

Contents

Preface to the First Edition

xv

Preface to the Second Edition

xix

Acknowledgments

xxi

1 What are Theory, Computation, and Modeling?

1

1.1 Definition of Terms

1

1.2 Quantum Mechanics

4

1.3 Computable Quantities

5

1.3.1 Structure

5

1.3.2 Potential Energy Surfaces

6

1.3.3 Chemical Properties

10

1.4 Cost and Efficiency

11

1.4.1 Intrinsic Value

11

1.4.2 Hardware and Software

12

1.4.3 Algorithms

14

1.5 Note on Units

15

Bibliography and Suggested Additional Reading

15

References

16

2 Molecular Mechanics

17

2.1 History and Fundamental Assumptions

17

2.2 Potential Energy Functional Forms

19

2.2.1 Bond Stretching

19

2.2.2 Valence Angle Bending

21

2.2.3 Torsions

22

2.2.4 van der Waals Interactions

27

2.2.5 Electrostatic Interactions

30

2.2.6 Cross Terms and Additional Non-bonded Terms

34

2.2.7 Parameterization Strategies

36

2.3 Force-field Energies and Thermodynamics

39

2.4 Geometry Optimization

40

2.4.1 Optimization Algorithms

41

2.4.2 Optimization Aspects Specific to Force Fields

46

2.5	Menagerie of Modern Force Fields	50
2.5.1	Available Force Fields	50
2.5.2	Validation	59
2.6	Force Fields and Docking	62
2.7	Case Study: (2 <i>R</i> *,4 <i>S</i> *)-1-Hydroxy-2,4-dimethylhex-5-ene	64
	Bibliography and Suggested Additional Reading	66
	References	67
3	Simulations of Molecular Ensembles	69
3.1	Relationship Between MM Optima and Real Systems	69
3.2	Phase Space and Trajectories	70
3.2.1	Properties as Ensemble Averages	70
3.2.2	Properties as Time Averages of Trajectories	71
3.3	Molecular Dynamics	72
3.3.1	Harmonic Oscillator Trajectories	72
3.3.2	Non-analytical Systems	74
3.3.3	Practical Issues in Propagation	77
3.3.4	Stochastic Dynamics	79
3.4	Monte Carlo	80
3.4.1	Manipulation of Phase-space Integrals	80
3.4.2	Metropolis Sampling	81
3.5	Ensemble and Dynamical Property Examples	82
3.6	Key Details in Formalism	88
3.6.1	Cutoffs and Boundary Conditions	88
3.6.2	Polarization	90
3.6.3	Control of System Variables	91
3.6.4	Simulation Convergence	93
3.6.5	The Multiple Minima Problem	96
3.7	Force Field Performance in Simulations	98
3.8	Case Study: Silica Sodalite	99
	Bibliography and Suggested Additional Reading	101
	References	102
4	Foundations of Molecular Orbital Theory	105
4.1	Quantum Mechanics and the Wave Function	105
4.2	The Hamiltonian Operator	106
4.2.1	General Features	106
4.2.2	The Variational Principle	108
4.2.3	The Born–Oppenheimer Approximation	110
4.3	Construction of Trial Wave Functions	111
4.3.1	The LCAO Basis Set Approach	111
4.3.2	The Secular Equation	113
4.4	Hückel Theory	115
4.4.1	Fundamental Principles	115
4.4.2	Application to the Allyl System	116
4.5	Many-electron Wave Functions	119
4.5.1	Hartree-product Wave Functions	120
4.5.2	The Hartree Hamiltonian	121
4.5.3	Electron Spin and Antisymmetry	122
4.5.4	Slater Determinants	124
4.5.5	The Hartree-Fock Self-consistent Field Method	126
	Bibliography and Suggested Additional Reading	129
	References	130

5	Semiempirical Implementations of Molecular Orbital Theory	131
5.1	Semiempirical Philosophy	131
5.1.1	Chemically Virtuous Approximations	131
5.1.2	Analytic Derivatives	133
5.2	Extended Hückel Theory	134
5.3	CNDO Formalism	136
5.4	INDO Formalism	139
5.4.1	INDO and INDO/S	139
5.4.2	MINDO/3 and SINDO1	141
5.5	Basic NDDO Formalism	143
5.5.1	MNDO	143
5.5.2	AM1	145
5.5.3	PM3	146
5.6	General Performance Overview of Basic NDDO Models	147
5.6.1	Energetics	147
5.6.2	Geometries	150
5.6.3	Charge Distributions	151
5.7	Ongoing Developments in Semiempirical MO Theory	152
5.7.1	Use of Semiempirical Properties in SAR	152
5.7.2	d Orbitals in NDDO Models	153
5.7.3	SRP Models	155
5.7.4	Linear Scaling	157
5.7.5	Other Changes in Functional Form	157
5.8	Case Study: Asymmetric Alkylation of Benzaldehyde	159
	Bibliography and Suggested Additional Reading	162
	References	163
6	<i>Ab Initio</i> Implementations of Hartree–Fock Molecular Orbital Theory	165
6.1	<i>Ab Initio</i> Philosophy	165
6.2	Basis Sets	166
6.2.1	Functional Forms	167
6.2.2	Contracted Gaussian Functions	168
6.2.3	Single- ζ , Multiple- ζ , and Split-Valence	170
6.2.4	Polarization Functions	173
6.2.5	Diffuse Functions	176
6.2.6	The HF Limit	176
6.2.7	Effective Core Potentials	178
6.2.8	Sources	180
6.3	Key Technical and Practical Points of Hartree–Fock Theory	180
6.3.1	SCF Convergence	181
6.3.2	Symmetry	182
6.3.3	Open-shell Systems	188
6.3.4	Efficiency of Implementation and Use	190
6.4	General Performance Overview of <i>Ab Initio</i> HF Theory	192
6.4.1	Energetics	192
6.4.2	Geometries	196
6.4.3	Charge Distributions	198
6.5	Case Study: Polymerization of 4-Substituted Aromatic Enynes	199
	Bibliography and Suggested Additional Reading	201
	References	201

7	Including Electron Correlation in Molecular Orbital Theory	203
7.1	Dynamical vs. Non-dynamical Electron Correlation	203
7.2	Multiconfiguration Self-Consistent Field Theory	205
7.2.1	Conceptual Basis	205
7.2.2	Active Space Specification	207
7.2.3	Full Configuration Interaction	211
7.3	Configuration Interaction	211
7.3.1	Single-determinant Reference	211
7.3.2	Multireference	216
7.4	Perturbation Theory	216
7.4.1	General Principles	216
7.4.2	Single-reference	219
7.4.3	Multireference	223
7.4.4	First-order Perturbation Theory for Some Relativistic Effects	223
7.5	Coupled-cluster Theory	224
7.6	Practical Issues in Application	227
7.6.1	Basis Set Convergence	227
7.6.2	Sensitivity to Reference Wave Function	230
7.6.3	Price/Performance Summary	235
7.7	Parameterized Methods	237
7.7.1	Scaling Correlation Energies	238
7.7.2	Extrapolation	239
7.7.3	Multilevel Methods	239
7.8	Case Study: Ethylenedione Radical Anion	244
	Bibliography and Suggested Additional Reading	246
	References	247
8	Density Functional Theory	249
8.1	Theoretical Motivation	249
8.1.1	Philosophy	249
8.1.2	Early Approximations	250
8.2	Rigorous Foundation	252
8.2.1	The Hohenberg–Kohn Existence Theorem	252
8.2.2	The Hohenberg–Kohn Variational Theorem	254
8.3	Kohn–Sham Self-consistent Field Methodology	255
8.4	Exchange-correlation Functionals	257
8.4.1	Local Density Approximation	258
8.4.2	Density Gradient and Kinetic Energy Density Corrections	263
8.4.3	Adiabatic Connection Methods	264
8.4.4	Semiempirical DFT	268
8.5	Advantages and Disadvantages of DFT Compared to MO Theory	271
8.5.1	Densities vs. Wave Functions	271
8.5.2	Computational Efficiency	273
8.5.3	Limitations of the KS Formalism	274
8.5.4	Systematic Improvability	278
8.5.5	Worst-case Scenarios	278
8.6	General Performance Overview of DFT	280
8.6.1	Energetics	280
8.6.2	Geometries	291
8.6.3	Charge Distributions	294
8.7	Case Study: Transition-Metal Catalyzed Carbonylation of Methanol	299
	Bibliography and Suggested Additional Reading	300
	References	301

9	Charge Distribution and Spectroscopic Properties	305
9.1	Properties Related to Charge Distribution	305
9.1.1	Electric Multipole Moments	305
9.1.2	Molecular Electrostatic Potential	308
9.1.3	Partial Atomic Charges	309
9.1.4	Total Spin	324
9.1.5	Polarizability and Hyperpolarizability	325
9.1.6	ESR Hyperfine Coupling Constants	327
9.2	Ionization Potentials and Electron Affinities	330
9.3	Spectroscopy of Nuclear Motion	331
9.3.1	Rotational	332
9.3.2	Vibrational	334
9.4	NMR Spectral Properties	344
9.4.1	Technical Issues	344
9.4.2	Chemical Shifts and Spin-spin Coupling Constants	345
9.5	Case Study: Matrix Isolation of Perfluorinated <i>p</i> -Benzyne	349
	Bibliography and Suggested Additional Reading	351
	References	351
10	Thermodynamic Properties	355
10.1	Microscopic-macroscopic Connection	355
10.2	Zero-point Vibrational Energy	356
10.3	Ensemble Properties and Basic Statistical Mechanics	357
10.3.1	Ideal Gas Assumption	358
10.3.2	Separability of Energy Components	359
10.3.3	Molecular Electronic Partition Function	360
10.3.4	Molecular Translational Partition Function	361
10.3.5	Molecular Rotational Partition Function	362
10.3.6	Molecular Vibrational Partition Function	364
10.4	Standard-state Heats and Free Energies of Formation and Reaction	366
10.4.1	Direct Computation	367
10.4.2	Parametric Improvement	370
10.4.3	Isodesmic Equations	372
10.5	Technical Caveats	375
10.5.1	Semiempirical Heats of Formation	375
10.5.2	Low-frequency Motions	375
10.5.3	Equilibrium Populations over Multiple Minima	377
10.5.4	Standard-state Conversions	378
10.5.5	Standard-state Free Energies, Equilibrium Constants, and Concentrations	379
10.6	Case Study: Heat of Formation of H_2NOH	381
	Bibliography and Suggested Additional Reading	383
	References	383
11	Implicit Models for Condensed Phases	385
11.1	Condensed-phase Effects on Structure and Reactivity	385
11.1.1	Free Energy of Transfer and Its Physical Components	386
11.1.2	Solvation as It Affects Potential Energy Surfaces	389
11.2	Electrostatic Interactions with a Continuum	393
11.2.1	The Poisson Equation	394
11.2.2	Generalized Born	402
11.2.3	Conductor-like Screening Model	404
11.3	Continuum Models for Non-electrostatic Interactions	406
11.3.1	Specific Component Models	406
11.3.2	Atomic Surface Tensions	407

11.4	Strengths and Weaknesses of Continuum Solvation Models	410
11.4.1	General Performance for Solvation Free Energies	410
11.4.2	Partitioning	416
11.4.3	Non-isotropic Media	416
11.4.4	Potentials of Mean Force and Solvent Structure	419
11.4.5	Molecular Dynamics with Implicit Solvent	420
11.4.6	Equilibrium vs. Non-equilibrium Solvation	421
11.5	Case Study: Aqueous Reductive Dechlorination of Hexachloroethane	422
	Bibliography and Suggested Additional Reading	424
	References	425
12	Explicit Models for Condensed Phases	429
12.1	Motivation	429
12.2	Computing Free-energy Differences	429
12.2.1	Raw Differences	430
12.2.2	Free-energy Perturbation	432
12.2.3	Slow Growth and Thermodynamic Integration	435
12.2.4	Free-energy Cycles	437
12.2.5	Potentials of Mean Force	439
12.2.6	Technical Issues and Error Analysis	443
12.3	Other Thermodynamic Properties	444
12.4	Solvent Models	445
12.4.1	Classical Models	445
12.4.2	Quantal Models	447
12.5	Relative Merits of Explicit and Implicit Solvent Models	448
12.5.1	Analysis of Solvation Shell Structure and Energetics	448
12.5.2	Speed/Efficiency	450
12.5.3	Non-equilibrium Solvation	450
12.5.4	Mixed Explicit/Implicit Models	451
12.6	Case Study: Binding of Biotin Analogs to Avidin	452
	Bibliography and Suggested Additional Reading	454
	References	455
13	Hybrid Quantal/Classical Models	457
13.1	Motivation	457
13.2	Boundaries Through Space	458
13.2.1	Unpolarized Interactions	459
13.2.2	Polarized QM/Unpolarized MM	461
13.2.3	Fully Polarized Interactions	466
13.3	Boundaries Through Bonds	467
13.3.1	Linear Combinations of Model Compounds	467
13.3.2	Link Atoms	473
13.3.3	Frozen Orbitals	475
13.4	Empirical Valence Bond Methods	477
13.4.1	Potential Energy Surfaces	478
13.4.2	Following Reaction Paths	480
13.4.3	Generalization to QM/MM	481
13.5	Case Study: Catalytic Mechanism of Yeast Enolase	482
	Bibliography and Suggested Additional Reading	484
	References	485
14	Excited Electronic States	487
14.1	Determinantal/Configurational Representation of Excited States	487

14.2	Singly Excited States	492
14.2.1	SCF Applicability	493
14.2.2	CI Singles	496
14.2.3	Rydberg States	498
14.3	General Excited State Methods	499
14.3.1	Higher Roots in MCSCF and CI Calculations	499
14.3.2	Propagator Methods and Time-dependent DFT	501
14.4	Sum and Projection Methods	504
14.5	Transition Probabilities	507
14.6	Solvatochromism	511
14.7	Case Study: Organic Light Emitting Diode Alq3	513
	Bibliography and Suggested Additional Reading	515
	References	516
15	Adiabatic Reaction Dynamics	519
15.1	Reaction Kinetics and Rate Constants	519
15.1.1	Unimolecular Reactions	520
15.1.2	Bimolecular Reactions	521
15.2	Reaction Paths and Transition States	522
15.3	Transition-state Theory	524
15.3.1	Canonical Equation	524
15.3.2	Variational Transition-state Theory	531
15.3.3	Quantum Effects on the Rate Constant	533
15.4	Condensed-phase Dynamics	538
15.5	Non-adiabatic Dynamics	539
15.5.1	General Surface Crossings	539
15.5.2	Marcus Theory	541
15.6	Case Study: Isomerization of Propylene Oxide	544
	Bibliography and Suggested Additional Reading	546
	References	546
Appendix A	Acronym Glossary	549
Appendix B	Symmetry and Group Theory	557
B.1	Symmetry Elements	557
B.2	Molecular Point Groups and Irreducible Representations	559
B.3	Assigning Electronic State Symmetries	561
B.4	Symmetry in the Evaluation of Integrals and Partition Functions	562
Appendix C	Spin Algebra	565
C.1	Spin Operators	565
C.2	Pure- and Mixed-spin Wave Functions	566
C.3	UHF Wave Functions	571
C.4	Spin Projection/Annihilation	571
	Reference	574
Appendix D	Orbital Localization	575
D.1	Orbitals as Empirical Constructs	575
D.2	Natural Bond Orbital Analysis	578
	References	579
Index		581