

Contents

Acknowledgment	<i>VII</i>
Congratulations to Professor Ada Yonath for Winning the 2009 Nobel Prize in Chemistry	<i>IX</i>
Introductory Reflections on Quantum Biochemistry: From Context to Contents	<i>XI</i>
<i>Chérif F. Matta</i>	
List of Contributors	<i>LI</i>

Vol I

Part One	Novel Theoretical, Computational, and Experimental Methods and Techniques	<i>1</i>
1	Quantum Kernels and Quantum Crystallography: Applications in Biochemistry	<i>3</i>
	<i>Lulu Huang, Lou Massa, and Jerome Karle</i>	
1.1	Introduction	<i>3</i>
1.2	Origins of Quantum Crystallography (QCr)	<i>4</i>
1.2.1	General Problem of <i>N</i> -Representability	<i>4</i>
1.2.2	Single Determinant <i>N</i> -Representability	<i>5</i>
1.2.3	Example Applications of Clinton's Equations	<i>7</i>
1.2.3.1	Beryllium	<i>7</i>
1.2.3.2	Maleic Anhydride	<i>9</i>
1.3	Beginnings of Quantum Kernels	<i>10</i>
1.3.1	Computational Difficulty of Large Molecules	<i>10</i>
1.3.2	Quantum Kernel Formalism	<i>11</i>
1.3.3	Kernel Matrices: Example and Results	<i>14</i>
1.3.4	Applications of the Idea of Kernels	<i>17</i>
1.3.4.1	Hydrated Hexapeptide Molecule	<i>17</i>
1.3.4.2	Hydrated Leu ¹ -Zervamicin	<i>18</i>
1.4	Kernel Density Matrices Led to Kernel Energies	<i>22</i>
1.4.1	KEM Applied to Peptides	<i>24</i>

1.4.2	Quantum Models within KEM	29
1.4.2.1	Calculations and Results Using Different Basis Functions for the ADPGV7b Molecule	32
1.4.2.2	Calculations and Results Using Different Quantum Methods for the Zaib4 Molecule	34
1.4.2.3	Comments Regarding KEM	36
1.4.3	KEM Applied to Insulin	36
1.4.3.1	KEM Calculation Results	36
1.4.3.2	Comments Regarding the Insulin Calculations	38
1.4.4	KEM Applied to DNA	39
1.4.4.1	KEM Calculation Results	39
1.4.4.2	Comments Regarding the DNA Calculations	41
1.4.5	KEM Applied to tRNA	41
1.4.6	KEM Applied to Rational Design of Drugs	43
1.4.6.1	Importance of the Interaction Energy for Rational Drug Design	43
1.4.6.2	Sample Calculation: Antibiotic Drug in Complex (1O9M) with a Model Aminoacyl Site of the 30s Ribosomal Subunit	44
1.4.6.3	Comments Regarding the Drug–Target Interaction Calculations	46
1.4.7	KEM Applied to Collagen	47
1.4.7.1	Interaction Energies	47
1.4.7.2	Collagen 1A89	47
1.4.7.3	Comments Regarding the Collagen Calculations	50
1.4.8	KEM Fourth-Order Calculation of Accuracy	50
1.4.8.1	Molecular Energy as a Sum over Kernel Energies	50
1.4.8.2	Application to Leu ¹ -zervamicin of the Fourth-Order Approximation of KEM	51
1.4.9	KEM Applied to Vesicular Stomatitis Virus Nucleoprotein, 33 000 Atom Molecule	53
1.4.9.1	Vesicular Stomatitis Virus Nucleoprotein (2QVJ) Molecule	53
1.4.9.2	Hydrogen Bond Calculations	54
1.4.9.3	Comments regarding the 2QVJ Calculations	54
1.5	Summary and Conclusions	55
	References	57
2	Getting the Most out of ONIOM: Guidelines and Pitfalls	61
	<i>Fernando R. Clemente, Thom Vreven, and Michael J. Frisch</i>	
2.1	Introduction	61
2.2	QM/MM	62
2.3	ONIOM	63
2.4	Guidelines for the Application of ONIOM	65
2.4.1	Summary	72
2.5	The Cancellation Problem	72
2.6	Use of Point Charges	77
2.7	Conclusions	81
	References	82

3	Modeling Enzymatic Reactions in Metalloenzymes and Photobiology by Quantum Mechanics (QM) and Quantum Mechanics/Molecular Mechanics (QM/MM) Calculations	85
	<i>Lung Wa Chung, Xin Li, and Keiji Morokuma</i>	
3.1	Introduction	85
3.2	Computational Strategies (Methods and Models)	86
3.2.1	Quantum Mechanical (QM) Methods	86
3.2.2	Active-Site Model	88
3.2.3	QM/MM Methods	88
3.2.4	QM/MM Model and Setup	90
3.3	Metalloenzymes	91
3.3.1	Heme-Containing Enzymes	91
3.3.1.1	Binding and Photodissociation of Diatomic Molecules	91
3.3.1.2	Heme Oxygenase (HO)	95
3.3.1.3	Indoleamines Dioxygenase (IDO) and Tryptophan Dioxygenase (TDO)	97
3.3.1.4	Nitric Oxide Synthase (NOS)	101
3.3.2	Cobalamin-Dependent Enzymes	105
3.3.2.1	Methylmalonyl-CoA Mutase	105
3.3.2.2	Glutamine Mutase	108
3.4	Photobiology	109
3.4.1	Fluorescent Proteins (FPs)	109
3.4.1.1	Green Fluorescent Proteins (GFP)	110
3.4.1.2	Reversible Photoswitching Fluorescent Proteins (RFPs)	111
3.4.1.3	Photoconversion of Fluorescent Proteins	115
3.4.2	Luciferases	117
3.5	Conclusion	120
	References	120
4	From Molecular Electrostatic Potentials to Solvation Models and Ending with Biomolecular Photophysical Processes	131
	<i>Jacopo Tomasi, Chiara Cappelli, Benedetta Mennucci, and Roberto Cammi</i>	<i>131</i>
4.1	Introduction	131
4.2	The Molecular Electrostatic Potential and Noncovalent Interactions among Molecules	132
4.2.1	Molecular Electrostatic Potential	132
4.2.1.1	Use of MEP	133
4.2.1.2	Semiclassical Approximation	133
4.2.1.3	MEP as a Component of the Intermolecular Interaction	134
4.2.1.4	Definition of the Coulomb Interaction Term	135
4.2.1.5	Simplifications in the Expression of E_{es} : Point Charge Descriptions	135
4.2.1.6	Simplifications in the Expression of E_{es} : Atomic Charges	136
4.2.1.7	Simplifications in the Expression of E_{es} : Multipolar Expansions	136

4.2.2	Interaction Energy between Two Molecules	137
4.2.3	Examples of Energy Decomposition Analyses	139
4.2.3.1	Interactions with a Proton	139
4.2.3.2	Interactions with Other Cations	139
4.2.3.3	Hydrogen Bonding	140
4.2.4	Interaction Potentials (Force Fields) for Computer Simulations of Liquid Systems	140
4.3	Solvation: the “Continuum Model”	142
4.3.1	Basic Formulation of PCM	142
4.3.2	Beyond the Basic Formulation	146
4.3.2.1	Dielectric Function	146
4.3.2.2	Cavity Surface	147
4.3.2.3	Definition of the Apparent Charges	147
4.3.2.4	Description of the Solute	147
4.3.3	Other Continuum Solvation Methods	148
4.3.3.1	Apparent Surface Charge (ASC) Methods	148
4.3.3.2	Multipole Expansion Methods (MPE)	149
4.3.3.3	Generalized Born Model	149
4.3.3.4	Finite Element Method (FEM) and Finite Difference Method (FDM)	150
4.4	Applications of the PCM Method	150
4.4.1	Solvation Energies	150
4.4.2	About the PES	152
4.4.3	Chemical Equilibria	152
4.4.3.1	Tautomeric Equilibria	153
4.4.3.2	Equilibria in Molecular Aggregation	153
4.4.3.3	pK_a of Acids	153
4.4.4	Reaction Mechanisms	154
4.4.5	Solvent Effects on Molecular Properties and Spectroscopy	156
4.4.5.1	<i>N</i> -Acetylproline Amide (NAP)	157
4.4.5.2	Glucose	158
4.4.5.3	Local Field Effects	159
4.4.5.4	Dynamic Effects	160
4.4.6	Effect of the Environment on Formation and Relaxation of Excited States	161
4.4.7	Electronic Transitions and Related Spectroscopies	162
4.4.8	Photoinduced Electron and Energy Transfers	164
	References	166
5	The Fast Marching Method for Determining Chemical Reaction Mechanisms in Complex Systems	171
	<i>Yuli Liu, Steven K. Burger, Bijoy K. Dey, Utpal Sarkar, Marek R. Janicki, and Paul W. Ayers</i>	
5.1	Motivation	171

5.2	Background	172
5.2.1	Minimum Energy Path	172
5.2.2	Two End Methods	172
5.2.3	Surface Walking Algorithms	173
5.2.4	Metadynamics Methods	174
5.2.5	Fast Marching Method	174
5.3	Fast Marching Method	175
5.3.1	Introduction to FMM	175
5.3.2	Upwind Difference Approximation	176
5.3.3	Heapsort Technique	176
5.3.4	Shepard Interpolation	177
5.3.5	Interpolating Moving Least-Squares Method	179
5.3.6	FMM Program	180
5.3.6.1	Setup, Definitions and Notation	180
5.3.6.2	Initialize the Calculation	181
5.3.6.3	Updating the Heap	181
5.3.6.4	Backtracing from the Ending Point to the Starting Point on the Energy Cost Surface	181
5.3.7	Application	182
5.3.7.1	Four-Well Analytical PES	182
5.3.7.2	S_N2 Reaction	184
5.3.7.3	Dissociation of Ionized O-Methylhydroxylamine	185
5.4	Quantum Mechanics/Molecular Mechanics (QM/MM) Methods Applied to Enzyme-Catalyzed Reactions	187
5.4.1	QM/MM Methods	187
5.4.2	Incorporating the QM/MM-MFEP Methods with FMM	189
5.4.3	Application of the Incorporated FMM and QM/MM-MFEP Method to Enzyme-Catalyzed Reactions	190
5.4.3.1	S_N2 Reaction in Solvent	190
5.4.3.2	Isomerization Reaction Catalyzed by 4-Oxalocrotonate Tautomerase (4-OT)	190
5.4.3.3	Dechlorination Reaction Catalyzed by <i>trans</i> -3-Chloroacrylic Acid Dehalogenase (CAAD)	191
5.5	Summary	191
	References	192
Part Two	Nucleic Acids, Amino Acids, Peptides and Their Interactions	197
6	Chemical Origin of Life: How do Five HCN Molecules Combine to form Adenine under Prebiotic and Interstellar Conditions	199
	<i>Debjani Roy and Paul von Ragué Schleyer</i>	
6.1	Introduction	199
6.1.1	Prebiotic Chemistry: Experimental Endeavor to Synthesize the Building Blocks of Biopolymers	199

6.1.2	Key Role of HCN as a Precursor for Prebiotic Compounds	201
6.1.3	Prebiotic Experiments and Proposed Pathways for the Formation of Adenine	202
6.2	Computational Investigation	202
6.2.1	Method	204
6.2.2	Thermochemistry of Pentamerization	204
6.2.3	Detailed Step by Step Mechanism	205
6.2.3.1	DAMN vs AICN as Adenine Precursors	205
6.2.3.2	Is an Anionic Mechanism Feasible in Isolation?	205
6.2.3.3	Two Tautomeric forms of AICN: Which one is the Favorable Precursor for Adenine Formation under Prebiotic Conditions?	207
6.2.3.4	Validating the Methods Used for Computing Barrier Heights	213
6.3	Conclusion	213
	References	216
7	Hydrogen Bonding and Proton Transfer in ionized DNA Base Pairs, Amino Acids and Peptides	219
	<i>Luis Rodríguez-Santiago, Marc Noguera, Joan Bertran, and Mariona Sodupe</i>	
7.1	Introduction	219
7.2	Methodological Aspects	220
7.3	Ionization of DNA Base Pairs	221
7.3.1	Equilibrium Geometries and Dimerization Energies	222
7.3.2	Single and Double Proton Transfer Reactions	223
7.4	Ionization of Amino Acids	227
7.4.1	Structural Features of Neutral and Radical Cation Amino Acids	227
7.4.2	Intramolecular Proton-Transfer Processes	231
7.5	Ionization of Peptides	234
7.5.1	Ionization of <i>N</i> -Glycylglycine	234
7.5.2	Influence of Ionization on the Ramachandran Maps of Model Peptides	236
7.6	Conclusions	239
	References	241
8	To Nano-Biochemistry: Picture of the Interactions of DNA with Gold	245
	<i>Eugene S. Kryachko</i>	
8.1	Introductory Nanoscience Background	245
8.1.1	Gold in Nanodimensions	246
8.1.2	Gold and DNA: Meeting Points in Nanodimensions	248
8.2	DNA–Gold Bonding Patterns: Some Experimental Facts	253
8.3	Adenine–Gold Interaction	254
8.3.1	Adenine–Au and Adenine–Au ₃ Bonding Patterns	254
8.3.2	Propensity of Gold to Act as Nonconventional Proton Acceptor	257
8.3.2.1	Pause: A Short Excursion to Hydrogen Bonding Theory	259

8.3.2.2	Proof that $N-H \cup Au \equiv N-H \cdots Au$ in $A \cdot Au_3(N_{i=1,3,7})$	260
8.3.2.3	Nonconventional Hydrogen Bonds $N-H \cdots Au$ in $A \cdot Au_3(N_{i=1,3,7})$	261
8.3.3	Complex $A \cdot Au_3(N_6)$	262
8.3.4	Interaction between Adenine and Chain Au_3 Cluster	262
8.4	Guanine–Gold Interaction	263
8.5	Thymine–Gold Interactions	268
8.6	Cytosine–Gold Interactions	272
8.7	Basic Trends of DNA Base–Gold Interaction	273
8.7.1	Anchoring Bond in DNA Base–Gold Complexes	276
8.7.2	Energetics in $Z = 0$ Charge State	278
8.7.3	$Z = -1$ Charge State	282
8.8	Interaction of Watson–Crick DNA Base Pairs with Gold Clusters	286
8.8.1	General Background	286
8.8.2	$[A \cdot T] \cdot Au_3$ Complexes	289
8.8.3	$[G \cdot C] \cdot Au_3$ Complexes	293
8.8.4	Au_6 Cluster Bridges the WC G–C Pair	296
8.9	Summary and Perspectives	297
	References	298
9	Quantum Mechanical Studies of Noncovalent DNA–Protein Interactions	307
	<i>Lesley R. Rutledge and Stacey D. Wetmore</i>	
9.1	Introduction	307
9.2	Computational Approaches for Studying Noncovalent Interactions	308
9.3	Hydrogen-Bonding Interactions	315
9.3.1	Interactions between the Protein Backbone and DNA Nucleobases	315
9.3.2	Interactions between Protein Side Chains and DNA Backbone	316
9.3.3	Interactions between Protein Side Chains and DNA Nucleobases	317
9.4	Interactions between Aromatic DNA–Protein Components	318
9.4.1	Stacking Interactions	319
9.4.2	T-Shaped Interactions	323
9.5	Cation– π Interactions between DNA–Protein Components	326
9.5.1	Cation– π Interactions between Charged Nucleobases and Aromatic Amino Acids	326
9.5.2	Cation– π Interactions Involving Charged Aromatic Amino Acids	330
9.5.3	Cation– π Interactions Involving Charged Non-aromatic Amino Acids	330
9.5.4	Simultaneous Cation– π and Hydrogen-Bonding Interactions (DNA–Protein Stair Motifs)	332
9.6	Conclusions	333
	References	333

10	The Virial Field and Transferability in DNA Base-Pairing	337
	<i>Richard F.W. Bader and Fernando Cortés-Guzmán</i>	
10.1	A New Theorem Relating the Density of an Atom in a Molecule to the Energy	337
10.2	Computations	339
10.3	Chemical Transferability and the One-Electron Density Matrix	339
10.3.1	The Virial Field	340
10.3.2	Short-Range Nature of the Virial Field and Transferability	342
10.4	Changes in Atomic Energies Encountered in DNA Base Pairing	343
10.4.1	Dimerization of the Four Bases A, C, G and T	346
10.4.2	Energy Changes in CC	349
10.4.3	Energy Changes in AA1	349
10.4.4	Energy Changes in GG4	350
10.4.5	Energy Changes in TT2	350
10.5	Energy Changes in the WC Pairs GC and AT	350
10.6	Discussion	355
10.6.1	Attractive and Repulsive Contributions to the Atomic Virial and its Short-Range Nature	356
10.6.2	Can One Go Directly to the Virial Field?	360
	References	363
11	An Electron Density-Based Approach to the Origin of Stacking Interactions	365
	<i>Ricardo A. Mosquera, María J. González Moa, Laura Estévez, Marcos Mandado, and Ana M. Graña</i>	
11.1	Introduction	365
11.2	Computational Method	366
11.3	Charge-Transfer Complexes: Quinhydrone	367
11.4	π - π Interactions in Hetero-Molecular Complexes: Methyl Gallate-Caffeine Adduct	371
11.5	π - π Interactions between DNA Base Pair Steps	374
11.6	π - π Interactions in Homo-Molecular Complexes: Catechol	378
11.7	C-H/ π Complexes	381
11.8	Provisional Conclusions and Future Research	385
	References	385
12	Polarizabilities of Amino Acids: Additive Models and <i>Ab Initio</i> Calculations	389
	<i>Noureddin El-Bakali Kassimi and Ajit J. Thakkar</i>	
12.1	Introduction	389
12.2	Models of Polarizability	389
12.3	Polarizabilities of the Amino Acids	393

12.4	Concluding Remarks	398
	References	400
13	Methods in Biocomputational Chemistry: A Lesson from the Amino Acids	403
	<i>Hugo J. Bohórquez, Constanza Cárdenas, Chérif F. Matta, Russell J. Boyd, and Manuel E. Patarroyo</i>	
13.1	Introduction	403
13.2	Conformers, Rotamers and Physicochemical Variables	404
13.3	QTAIM Side Chain Polarizations and the Theoretical Classification of Amino Acids	408
13.4	Quantum Mechanical Studies of Peptide–Host Interactions	414
13.5	Conclusions	419
	References	420
14	From Atoms in Amino Acids to the Genetic Code and Protein Stability, and Backwards	423
	<i>Chérif F. Matta</i>	
14.1	Context of the Work	423
14.2	The Electron Density $\rho(r)$ as an Indirectly Measurable Dirac Observable	426
14.3	Brief Review of Some Basic Concepts of the Quantum Theory of Atoms in Molecules	430
14.4	Computational Approach and Level of Theory	438
14.5	Empirical Correlations of QTAIM Atomic Properties of Amino Acid Side Chains with Experiment	439
14.5.1	Partial Molar Volumes	439
14.5.2	Free Energy of Transfer from the Gas to the Aqueous Phase	448
14.5.3	Simulation of Genetic Mutations with Amino Acids Partition Coefficients	448
14.5.4	Effect of Genetic Mutation on Protein Stability	451
14.5.5	From the Genetic Code to the Density and Back	454
14.6	Molecular Complementarity	456
14.7	Closing Remarks	462
14.8	Appendix A X-Ray and Neutron Diffraction Geometries of the Amino Acids in the Literature	462
	References	467
15	Energy Richness of ATP in Terms of Atomic Energies: A First Step	473
	<i>Chérif F. Matta and Alya A. Arabi</i>	
15.1	Introduction	473
15.2	How “(De)Localized” is the Enthalpy of Bond Dissociation?	474
15.3	The Choice of a Theoretical Level	477
15.3.1	The Problem	477

15.3.2	Empirical Correlation of Trends in the Atomic Contributions to BDE: Comparison of MP2 and DFT(B3LYP) Results	478
15.3.3	Theory	478
15.3.3.1	QTAIM Atomic Energies from the <i>ab initio</i> Methods	478
15.3.3.2	Atomic Energies from Kohn–Sham Density Functional Theory Methods	482
15.3.3.3	Atomic Contributions to the Energy of Reaction	484
15.4	Computational Details	484
15.5	(Global) Energies of the Hydrolysis of ATP in the Absence and Presence of Mg^{2+}	485
15.6	How “(De)Localized” is the Energy of Hydrolysis of ATP?	485
15.6.1	Phosphate Group Energies and Modified Lipmann’s Group Transfer Potentials	485
15.6.2	Atomic Contributions to the Energy of Hydrolysis of ATP in the Absence and Presence of Mg^{2+}	487
15.7	Other Changes upon Hydrolysis of ATP in the Presence and Absence of Mg^{2+}	487
15.7.1	Bond Properties and Molecular Graphs	487
15.7.2	Group Charges in ATP in the Absence and Presence of Mg^{2+}	491
15.7.3	Molecular Electrostatic Potential in the Absence and Presence of Mg^{2+}	492
15.8	Conclusions	493
	References	496

Vol II

Part Three Reactivity, Enzyme Catalysis, Biochemical Reaction Paths and Mechanisms 499

16	Quantum Transition State for Peptide Bond Formation in the Ribosome	501
	<i>Lou Massa, Chérif F. Matta, Ada Yonath, and Jerome Karle</i>	
16.1	Introduction	501
16.2	Methodology: Searching for the Transition State and Calculating its Properties	502
16.3	Results: The Quantum Mechanical Transition State	506
16.4	Discussion	511
16.5	Summary and Conclusions	513
	References	514
17	Hybrid QM/MM Simulations of Enzyme-Catalyzed DNA Repair Reactions	517
	<i>Denis Bucher, Fanny Masson, J. Samuel Arey, and Ursula Röthlisberger</i>	
17.1	Introduction	517
17.2	Theoretical Background	518
17.3	Applications	521

17.3.1	Thymine Dimer Splitting Catalyzed by DNA Photolyase	521
17.3.2	Reaction Mechanism of Endonuclease IV	525
17.3.3	Role of Water in the Catalysis Mechanism of DNA Repair Enzyme, MutY	529
17.4	Conclusions	533
	References	534
18	Computational Electronic Structure of Spin-Coupled Diiron-Oxo Proteins	537
	<i>Jorge H. Rodriguez</i>	
18.1	Introduction	537
18.2	(Anti)ferromagnetic Spin Coupling	538
18.3	Spin Density Functional Theory of Antiferromagnetic Diiron Complexes	539
18.4	Phenomenological Simulation of Mössbauer Spectra of Diiron-oxo Proteins	542
18.4.1	Antiferromagnetic Diiron Center of Hemerythrin	542
18.4.2	Nitric Oxide Derivative of Hr	543
18.4.3	Antiferromagnetic Diiron Center of Reduced Uteroferrin	545
18.5	Conclusion	546
	References	548
19	Accurate Description of Spin States and its Implications for Catalysis	551
	<i>Marcel Swart, Mireia Güell, and Miquel Solà</i>	
19.1	Introduction	551
19.2	Influence of the Basis Set	553
19.3	Spin-Contamination Corrections	556
19.4	Influence of Self-Consistency	558
19.5	Spin-States of Model Complexes	559
19.6	Spin-States Involved in Catalytic Cycles	564
19.6.1	Cytochrome P450cam	564
19.6.2	His-Porphyrin Models	567
19.6.2.1	Reference Data (Harvey)	568
19.6.2.2	Reference Data (Ghosh)	570
19.6.2.3	Other Model Systems	571
19.6.3	NiFe Hydrogenase	574
19.7	Concluding Remarks	579
19.8	Computational Details	579
	References	580
20	Quantum Mechanical Approaches to Selenium Biochemistry	585
	<i>Jason K. Pearson and Russell J. Boyd</i>	
20.1	Introduction	585
20.2	Quantum Mechanical Methods for the Treatment of Selenium	586

20.3	Applications to Selenium Biochemistry	587
20.3.1	Computational Studies of GPx	587
20.3.2	Computational Studies on GPx Mimics	589
20.3.2.1	GPx-like Activity of Ebselen	589
20.3.2.2	Substituent Effects on the GPx-like Activity of Ebselen	596
20.3.2.3	Effect of the Molecular Environment on GPx-like Activity	598
20.4	Summary	600
	References	600

21 Catalytic Mechanism of Metallo β -Lactamases: Insights from Calculations and Experiments 605

Matteo Dal Peraro, Alejandro J. Vila, and Paolo Carloni

21.1	Introduction	605
21.2	Structural Information	607
21.3	Computational Details	608
21.4	Preliminary Comment on the Comparison between Theory and Experiment	609
21.5	Michaelis Complex in B1 M β Ls	610
21.5.1	Substrate Binding Determinants	610
21.5.2	Nucleophile Structural Determinants	611
21.6	Catalytic Mechanism of B1 M β Ls	612
21.6.1	Cefotaxime Enzymatic Hydrolysis in CcrA	613
21.6.2	Cefotaxime Enzymatic Hydrolysis in BcII	614
21.6.3	Zinc Content and Reactivity of B1 M β Ls	615
21.6.4	Reactivity of β -Lactam Antibiotics other than Cefotaxime	615
21.7	Michaelis Complexes of other M β Ls	616
21.7.1	B2 Mono-Zn M β L Subclass	616
21.7.2	B3 M β L Subclass	616
21.8	Concluding Remarks	617
	References	618

22 Computational Simulation of the Terminal Biogenesis of Sesquiterpenes: The Case of 8-Epiconfertifin 623

José Enrique Barquera-Lozada and Gabriel Cuevas

22.1	Introduction	623
22.2	Reaction Mechanism	627
22.3	Conclusions	639
	References	640

23 Mechanistics of Enzyme Catalysis: From Small to Large Active-Site Models 643

Jorge Llano and James W. Gauld

23.1	Introduction	
23.1.1	Factors Influencing the Catalytic Performance of Enzymes	643

23.1.2	Computational Modeling in Enzymology	648
23.2	Active-Site Models of Enzymatic Catalysis: Methods and Accuracy	650
23.3	Redox Catalytic Mechanisms	652
23.3.1	NO Formation in Nitric Oxide Synthase	652
23.3.2	Oxidative Dealkylation in the AlkB Family	654
23.4	General Acid–Base Catalytic Mechanism of Deacetylation in LpxC	658
23.5	Summary	660
	References	662
Part Four	From Quantum Biochemistry to Quantum Pharmacology, Therapeutics, and Drug Design	667
24	Developing Quantum Topological Molecular Similarity (QTMS)	669
	<i>Paul L.A. Popelier</i>	
24.1	Introduction	669
24.2	Anchoring in Physical Organic Chemistry	671
24.3	Equilibrium Bond Lengths: “Threat” or “Opportunity”?	678
24.4	Introducing Chemometrics: Going Beyond r^2	679
24.5	A Hopping Center of Action	681
24.6	A Leap	684
24.7	A Couple of General Reflections	687
24.8	Conclusions	688
	References	689
25	Quantum-Chemical Descriptors in QSAR/QSPR Modeling: Achievements, Perspectives and Trends	693
	<i>Anna V. Gubskaya</i>	
25.1	Introduction	693
25.2	Quantum-Chemical Methods and Descriptors	694
25.2.1	Quantum-Chemical Methods	694
25.2.2	Quantum-Chemical Descriptors: Classification, Updates	697
25.3	Computational Approaches for Establishing Quantitative Structure–Activity Relationships	703
25.3.1	Selection of Descriptors	703
25.3.2	Linear Regression Techniques	705
25.3.3	Machine-Learning Algorithms	706
25.4	Quantum-Chemical Descriptors in QSAR/QSPR Models	710
25.4.1	Biochemistry and Molecular Biology	710
25.4.2	Medicinal Chemistry and Drug Design	712
25.4.3	Material and Biomaterial Science	714
25.5	Summary and Conclusions	715
	References	717

- 26 Platinum Complexes as Anti-Cancer Drugs: Modeling of Structure, Activation and Function 723**
Konstantinos Gkionis, Mark Hicks, Arturo Robertazzi, J. Grant Hill, and James A. Platts
- 26.1 Introduction to Cisplatin Chemistry and Biochemistry 723
- 26.2 Calculation of Cisplatin Structure, Activation and DNA Interactions 726
- 26.3 Platinum-Based Alternatives 732
- 26.4 Non-platinum Alternatives 735
- 26.5 Absorption, Distribution, Metabolism, Excretion (ADME) Aspects 739
- References 740
- 27 Protein Misfolding: The Quantum Biochemical Search for a Solution to Alzheimer's Disease 743**
Donald F. Weaver
- 27.1 Introduction 743
- 27.2 Protein Folding and Misfolding 744
- 27.2.1 Protein Folding 744
- 27.2.2 Protein Misfolding 745
- 27.3 Quantum Biochemistry in the Study of Protein Misfolding 745
- 27.3.1 Molecular Mechanics 746
- 27.4 Alzheimer's Disease: A Disorder of Protein Misfolding 747
- 27.4.1 Alzheimer's – A Protein Misfolding Disorder 748
- 27.4.2 Protein Misfolding of Beta-Amyloid 748
- 27.5 Quantum Biochemistry and Designing Drugs for Alzheimer's Disease 750
- 27.5.1 Approach 1 – Homotaurine 751
- 27.5.2 Approach 2 – Melatonin 752
- 27.6 Conclusions 753
- References 754
- 28 Targeting Butyrylcholinesterase for Alzheimer's Disease Therapy 757**
Katherine V. Darvesh, Ian R. Pottie, Robert S. McDonald, Earl Martin, and Sultan Darvesh
- 28.1 Butyrylcholinesterase and the Regulation of Cholinergic Neurotransmission 757
- 28.2 Butyrylcholinesterase: The Significant other Cholinesterase, in Sickness and in Health 760
- 28.3 Optimizing Specific Inhibitors of Butyrylcholinesterase Based on the Phenothiazine Scaffold 761
- 28.4 Biological Evaluation of Phenothiazine Derivatives as Cholinesterase Inhibitors 761
- 28.5 Computation of Physical Parameters to Interpret Structure–Activity Relationships 769

28.6	Enzyme–Inhibitor Structure–Activity Relationships	772
28.7	Conclusions	777
	References	778
29	Reduction Potentials of Peptide-Bound Copper (II) – Relevance for Alzheimer’s Disease and Prion Diseases	781
	<i>Arvi Rauk</i>	
29.1	Introduction	781
29.2	Copper Binding in Albumin – Type 2	783
29.3	Copper Binding to Ceruloplasmin – Type 1	785
29.4	The Prion Protein Octarepeat Region	787
29.5	Copper and the Amyloid Beta Peptide (A β) of Alzheimer’s Disease	789
29.6	Cu(II)/Cu(I) Reduction Potentials in Cu/A β	791
29.7	Concluding Remarks	794
29.A	Appendix	795
29.A.1	Calculation of Reduction Potentials, E $^{\circ}$, of Copper/Peptide Complexes	795
29.A.2	Computational Methodology	796
	References	798
30	Theoretical Investigation of NSAID Photodegradation Mechanisms	805
	<i>Klefa A.K. Musa and Leif A. Eriksson</i>	
30.1	Drug Safety	805
30.2	Drug Photosensitivity	806
30.2.1	Photoallergies	807
30.2.2	Photophobia	807
30.2.3	Phototoxicity	807
30.3	Non-Steroid Anti-Inflammatory Drugs (NSAIDs)	808
30.3.1	NSAID: Definition and Classification	808
30.3.2	Pharmacological Action	808
30.3.3	NSAID Uses	809
30.3.4	Side Effects	810
30.4	NSAID Phototoxicity	811
30.5	Theoretical Studies	812
30.5.1	Overview	812
30.5.2	Methodology	814
30.6	Redox Chemistry	815
30.7	NSAID Orbital Structures	817
30.8	NSAID Absorption Spectra	820
30.9	Excited State Reactions	823
30.9.1	Photodegradation from the T $_1$ State	825
30.9.2	Possible Photodegradation from Singlet Excited States	826
30.10	Reactive Oxygen Species (ROS) and Radical Formation	827

- 30.11 Effects of the Formed ROS and Radicals during the Photodegradation Mechanisms 828
- 30.12 Conclusions 830
References 831

Part Five Biochemical Signature of Quantum Indeterminism 835

31 Quantum Indeterminism, Mutation, Natural Selection, and the Meaning of Life 837

David N. Stamos

- 31.1 Introduction 837
- 31.2 A Short History of the Debate in Philosophy of Biology 839
- 31.3 Replies to My Paper 842
- 31.4 The Quantum Indeterministic Basis of Mutations 845
 - 31.4.1 Tautomeric Shifts 845
 - 31.4.2 Proton Tunneling 849
 - 31.4.3 Aqueous Thermal Motion 852
- 31.5 Mutation and the Direction of Evolution 853
- 31.6 Mutational Order 855
- 31.7 The Nature of Natural Selection 857
- 31.8 The Meaning of Life 863
References 867

32 Molecular Orbitals: Dispositions or Predictive Structures? 873

Jean-Pierre Llored and Michel Bitbol

- 32.1 Origins of Quantum Models in Chemistry: The Composite and the Aggregate 874
- 32.2 Evolution of the Quantum Approaches and Biology 876
- 32.3 Philosophical Implications of Molecular Quantum Holism: Dispositions and Predictive Structures 882
 - 32.3.1 Molecular Landscapes and Process 882
 - 32.3.2 Realism of Disposition and Predictive Structures 886
- 32.4 Closing Remarks 893
References 893

Index 897