
splittings, singlet-triplet, 39
split-valence basis set, table of KLM values, 258
split-valence basis sets, 257
star in basis set name, 261
state, excited, 232
state, lowest, 232
static field, classical, 246, 267
stationary points, 17
statistical mechanical averages, dynamics, 312

steepest descent, 58
steepest descent optimization, 122, 303
step size, molecular dynamics, 89
STO, 43, 252
STO-3G exponents, table, 256
STO-NG method, 255
stretch-bend cross term, 102
stretch-bend interactions, 186, 211
structural optimizations, 132
structural restraints, 81
switching function, 104, 181
switching function, potential, 29
symmetrical systems, 39
synchronous transit, 67, 122, 309

T

temperature regulation, 71
temperature, constant, 72, 77, 87
temperature, constant dynamics, 314, 317
temperature, dynamics, 310
temperature, reaction simulation, 330
temperature, solvent, 75
termination condition, optimization, 61
time step, trajectory, 314
TIP3P water model, 62
torsional angle rotation, 174
torsional angles, 175
torsional energy, 187, 189, 194, 211
torsional potential, 25
torsions, improper, 176
total electron density, 52
total spin density, 52
trajectory phases, 313
trajectory, classical, 328
transition dipole, 336
transition state search, 17, 65, 122, 308
transition states, 32, 133
Transition Structures, 307
triple zeta, 260
triplet, 112, 218, 232
triplet ground states, 45
triplet open-shell ground states, 38
two-electron integral cutoff, 113
two-electron integrals, 262
format, 114

Raffenetti format, 114
txt files, parameters, 197
types, atom, 168, 169
typing rules, atom, 170

U

UHF, 37, 44, 112, 227, 230 to 234
United Atom force fields, 28
united atoms, 170, 189, 192, 193
units, force constants, 183
unpaired spins, 37
Unrestricted Hartree-Fock (UHF), 37, 112, 230 to 234
Urey-Bradley term, 102
user interface, 155
UV-visible spectra, 39, 125
 computing, 331
 theory, 331
UV-visible spectra, characteristic, 147

V

valence atomic orbitals, 269
Valence state ionization energy (VSIE), 270
van der Waals, 174, 176, 187, 190, 192, 195, 213
van der Waals interactions, 26
velocities, distribution of atom, 73
velocities, random distribution, 312
velocities, rescaling, 314
velocities, restart, 312
Verlet algorithm, 93
vibrational analysis, 124, 143
 and IR spectroscopy, 332 to 338
vicinal interactions, 174, 182
virtual orbitals, 41, 44
VSIE, 270
VSIE values, table, 271

W

Walsh's rules, 41
water box, 202

water model, TIP3P, 62
wave function, 36
wild-card approach, parameters, 205
Woodward-Hoffmann rules, 41

Z

ZDO, 273
zero differential overlap (ZDO), 273
zeta, double, 260
zeta, triple and quadruple, 260
ZINDO/1, 119, 127, 151, 239, 242, 294 to 296
ZINDO/S, 119, 127, 151, 239, 242, 295 to 297

