Molecular Modelling

PRINCIPLES AND APPLICATIONS

Second edition

Andrew R. Leach
Glaxo Wellcome Research and Development



Contents

Preface to the First Edition Symbols and Physical Constants Acknowledgements 1 Useful Concepts in Molecular Modelling 1.1 Introduction 1.2 Coordinate Systems 1.3 Potential Energy Surfaces 1.4 Molecular Graphics 1.5 Surfaces 1.6 Computer Hardware and Software 1.7 Units of Length and Energy 1.8 The Molecular Modelling Literature 1.9 The Internet 1.10 Mathematical Concepts Further Reading References 2 An Introduction to Computational Quantum Mechanics 2.1 Introduction 2.2 One-electron Atoms 2.3 Polyelectronic Atoms and Molecules 2.4 Molecular Orbital Calculations	xiii				
Sy	Preface to the First Edition Symbols and Physical Constants Acknowledgements 1 Useful Concepts in Molecular Modelling 1.1 Introduction 1.2 Coordinate Systems 1.3 Potential Energy Surfaces 1.4 Molecular Graphics 1.5 Surfaces 1.6 Computer Hardware and Software 1.7 Units of Length and Energy 1.8 The Molecular Modelling Literature 1.9 The Internet 1.10 Mathematical Concepts Further Reading References 2 An Introduction 2 One-electron Atoms 2.3 Polyelectronic Atoms and Molecules 2.4 Molecular Orbital Calculations 2.5 The Hartree-Fock Equations 2.6 Basis Sets 2.7 Calculating Molecular Properties Using ab initio Quantum Mechanics 2.8 Approximate Molecular Orbital Theories 2.9 Semi-empirical Methods 2.10 Hückel Theory	xvii			
Ac	knowl	edgements	xxi		
1	Useft	ıl Concepts in Molecular Modelling	1		
			1		
	1.2	Coordinate Systems	2		
	1.3		4		
	1.4	Molecular Graphics	5		
	1.5	Surfaces	6		
	1.6	Computer Hardware and Software	8		
	1.7	Units of Length and Energy	9		
	1.8	The Molecular Modelling Literature	9		
	1.9	The Internet	9		
	1.10	Mathematical Concepts	10		
			24		
	Refer	ences	24		
2	An Introduction to Computational Quantum Mechanics				
		•	26		
	2.2	One-electron Atoms	30		
	2.3	Polyelectronic Atoms and Molecules	34		
	2.4	Molecular Orbital Calculations	41		
	2.5	The Hartree-Fock Equations	51		
	2.6	Basis Sets	65		
	2.7	Calculating Molecular Properties Using ab initio Quantum Mechanics	74		
	2.8	Approximate Molecular Orbital Theories	86		
	2.9	Semi-empirical Methods	86		
	2.10	Hückel Theory	99		
	2.11	Performance of Semi-empirical Methods	102		
	Appendix 2.1 Some Common Acronyms Used in Computational				
		Quantum Chemistry	104 105		
	Further Reading				
	Refer	ences	105		

3	Adv	anced ab initio Methods, Density Functional Theory and Solid-state	
	Qua	ntum Mechanics	108
	3.1	Introduction	108
	3.2	Open-shell Systems	108
	3.3	Electron Correlation	110
	3.4	Practical Considerations When Performing ab initio Calculations	117
	3.5	Energy Component Analysis	122
	3.6	Valence Bond Theories	124
	3.7	Density Functional Theory	126
	3.8	Quantum Mechanical Methods for Studying the Solid State	138
	3.9	The Future Role of Quantum Mechanics: Theory and Experiment Working Together	160
	App	endix 3.1 Alternative Expression for a Wavefunction Satisfying Bloch's Function	161
	Furtl	ner Reading	161
	Refe	rences	162
4	Emp	irical Force Field Models: Molecular Mechanics	165
	4.1	Introduction	165
	4.2	Some General Features of Molecular Mechanics Force Fields	168
	4.3	Bond Stretching	170
	4.4	Angle Bending	173
	4.5	Torsional Terms	173
	4.6	Improper Torsions and Out-of-plane Bending Motions	176
	4.7	Cross Terms: Class 1, 2 and 3 Force Fields	178
	4.8	Introduction to Non-bonded Interactions	181
	4.9	Electrostatic Interactions	181
	4.10	Van der Waals Interactions	204
	4.11	Many-body Effects in Empirical Potentials	212
	4.12	Effective Pair Potentials	214
	4.13	Hydrogen Bonding in Molecular Mechanics	215
	4.14	Force Field Models for the Simulation of Liquid Water	216
	4.15	United Atom Force Fields and Reduced Representations	221
	4.16	Derivatives of the Molecular Mechanics Energy Function	225
	4.17	Calculating Thermodynamic Properties Using a Force Field	226
	4.18	Force Field Parametrisation	228
	4.19	Transferability of Force Field Parameters	231
	4.20	The Treatment of Delocalised π Systems	233
	4.21	Force Fields for Inorganic Molecules	234
	4.22	Force Fields for Solid-state Systems	236
	4.23	Empirical Potentials for Metals and Semiconductors	240
		ndix 4.1 The Interaction Between Two Drude Molecules	246
		er Reading	247
	Refer	ences	247

Contents

5	Energ	y Minimisation and Related Methods for Exploring the Energy Surface	253 253		
	5.1 Introduction				
	5.2	Non-derivative Minimisation Methods	258		
	5.3	Introduction to Derivative Minimisation Methods	261		
	5.4	First-order Minimisation Methods	262		
	5.5	Second Derivative Methods: The Newton-Raphson Method	267 268		
	5.6 Quasi-Newton Methods				
	5.7	Which Minimisation Method Should I Use?	270		
	5.8	Applications of Energy Minimisation	273 279		
	5.9 Determination of Transition Structures and Reaction Pathways				
	5.10	Solid-state Systems: Lattice Statics and Lattice Dynamics	295		
	Furth	er Reading	300		
	Refere	ences	301		
6	Comp	outer Simulation Methods	303		
	6.1	Introduction	303		
	6.2	Calculation of Simple Thermodynamic Properties	307		
	6.3	Phase Space	312		
	6.4	Practical Aspects of Computer Simulation	315		
	6.5	Boundaries	317		
	6.6	Monitoring the Equilibration	321		
	6.7 Truncating the Potential and the Minimum Image Convention		324		
	6.8	Long-range Forces	334 343		
	6.9 Analysing the Results of a Simulation and Estimating Errors				
	Appendix 6.1 Basic Statistical Mechanics				
		ndix 6.2 Heat Capacity and Energy Fluctuations	348		
	Appendix 6.3 The Real Gas Contribution to the Virial				
	Appendix 6.4 Translating Particle Back into Central Box for Three Box Shapes				
	Further Reading				
	References				
7	Molecular Dynamics Simulation Methods 3				
	7.1	Introduction	353 353		
	7.2	, , ,			
	7.3				
	7.4 Setting up and Running a Molecular Dynamics Simulation				
	7.5	7.5 Constraint Dynamics			
	7.6	7.6 Time-dependent Properties			
	7.7				
	7.8 Incorporating Solvent Effects into Molecular Dynamics: Potentials of				
	-	Mean Force and Stochastic Dynamics	387		
	7.9	Conformational Changes from Molecular Dynamics Simulations	392		
	710	Molecular Dynamics Simulations of Chain Amphiphiles	394		

		endix 7.1 Energy Conservation in Molecular Dynamics ner Reading	405 406
		rences	406
8	Mon	te Carlo Simulation Methods	410
	8.1	Introduction	410
	8.2	Calculating Properties by Integration	412
	8.3	Some Theoretical Background to the Metropolis Method	414
	8.4	Implementation of the Metropolis Monte Carlo Method	417
	8.5	Monte Carlo Simulation of Molecules	420
	8.6	Models Used in Monte Carlo Simulations of Polymers	423
	8.7	'Biased' Monte Carlo Methods	432
	8.8	Tackling the Problem of Quasi-ergodicity: J-walking and Multicanonical Monte Carlo	433
	8.9	Monte Carlo Sampling from Different Ensembles	438
	8.10	Calculating the Chemical Potential	442
	8.11	The Configurational Bias Monte Carlo Method	443
	8.12	Simulating Phase Equilibria by the Gibbs Ensemble Monte Carlo Method	450
	8.13	Monte Carlo or Molecular Dynamics?	452
		endix 8.1 The Marsaglia Random Number Generator	453
		ner Reading	454
	Refer	rences	454
9	Conf	ormational Analysis	457
-	9,1	Introduction	457
	9.2	Systematic Methods for Exploring Conformational Space	458
	9.3	Model-building Approaches	464
	9.4	Random Search Methods	465
	9.5	Distance Geometry	467
	9.6	Exploring Conformational Space Using Simulation Methods	475
	9.7	Which Conformational Search Method Should I Use? A Comparison of	1,0
		Different Approaches	476
	9.8	Variations on the Standard Methods	477
	9.9	Finding the Global Energy Minimum: Evolutionary Algorithms and	
		Simulated Annealing	479
	9.10	Solving Protein Structures Using Restrained Molecular Dynamics and	
		Simulated Annealing	483
	9.11	Structural Databases	489
	9.12	Molecular Fitting	490
	9.13	Clustering Algorithms and Pattern Recognition Techniques	491
	9.14	Reducing the Dimensionality of a Data Set	497
	9.15	Covering Conformational Space: Poling	499
	9.16	A 'Classic' Optimisation Problem: Predicting Crystal Structures	501

Contents	ix

	Furthe Refere	r Reading nces		505 506
10	Protei	n Structui	re Prediction, Sequence Analysis and Protein Folding	509
	10.1	Introduct	ion	509
	10.2	Some Bas	sic Principles of Protein Structure	513
	10.3	First-prin	ciples Methods for Predicting Protein Structure	517
	10.4	Introduct	ion to Comparative Modelling	522
	10.5	Sequence	Alignment	522
	10.6	Construct	ting and Evaluating a Comparative Model	539
	10.7	Predicting	g Protein Structures by 'Threading'	545
	10.8	A Compa	arison of Protein Structure Prediction Methods: CASP	547
	10.9	Protein F	olding and Unfolding	549
	Apper	ndix 10.1	Some Common Abbreviations and Acronyms Used in	
	••		Bioinformatics	553
	Apper	ndix 10.2	Some of the Most Common Sequence and Structural Databases	
			Used in Bioinformatics	555
	Apper	ndix 10.3	Mutation Probability Matrix for 1 PAM	556
		ndix 10.4	Mutation Probability Matrix for 250 PAM	557
		r Reading		557
	Refere	ences		558
11			s in Molecular Modelling: Free Energies, Solvation, Reactions	
	and S	olid-state		563
	11.1		rgy Calculations	563
	11.2		ulation of Free Energy Differences	564
	11.3		ions of Methods for Calculating Free Energy Differences	569
	11.4	The Calc	ulation of Enthalpy and Entropy Differences	574
	11.5		ing the Free Energy	574
	11.6		Pitfalls with Free Energy Calculations	577
	11.7		s of Mean Force	580
	11.8		mate/'Rapid' Free Energy Methods	585
	11.9		ım Representations of the Solvent	592
	11.10		trostatic Contribution to the Free Energy of Solvation:	
			and Onsager Models	593
	11.11	Non-elec	trostatic Contributions to the Solvation Free Energy	608
	11.12	Very Sim	ple Solvation Models	609
	11.13	Modellin	g Chemical Reactions	610
			g Solid-state Defects	622
	Appe	ndix 11.1	Calculating Free Energy Differences Using Thermodynamic	
			Integration	630
	Appendix 11.2 Using the Slow Growth Method for Calculating Free Energy			
Differences			Differences	631

	Furth	endix 11.3 Expansion of Zwanzig Expression for the Free Energy Difference for the Linear Response Method ner Reading rences	631 632 633
12	The I	Use of Molecular Modelling and Chemoinformatics to Discover and	
	Desig	gn New Molecules	640
	12.1	Molecular Modelling in Drug Discovery	640
	12.2	Computer Representations of Molecules, Chemical Databases and 2D	
		Substructure Searching	642
	12.3	3D Database Searching	647
	12.4	Deriving and Using Three-dimensional Pharmacophores	648
	12.5	Sources of Data for 3D Databases	659
	12.6	Molecular Docking	661
	12.7	Applications of 3D Database Searching and Docking	667
	12.8	Molecular Similarity and Similarity Searching	668
	12.9	Molecular Descriptors	668
	12,10	O	680
	12.11		687
		Quantitative Structure-Activity Relationships	695
		Partial Least Squares	7 06
		Combinatorial Libraries	711
		er Reading	719
	Refere	ences	720
Ind	ex		727