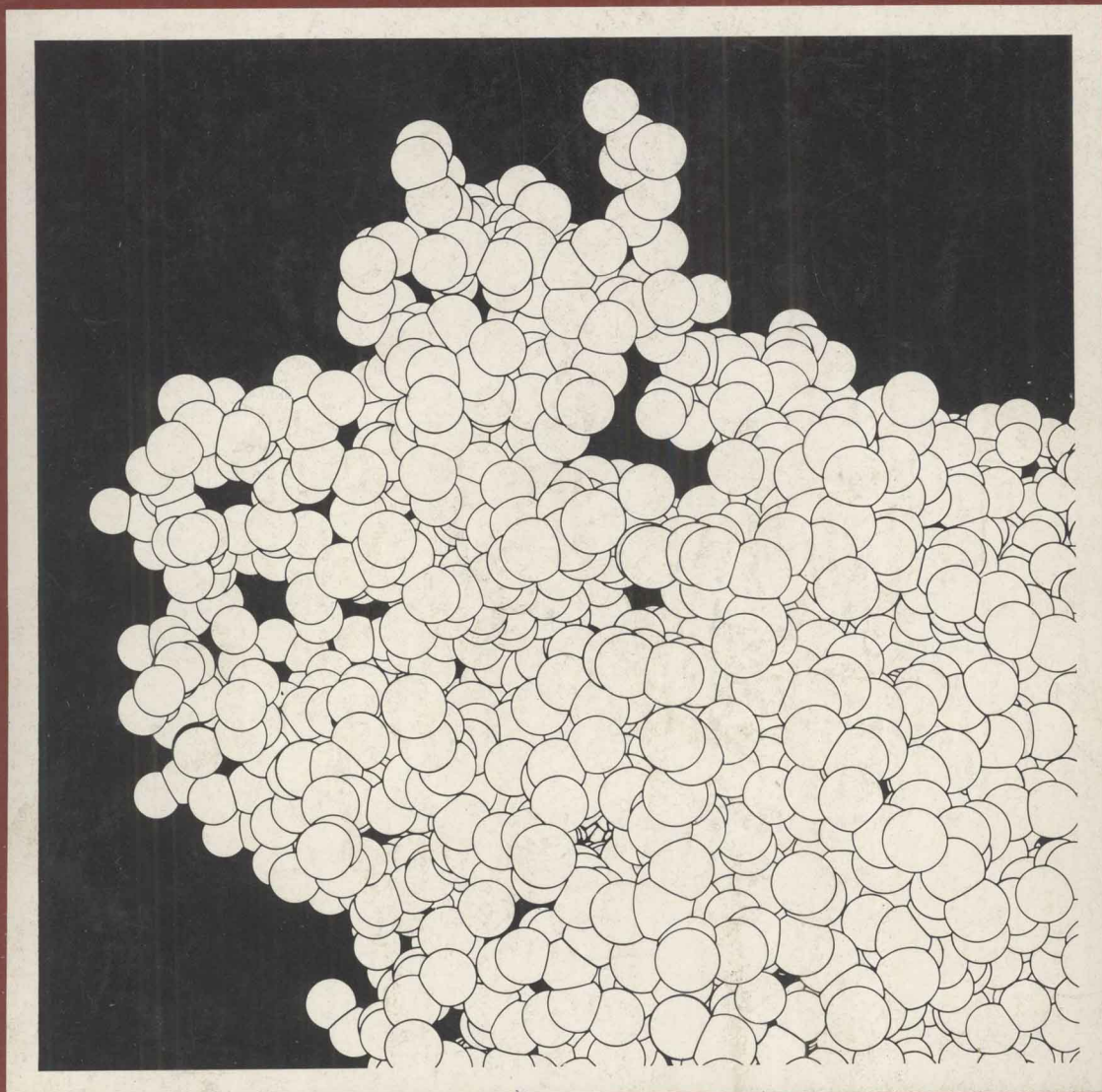


BIOPHYSICAL CHEMISTRY

Part I: The conformation of biological macromolecules

Cantor and Schimmel



BIOPHYSICAL CHEMISTRY

PART

I

THE CONFORMATION OF BIOLOGICAL MACROMOLECULES

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W. H. FREEMAN AND COMPANY
San Francisco

Cover drawing created by Steve Levine of the Lawrence Livermore Laboratories, using the Atoms program written by Ken Knowlton and Lorinda Cherry of Bell Laboratories and coordinates provided by R. G. Shulman.

Sponsoring Editor: Arthur C. Bartlett
Project Editor: Pearl C. Vapnek
Manuscript Editor: Lawrence W. McCombs
Designer: Robert Ishi
Production Coordinator: Linda Jupiter
Illustration Coordinator: Cheryl Nufer
Artists: Irving Geis and Eric Hieber
Compositor: Syntax International
Printer and Binder: R. R. Donnelley & Sons Company

Figures 1-1, 1-4a, 1-5, 1-12, 2-10, 2-12, 2-18, 2-20, 2-23, 2-25, 2-31, 2-32, 2-33, 2-36, 2-44, 2-45, in Box 2-5, 3-12, 3-13, 3-17c, 3-21, 4-4b, 5-16, 5-18 copyright © 1980 by Irving Geis.

Library of Congress Cataloging in Publication Data

Cantor, Charles R. 1942–
The conformation of biological macromolecules.
(Their Biophysical chemistry; pt. 1)
Includes bibliographies and indexes.
1. Macromolecules. 2. Chemistry, Physical organic—Technique. I. Schimmel, Paul Reinhard, 1940– joint author. II. Title.
QH345.C36 pt. 1 574.1'9283s [574.1'924] 79-22043
ISBN 0-7167-1042-0
ISBN 0-7167-1188-5 pbk.

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Printed in the United States of America

9 8 7 6 5 4 3 2 1

BIOPHYSICAL CHEMISTRY

***To Louis and Ida Dianne Cantor
and Alfred and Doris Schimmel***

Preface

Biophysical Chemistry is concerned with biological macromolecules and complexes or arrays of macromolecules. The work deals with the conformation, shape, structure, conformational changes, dynamics, and interactions of such systems. Our goal is to convey the major principles and concepts that are at the heart of the field. These principles and concepts are drawn from physics, chemistry, and biology.

We have aimed at creating a multilevel textbook in three separately bound parts. The material covers a broad range of sophistication so that the text can be used in both undergraduate and graduate courses. It also should be of value to general scientific readers who simply wish to become familiar with the field, as well as to experienced research scientists in the biophysical area. For example, perhaps half of the material requires only the background provided by a one-semester undergraduate course in physical chemistry. A somewhat smaller fraction necessitates the use of concepts and mathematical techniques generally associated with a more sophisticated background, such as elementary statistical thermodynamics and quantum mechanics.

Biophysical Chemistry is organized into three parts. The first part deals with the structure of biological macromolecules and the forces that determine this structure. Chapter 1 introduces the fundamental questions of interest to biophysical chemists, Chapters 2–4 summarize the known structures of proteins, nucleic acids, and other biopolymers, and Chapters 5–6 treat noncovalent forces and conformational analysis.

Part II summarizes some of the techniques used in studying biological structure and function. The emphasis is on a detailed discussion of a few techniques rather than an attempt to describe every known technique. Chapters 7–9 cover spectroscopic methods, Chapters 10–12 deal with hydrodynamic methods, and Chapters 13–14 discuss x-ray and other scattering and diffraction techniques.

Part III demonstrates how techniques and principles are used in concert to gain an understanding of the behavior and properties of biological macromolecules. The focus is on the thermodynamics and kinetics of conformational changes and ligand interactions. New techniques are introduced as needed, and a few selected case

histories or systems are discussed in considerable detail. The topics include ligand interactions (Chapters 15–17), the special theories and techniques used to study molecules that are statistical chains rather than definite folded conformations (Chapters 18–19), protein conformational changes (Chapters 20–21), nucleic acid conformational changes (Chapters 22–24), and membranes (Chapter 25).

We have made every effort to keep the chapters as independent as possible, so that the reader has a wide choice of both the material to be covered and the order in which it is to be treated. Extensive cross-references to various chapters are included to help the reader find necessary background material if the parts are not read in sequence. Where possible, examples are taken repeatedly from a small number of systems, so that the reader can have the experience of contrasting information gained about the same protein or nucleic acid from a variety of different approaches.

Within each chapter, we have attempted to maintain a uniform level of rigor or sophistication. Short digressions from this level are segregated into boxes; longer digressions are indicated by a bullet (•) preceding the section or subsection heading. Readers with a less rigorous background in physics, mathematics, and physical chemistry should find helpful the many boxes that review elementary material and make the text fairly self-contained; Appendix A provides a basic review of principles of matrix algebra. Other boxes and special subsections are aimed at advanced readers; in many cases, these discussions attempt to illuminate points that we ourselves found confusing.

In different sections, the level of mathematical sophistication varies quite significantly. We have tried to use the simplest mathematical formulation that permits a clear presentation of each subject. For example, hydrodynamic properties are treated in one dimension only. The form of a number of the fundamental equations is extracted by dimensional analysis rather than through lengthy (and not particularly instructive) solutions of hydrodynamic boundary-value problems. On the other hand, x-ray and other scattering phenomena are treated by Fourier transforms, and many problems in statistical mechanics are treated with matrix methods. These advanced mathematical techniques are used in only a few chapters, and numerous boxes are provided to assist the reader with no previous exposure to such methods. The remaining sections and chapters are self-contained and can be understood completely without this advanced mathematical formalism.

Some techniques and systems are not covered in any fair detail. This represents a biased choice by the authors, not necessarily of which techniques we feel are important, but simply of which are instructive for the beginning student in this field.

Each chapter concludes with a summary of the major ideas covered. In addition, each chapter is heavily illustrated, including some special drawings by Irving Geis. Certainly, much can be learned simply by reading the chapter summaries and by studying the illustrations. Also, we believe the illustrations convey some of the excitement of the field.

Problems are provided at the end of each chapter. These vary in difficulty from relatively simple to a few where the full answer is not known, at least to the authors. Answers to problems are provided in Appendix B.

Detailed literature citations are not included, except to acknowledge the source of published material reproduced or adapted here. However, a list of critical references for each chapter is included. In virtually all cases, these articles will provide an immediate entrée to the original papers needed for more detailed study.

The problem of notation and abbreviations in this field is a difficult one. In drawing together material from so many different types of research, we have had to adapt the notation to achieve consistency and to avoid confusion among similar symbols. Wherever possible, we have followed the recommendations of the American Chemical Society, but inevitably we have had to develop some conventions of our own. A glossary of some of the more frequently used symbols is provided.

At MIT some of this material has been used in an undergraduate course in biophysical chemistry. The course was designed to meet the needs of students wishing a second course in physical chemistry, but developed in a biochemical framework. The idea was to construct a course that covered much of the same material with the same rigor as a parallel, more traditional course. The only preparation required was a one-semester course in undergraduate physical chemistry, which at MIT is largely concerned with chemical thermodynamics.

Over the years graduate courses in biophysical chemistry at MIT and at Columbia have made use of much of the material presented here. In addition, a special-topics course in protein structure has used some of the material. Because a broad range of subjects is covered, its usefulness as a text will hopefully meet a variety of individual teaching tastes and preferences, as well as enable instructors to vary content as needs develop and change.

It is obvious that a work of this complexity cannot represent solely the efforts of its two authors. As we sought to master and explain the wide range of topics represented in biophysical chemistry, we learned why so few books have been written in this field in the past two decades. We owe a great debt to many who helped us in ways ranging from sharing their understanding to providing original research data.

We give special thanks to Irving Geis, for his effort on a number of complex illustrations and for his helpful advice on numerous other drawings; to Wilma Olson, for reading a major portion of the entire manuscript; to Robert Alberty and Gordon Hammes, for their influence, through teaching and discussions, on the material on biochemical equilibria and kinetics; to Richard Dickerson, for providing material and advice that were essential for the preparation of Chapter 13; to Paul Flory, for inspiring our treatment of conformational energies and configurational statistics of macromolecules; to Howard Schachman, whose course at Berkeley inspired parts of several chapters; to R. Wayne Oler, for bringing the authors together for this undertaking, and to Bruce Armbruster, for sealing the commitment; to the helpful people at W. H. Freeman and Company, including Ruth Allen, Arthur Bartlett, Robert Ishi, Larry McCombs, and Pearl Vapnek; to Kim Engel, Karen Haynes, Marie Ludwig, Joanne Meshna, Peggy Nelson, Cathy Putland, and Judy Schimmel, for typing and related work associated with the manuscript; and to Cassandra Smith and to Judy, Kathy, and Kirsten Schimmel, for their patience with the intrusion this work has made on the authors' lives.

Many people read and commented on specific chapters, provided figures, notes and materials, and spent much time with us in helpful discussions. We gratefully thank these people: Robert Alberty, Arthur Arnone, Struther Arnott, P. W. Atkins, Robert Baldwin, Larry Berliner, Bruce Berne, Richard Bersohn, Sherman Beychok, Victor Bloomfield, David Brandt, John Brandts, John Chambers, Sunney Chan, Patricia Cole, Robert Crichton, Francis Crick, Donald Crothers, Norman Davidson, Richard Dickerson, David Eisenberg, Robert Fairclough, Gerry Fasman, George Flynn, David Freifelder, Ronald Gamble, Robert Gennis, Murray Goodman, Jonathan Greer, O. Hayes Griffith, Gordon Hammes, John Hearst, Ellen Henderson, James Hildebrandt, Wray Huestis, Sung Hou Kim, Aaron Klug, Nelson Leonard, H. J. Li, Stephen Lippard, Richard Lord, Brian Matthews, Harden McConnell, Peter Moore, Garth Nicolson, Leonard Peller, Richard Perham, Michael Raftery, Alexander Rich, Frederick Richards, David Richardson, Wolfram Saenger, Howard Schachman, Harold Scheraga, Benno Schoenborn, Verne Schumaker, Nadrian Seeman, Robert Shulman, Mavis Shure, Louise Slade, Cassandra Smith, Hank Sobell, Thomas Steitz, Robert Stroud, Lubert Stryer, Serge Timasheff, Ignacio Tinoco, Jr., Richard Vandlen, Jerome Vinograd, Peter von Hippel, Christopher Walsh, James Wang, Gregorio Weber, Peter Wellauer, Barbara Wells, Robert Wells, William Winter, Harold Wyckoff, Jeffries Wyman, and Bruno Zimm.

November 1979

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Glossary of symbols

This glossary includes some of the symbols used extensively throughout the text. In many cases, the same or very similar symbols are used in certain contexts with other meanings; the meaning of a symbol is explained in the text where it is introduced.

Symbol	Meaning	Symbol	Meaning
A	Absorbance.	c_p	Plateau weight concentration.
A_{ij}	Amplitude of kinetic decay.	\hat{c}_i	Weight concentration of i th species or component.
\AA	Angstroms.	\mathbf{c}	Unit cell basis vector.
a	Hyperfine splitting constant. Long semi-axis of ellipse. Persistence length.	\mathbf{c}^*	Reciprocal cell basis vector.
\mathbf{a}	Unit cell basis vector.	D	Debye.
\mathbf{a}^*	Reciprocal cell basis vector.	D	Translational diffusion constant.
a_{ij}	Parameters composed of rate constants.	D_n	Dihedral symmetry group element.
a_s	Exponent relating sedimentation to chain length.	D_{rot}	Rotational diffusion constant.
a_η	Exponent relating viscosity to chain length.	$D_{20,w}$	D extrapolated to 20° C, water.
b	Short semiaxis of ellipse.	E_a	Activation energy.
\mathbf{b}	Unit cell basis vector.	E_d	Interaction energy between two dipoles.
\mathbf{b}^*	Reciprocal cell basis vector.	E_{kl}	Nonbonded pair interaction potential.
C	Molar concentration.	E_{tor}	Torsional potential energy.
C_n	Rotational symmetry group element.	$E(\Phi_i, \Psi_i),$	
	Characteristic ratio.	E_i	Total rotational potential for residue i .
C_∞	Limiting characteristic ratio.	\mathbf{E}	Electric field.
ΔC_p^0	Standard constant pressure heat capacity change per mole.	e	Exponential function. Unit of charge on electron.
c	Velocity of light in vacuum. Ratio of k_R/k_T . Weight concentration.	F	Frictional coefficient ratio.
		$F(\mathbf{S})$	Structure factor.
		$F_H(\mathbf{S})$	Structure factor, heavy-atom contribution.

Symbol	Meaning	Symbol	Meaning
$F_{\text{Tot}}(\text{S})$	Structure factor for an array.	\mathbf{H}_{res}	Magnetic field at which resonance occurs.
$F_{\text{m}}(\text{S})$	Molecular structure factor.	\mathbf{H}	Hamiltonian operator.
\mathbf{F}	Force.	$\Delta\mathbf{H}_{\text{loc}}$	Magnetic field generated by local environment.
\mathcal{F}	The Faraday.	h	Planck's constant.
f	Translational frictional coefficient.	\hbar	$h/2\pi$
f_{app}	Apparent fractional denaturation.	I	Intensity of radiation. Nuclear spin quantum number. Ionic strength.
f_{D}	Fraction in denatured state.	$I(\text{S})$	Scattering intensity relative to a single electron at the origin.
f_{N}	Fraction in native state.	i	$\sqrt{-1}$
f_{min}	Translational friction coefficient of anhydrous sphere.	$\hat{\mathbf{i}}$	Cartesian unit vector.
f_{rot}	Rotational friction coefficient for sphere.	J	NMR coupling constant.
f_{sph}	Translational friction coefficient for sphere.	\mathbf{J}_2	Solute flux.
f_a, f_b	Rotational friction coefficient around a , b axis of ellipse.	$\hat{\mathbf{j}}$	Cartesian unit vector.
G	Gibbs free energy.	K_{D}	True equilibrium constant for conversion from fully native to fully denatured state.
ΔG^0	Standard Gibbs free energy change per mole.	K_{p}	Michaelis constant for product.
$\Delta\bar{G}^0$	Intrinsic standard free energy change (with statistical component removed).	K_{S}	Michaelis constant for substrate.
$\Delta G_{\text{I},ij}$	Free energy of interaction between two ligands.	K_{η}	Coefficient relating viscosity to chain length.
ΔG_{r}	ΔG per residue.	K_{s}	Coefficient relating sedimentation to chain length.
ΔG_{Tot}	Total free energy change per mole.	K_{app}	Apparent equilibrium constant for conversion from fully native to fully denatured state.
ΔG_{el}	Change in electrostatic free energy.	K_i	Macroscopic equilibrium constant. Equilibrium constant for forming i th configuration. Equilibrium constant for transition from native state to intermediate state i .
ΔG_{T}	Total free energy of formation of configuration.	\tilde{K}_i	Apparent dissociation constant, one-ligand system.
$\Delta\Delta G_{\text{T}}$	Difference in ΔG_{T} between two configurations.	\tilde{K}_{ij}	Apparent dissociation constant, two-ligand system.
$\Delta\bar{G}_{\text{gr}}$	Average helix growth free energy change per residue pair.	k	Boltzmann's constant. Microscopic equilibrium dissociation constant.
g	g value for free electron, 2.00232.	k_{R}	Microscopic dissociation constant for R state.
g_x , etc.	Component of g -factor tensor.	k_{T}	Microscopic dissociation constant for T state.
H	Enthalpy.	k_i	Microscopic equilibrium constant.
H_{xy}	Magnetic field in xy plane.	$\hat{\mathbf{k}}$	Cartesian unit vector.
ΔH	Enthalpy change per mole.		
ΔH^0	Standard enthalpy change per mole.		
ΔH_{r}	ΔH per residue.		
ΔH_{D}	Enthalpy change for conversion from fully native to fully denatured state.		
ΔH_{app}	Apparent enthalpy change for conversion from fully native to fully denatured state.		
\mathbf{H}	Magnetic field.		

Symbol	Meaning	Symbol	Meaning
L_c	Contour length.	P_r	Axial ratio.
L, L'	Equilibrium constant for $R_0 \rightleftharpoons T_0$.	pK_a	$-\log_{10} K_a$
L	Angular momentum.	pO_2	Partial pressure of oxygen.
l	Length of one polymer bond.	$(pO_2)_{1/2}$	Partial pressure of oxygen at half saturation.
l_e	Length of statistical segment.	\hat{p}	Momentum operator.
M	Molecular weight.	Q	Configurational partition function.
\bar{M}_n	Number-average molecular weight.	R	Gas constant.
\bar{M}_w	Weight-average molecular weight.	R_G	Radius of gyration.
\bar{M}_i	Molecular weight of i th macromolecular species.	$\langle R_G^2 \rangle_0$	Unperturbed mean square radius of gyration.
M_{ij}	Species with i bound L_1 and j bound L_2 .	\bar{R}	Fraction of molecules in R state.
$M^{(j)}$	Set of all species with j bound L_2 .	\hat{R}	Nuclear position operator.
M	Magnetization.	$\hat{R}(\alpha, \beta)$	Coordinate transformation matrix.
M_{xy}	Magnetization in xy plane.	r	Distance of separation.
\bar{M}	Statistical weight matrix.	r_D	Donnan ratio.
m	Colligative molality. Mass of object.	r_e	Radius of equivalent sphere.
m_e	Mass of electron.	$\langle r^2 \rangle_0$	Unperturbed mean square end-to-end distance.
m_i	Molality of i th species.	r	Polymer end-to-end vector.
m_s	Quantum number of electron spin along z axis.	\hat{r}	Electron position operator.
m_l	Quantum number of nuclear spin along z axis.	S	Svedberg (unit of sedimentation coefficient).
m'	Total molality.	S_A	Partial molal entropy.
\hat{m}	Magnetic dipole operator.	S'_A	Unitary part of S_A .
N_0	Avogadro's number.	ΔS_r	ΔS per residue.
N_C	Number of carbons in amphiphile R chain.	ΔS^0	Standard entropy change.
N'_C	Number of carbons in amphiphile that are imbedded in hydrocarbon core of micelle.	ΔS_u^0	Unitary standard entropy change.
N_e	Number of statistical segments.	S	Scattering vector.
N_{Ch}	Number of chains in micelle.	s	Sedimentation coefficient. Statistical weight. Equilibrium constant for helix growth. Equilibrium constant for base-pair formation.
N_{hg}	Number of head groups in micelle.	$s_{20,w}$	Sedimentation coefficient corrected to 20° C, water.
n	Refractive index. Number of sites. Number of bonds in polymer.	\hat{s}	Unit vector along scattered radiation.
n_i	Number of moles of component i . Number of sites of certain type.	\hat{s}_0	Unit vector along incident radiation.
n_w	Weight-average degree of polymerization.	T	Temperature (in degrees Kelvin usually).
P	Pitch of helix. Pressure. Patterson function.	T_m	Melting temperature.
P_0	Solvent vapor pressure.	T_1	Longitudinal relaxation time.
P_v	Solvent vapor pressure in presence of solute.	T_2	Transverse relaxation time.
		\hat{T}_i	Transformation matrix.
		t	Time.

Symbol	Meaning	Symbol	Meaning
U_{mic}^0	Attractive part of μ_{mic}^0 .	Γ	Parameter affecting relaxation amplitudes.
u	Component of M_{xy} in phase with H_{xy} . Electrophoretic mobility.	γ	Magnetogyric ratio. $(A)/K_{\text{AR}}$ binding parameter. Velocity gradient dv_x/dz .
V	Volume.	δ	Chemical shift parameter. Phase shift.
V_h	Hydrated volume.	$\delta(x)$	Dirac delta function of argument x .
\bar{V}_i	Partial specific volume of component i .	δ_1	Hydration (in grams per gram).
V_p	Maximum reaction velocity in reverse direction.	δ_{ij}	Kronecker delta.
V_s	Maximum reaction velocity in forward direction.	ϵ	Dielectric constant. Molar decadic or residue extinction coefficient.
v	Speed (also called velocity). Component of M_{xy} out of phase with H_{xy} .	$\Delta\epsilon$	Circular dichroism ($\epsilon_L - \epsilon_R$).
v_i	Initial reaction velocity.	η	Solution viscosity.
$\langle v_2 \rangle$	Effective average solute velocity.	η_0	Solvent viscosity.
\bar{v}	Partial molar volume.	η_{rel}	Relative viscosity.
\bar{v}_s	Partial molar volume of pure solvent.	η_{sp}	Specific viscosity.
\mathbf{v}	Velocity.	$[\eta]$	Intrinsic viscosity.
$W(r)$	Radial distribution function of end-to-end distance.	Θ_i	Fractional saturation of i th site.
$W(x,y,z)$	End-to-end distance distribution function.	θ	Scattering angle. Fractional helicity.
W_{mic}^0	Repulsive part of μ_{mic}^0 .	$[\theta]$	Molar ellipticity.
(\bar{X}_i)	Equilibrium concentration.	$\hat{\Lambda}$	Matrix of λ_i 's.
$\Delta(X_i)$	Difference between temporal and equilibrium concentration.	$\tilde{\lambda}$	Eigenvalue. Wavelength. Kinetic decay time.
x_b	Bottom of cell.	λ_j	j th kinetic decay time of j th eigenvalue.
x_m	Meniscus position.	λ_1, λ_2	Parameters composed of rate constants.
y	General physical property.	μ_i	Chemical potential per mole.
y_D	Physical property of denatured state.	μ_i^0	Standard chemical potential per mole.
y_N	Physical property of native state.	$\hat{\mu}_i$	Chemical potential per gram.
\bar{y}	Fractional saturation of site.	$\hat{\mu}_i^0$	Standard chemical potential per gram.
\bar{y}_F	Fractional saturation with ligand F.	μ_{mic}^0	Standard chemical potential of amphiphile in micelle.
z	Charge on macromolecule or ion in units of e .	μ_w^0	Standard chemical potential of amphiphile in aqueous phase.
z_i	Ionic valence of i th ion.	μ_m	Magnetic moment.
α	Degree of association. Dimensionless binding parameter like $(F)/k_R$.	$\tilde{\mu}$	Electric dipole moment operator.
α_H	Hill constant.	ν	Frequency. Simha factor in viscosity. Moles of ligand bound per mole of macromolecule.
β	Dimensionless binding parameter.	ν_N	Saturation density for lattice with N units.
β_e	Bohr magneton.	π	Osmotic pressure.
β_n	Nuclear magneton.	ρ	Mass density (in grams per cm^3).
β_s	Mandelkern-Flory-Scheraga parameter.	$\rho(\mathbf{r})$	Electron density.
β'	Scheraga-Mandelkern parameter.	σ	Nucleation constant.

Symbol	Meaning
σ_h	Superhelix density.
τ	Number of supercoils.
τ_F	Fluorescence decay time.
τ_a, τ_b	Rotational relaxation time for a -, b -axis orientation.
τ_c	Rotational correlation time.
τ_r	Rotational relaxation time of sphere.
τ, τ_j	Reaction relaxation times.
Φ	Electrical potential. Voltage difference.
Φ_c	Universal constant for random coils $2 \cdot 1 \times 10^{23}$.
ϕ	N-C' torsional angle. Phase of complex number.
$\phi_{1a}, \phi_{20},$ etc.	Monomer wave functions.
ϕ_F	Fluorescence quantum yield.
ϕ_p	Practical osmotic coefficient.
ϕ', ϕ''	Nucleic acid backbone torsional angles.
$[\phi]$	Molar rotation per residue.
χ	Mole fraction of all solute species.
χ_i	Mole fraction of i th component.
χ_A	Mole fraction of A th component.
χ_{gc}	Mole fraction G + C.
χ	Glycosidic bond torsional angle.
ψ	C'-C torsional angle.
ψ', ψ''	Nucleic acid backbone torsional angles.
Ω_{jk}	Number of ways of putting k helical units into j separated sequences.
Ω_k	$(n - k + 1)$ number of ways of placing k helical units in one sequence within chain of n residues.
$\Omega_{n,i}$	Number of ways of assorting i items (ligands) in n boxes (sites).

Symbol	Meaning
ω	Circular frequency or angular velocity.
ω_0	Larmor frequency.
ω', ω''	Nucleic acid backbone torsional angles.
$\Delta\omega_{1/2}$	Line width.
ω	Angular velocity.
imag	Imaginary part of.
$\langle \rangle$	Average.
$\langle \rangle$	Overlap integral.
$\langle \rangle$	Expectation value integral.
*	Superscript, complex conjugate, as in F^* .
\parallel	Amplitude of complex number or length of vector, as in $ F $.
∇	Vector differential.
()	Molar concentration, as in (A).
\dagger	Superscript, transpose of matrix, as in A^\dagger .
\sim	Superscript, convolution product, as in $\hat{A}B$.

General Rules

K	Macroscopic equilibrium constant.
k	Microscopic equilibrium constant or rate constant.
C	Molar concentration.
c	Weight concentration.
\underline{M}	All matrices and operators.
\hat{i}	All unit vectors.
R_G	Radius of gyration.
χ	Mole fraction.
Φ	Voltage or electrical potential.

Contents in detail of Part I

Contents in Brief of Parts II and III xiii

Preface xix

Glossary of Symbols xxiii

PART I THE CONFORMATION OF BIOLOGICAL MACROMOLECULES 1

Chapter 1 An Introduction to the Strategy and Tactics of Biophysical Chemistry 3

- 1-1 Levels of Structures in Biological Macromolecules 3
 - Primary structure is the sequential order of the residues 6
 - Secondary structure describes helices of residues 7
 - Tertiary structure is the three-dimensional arrangement of residues 9
 - Quaternary structure is the arrangement of subunits 12
 - 1-2 Some Central Questions in Biophysical Chemistry 13
 - Questions about sample quality 13
 - Questions about structure 19
 - Questions about function 27
 - 1-3 Some Basic Strategies of Biophysical Chemistry 33
 - Use a smaller system as a model 34
 - Observe only one part of the system 34
 - Compare two systems that are almost identical 35
 - Isolate discrete states of the system 36
- Box 1-1 A general scheme for multicomponent analysis 37

Chapter 2 Structure of Proteins 41

- 2-1 Properties of Amino Acids 41
 - Ionization of amino and carboxyl groups in amino acids and peptides 42
- Box 2-1 Principles of ionization equilibria 44
- Ionization of side chains 46
 - Ionization equilibria in proteins 47
 - Polarity of amino acid side chains 51

2-2	Composition of Proteins	54
	Amino acid composition	54
	Predicting properties from amino acid compositions	57
	Many proteins contain more than the twenty normal amino acids	59
	Metals and other prosthetic groups	62
2-3	Primary Structure	66
	Disulfides and other cross-links	66
	Primary structure and the analysis of secondary and tertiary structures	68
	Primary structure and the prediction of secondary and tertiary structures	73
	Sequences and the analysis of function	76
	Sequence comparisons among closely related proteins	76
	Mutant proteins: hemoglobin	82
2-4	Secondary Structure	86
	Box 2-2 Studies on fibers formed by deoxyhemoglobin S	88
	The α helix	91
	β Sheets and other secondary structures	94
	Polyproline helices and collagen	95
	Box 2-3 β -Sheet topologies	96
	Occurrence of secondary structures in proteins	100
2-5	Tertiary Structure	102
	General organization of the peptide backbone	103
	Environment of individual residues	110
	Packing density of amino acids in folded proteins	112
	• Volumes and mass densities of proteins	115
	Is the tertiary structure static or dynamic?	117
	Methods of comparing tertiary structures	118
	Box 2-4 Molecular dynamics calculations on proteins	118
	Relationship between structural and functional similarity	122
2-6	Quaternary Structure	127
	Symmetry considerations	127
	Box 2-5 Symmetry operations	132
	Analysis of the number of subunits and chains	135
	Arrangement of subunits	137
	The quaternary structure of aspartate transcarbamoylase	139
	Stability of globular quaternary structures	144
	• Helical quaternary structures	145
	Determination of the length of helical assemblies	149
Chapter 3 Structure of Nucleic Acids 155		
3-1	Properties of Nucleosides and Nucleotides	155
	Ionization equilibria of nucleosides and nucleotides	157
3-2	Composition of Nucleic Acids	161
	Chargaff's rules and DNAs	161
	RNA base compositions	162
	Other constituents of nucleic acids	163
3-3	Primary Structure	163
	Covalent chain structure	163
	Nucleic acid sequences	166

- Secondary structure inferences from tRNA sequence comparisons 168
- Sequence information and the analysis of structure and function 170
- Techniques for direct sequence comparison 172
- 3-4 Secondary Structure 176
 - Base pairing as a central feature of nucleic acid double strands 176
 - Structure of nucleic acid double helices 177
 - Box 3-1 How to demonstrate antiparallel double strands 179
 - Structural differences between RNA and DNA 184
 - Other polynucleotide helices 186
- 3-5 Tertiary Structure 186
 - Tertiary hydrogen-bonded interactions in tRNA 186
 - Base stacking in tRNA 195
 - Biochemical and chemical properties and the tRNA^{Phe} tertiary structure 197
 - Tertiary structure in DNA 200
- 3-6 Quaternary Structure 201

Chapter 4 Other Biological Polymers 207

- 4-1 Polysaccharides 208
 - Primary structure 208
 - Levels of structure in polysaccharides 209
 - Questions about polysaccharide structure and function 212
- 4-2 Associations Formed Among Different Macromolecule Types 213
 - Saccharide combinations with peptides, proteins, or lipids in bacterial cell walls 213
 - Glycoproteins in animal-cell surfaces 216
 - Nucleoproteins: noncovalent complexes between proteins and nucleic acids 220
 - External protein and internal nucleic acid in viruses 222
 - Intimate protein–RNA contact in ribosomes 225
 - Chromatin: a hierarchy of organized structures 226
- 4-3 Lipids in Biological Membranes 227
 - Lipid components of membranes 227
 - Pure lipids in bilayers 231
 - Mixtures of lipids in bilayers 233
 - Lipid phase transitions 234
- 4-4 Proteins in Biological Membranes 235
 - Protein, lipid, and carbohydrate components 235
 - Types and arrangements of proteins 236
 - Surface location of proteins 237
 - Lateral arrangement of proteins 238
 - Electron microscopy of freeze-etched membranes 238
 - The distribution of particular macromolecules as seen by electron microscopy 241
 - General picture of structure 241
 - The erythrocyte membrane 243
- 4-5 Protein–Lipid Interactions 245
 - Contacts between proteins and lipids in bilayers 245
 - Lipoproteins 246
 - Unknown macromolecular associations 249