

Contents

<i>Preface</i>	xvii
<i>Acknowledgements</i>	xxi
<i>List of Abbreviations</i>	xxiii
 Chapter 1	
Introduction: The Protein	
Folding Problem — Some of the	
Myths Associated with the Protein	
Folding Theories	1
 Chapter 2	
From Frank and Evans'	
Iceberg Formation Conjecture	
to the Explanation of the	
Hydrophobic Effect	13
2.1 Abstract	13
2.2 The Origin of the Myth and Some	
Historical Notes	14
2.3 The Evolution of the Myth . . .	24
2.4 Some Theoretical Questions . .	27
2.4.1 How Can a Simple	
Nonpolar Solute, Such as	
Argon, Form "Icebergs"?	28

2.4.2	The General Statistical-Mechanical Expressions for the Thermodynamics of Solvation of Nonpolar Solutes in Water	37
2.4.3	Application of the Two-Structure Model for Water; the Low- and High-Local-Density Components	41
2.4.4	An Exact Argument Using a Hypothetical Hard Point Particle	46
2.4.5	An Approximate Estimate of the Contribution of Structural Changes to the Solvation Entropy	49
2.4.6	Generalization for $H\phi O$ Interaction and for Any Reaction	52
2.5	Does the Enhancement of the Structure of Water Explain the Large Positive Partial Molar Heat Capacity of Nonpolar Solutes in Water?	55
2.6	Conclusion	60

Chapter 3	From Schellman's Experiments to Fersht's Hydrogen Bond Inventory Argument	63
3.1	Abstract	63
3.2	The Origin of the Myth and Some Historical Notes	64
3.3	The Evolution of the Myth that HBs Are Insignificant in Protein Stability	68
3.4	Why the Hydrogen Bond Inventory Argument is Wrong	71
3.5	Another Way to Analyze the Gibbs Energy Change in the Formation of an HB	76
3.6	The Entropy and the Enthalpy Change Associated with the Reaction (3.3)	79
3.7	Conclusion	84
Chapter 4	From Kauzmann's Conjecture to the Myth That the Hydrophobic Effect is the Dominant Factor in Protein Stability	85
4.1	Abstract	85
4.2	The Origin of the Myth and Some Historical Notes	87

4.3	The Evolution of the Hydrophobic Effect in Protein Folding	91
4.4	Cracks in the Kauzmann Conjecture About the Hydrophobic Effect	94
4.5	An Inventory of All Possible Solvent-induced Effects	98
4.6	The "Evidence" in Favor of the $H\phi O$ Effects in Protein Folding	102
4.7	The Evidence in Favor of the $H\phi I$ Effects in Protein Folding	115
4.8	The Relevance of the $H\phi I$ Effects to Biochemical Processes Involving Proteins	119
4.9	Conclusion	124
Chapter 5	From Levinthal's Question to Resolving Levinthal's "Paradox"	127
5.1	Abstract	127
5.2	The Origin of the Myth and Some Historical Notes	128
5.3	Attempts to Resolve the Levinthal Paradox	132
5.4	Target-Based Versus Cause-Based Processes	136
5.5	What Is the Answer to Levinthal's Question?	139
5.6	The Hydrophilic Forces	142

5.7	Implementation of $H\phi I$ Forces in Protein Folding; the Answer to Levinthal's Question	153
5.8	Conclusion	160
Chapter 6	From Anfinsen's Hypothesis to the Frenetic Pursuit of the Global Minimum in the Gibbs Energy Landscape	163
6.1	Abstract	163
6.2	The Origin of the Myth	164
6.3	The Evolution of the "Folding Code" Myth	166
6.4	Why a Folding Code Is Unlikely to Exist	168
6.4.1	No One-to-One Code Exists	168
6.4.2	What Is the "Alphabet" of the 3D Structure?	170
6.4.3	Did Evolution "Solve" the Protein Folding Problem?	172
6.5	The Myth That the Native Structure Resides in the Global Minimum of the GEL	175
6.6	A Minimum of Gibbs Energy with Respect to What?	176
6.7	The Evolution of the Myth	180
6.8	The Search for a Global Minimum in the EL or in the Potential Energy Surface	186

6.9	The Search for the Structure of Protein by Simulation	189
6.9.1	The Anfinsen-Type Experiment	190
6.9.2	The Non-Anfinsen Type of Renaturation Experiment	198
6.9.3	Dependence on the Initial Conditions	202
6.10	Conclusion	211
Chapter 7	Some Candidates Which Can Potentially Evolve into New Myths	213
7.1	The Landscape Theory of Protein Folding	214
7.1.1	The Energy Landscape	215
7.1.2	The Gibbs Energy Landscape	220
7.1.3	The Thermodynamic Potential Energy Landscape	227
7.1.4	The Potential Energy Surface	228
7.2	A Funnel-like Theory of Protein Folding	231
7.3	The Principle of Consistency	238
7.4	The Application of Lattice Models for Studying Protein Folding	243

7.5	The Principle of Minimal Frustration	245
7.6	The Structure–Function Paradigm	260
Appendix A	The Definition of the Solvation Process and the Corresponding Thermodynamic Quantities	263
A.1	The Old Definition of the Solvation Process	264
A.2	The New Definition of the Solvation Process	265
A.3	Solvation Gibbs Energy of a Molecule with Internal Rotations	269
A.4	The Solvation Volume	275
A.5	The Solvation Enthalpy	277
A.6	The Solvation Entropy	278
Appendix B	The Definition of the Structure of Water and Changes in the Structure Induced by a Solute	281
Appendix C	Le Chatelier’s Principle Applied to the Two-Structure Model for Water	293
Appendix D	The Stability Condition for a Chemical Reaction: $A \rightleftharpoons B$	299

Appendix E	Solvation Gibbs Energy of the Hard Sphere and the Work of Cavity Formation	301
Appendix F	Formal Expression for the Thermodynamic Quantities of Solvation of a Nonpolar Solute	305
Appendix G	The Solvation Entropy and Solvation Energy; Structural Changes in the Solvent	309
Appendix H	The Solubility of a Simple Solute in Water and Structural Changes Induced in the Solvent	311
Appendix I	Ben-Naim's "Pitfalls": Don Quixote's Windmill	317
Appendix J	Examples of Gibbs Energy Landscapes and Gibbs Energy Functionals	325
Appendix K	The Existence of a <i>Single</i> Minimum of the Gibbs Energy Functional	347
Appendix L	Nonadditivity of the Gibbs Energy Function	359
	L.1 The Source of the Nonadditivity of the PMF . .	362
	L.2 Conclusion	370

Appendix M	Nonadditivity in Binding Systems	371
	M.1 The Model and Its Partition Function	371
	M.2 Probabilities and Correlations	374
Appendix N	Frustration in Three Dipoles on a Lattice: An Informational-Theoretical Approach	381
	N.1 The Three Dipoles at the Vertices of Regular Triangles .	381
	N.2 Some Numerical Results . . .	388
<i>Epilogue</i>		395
<i>References</i>		411
<i>Index</i>		421