Essentials of

Chemical Biology

Structure and Dynamics of Biological Macromolecules

Andrew Miller and Julian Tanner

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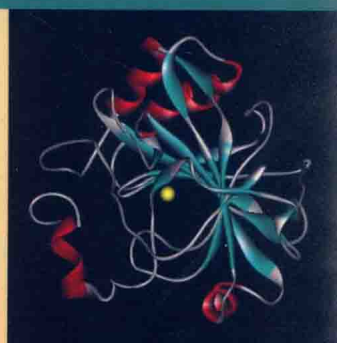

Essentials of Chemical Biology

Structure and Dynamics of Biological Macromolecules

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Essentials of Chemical Biology

To Izumi,

without whose love, patience, common sense
and great encouragement, this book
may never have been completed

Preface

Mapping the essentials of chemical biology

Chemical biology is a new, rapidly emerging branch of chemistry that represents all aspects of chemical endeavour, devoted to understanding the way biology works at the molecular level. Chemical biology is unashamedly inter-disciplinary, and chemical biology research is essentially problem driven and not discipline driven. Organic, physical, inorganic and analytical chemistry all contribute towards the chemical biology whole. Some might say that chemical biology is just another way to rebadge biochemistry. However, such a comment misses the point. Biochemistry may have started as a discipline devoted to the study of individual biological macromolecules, but this discipline has been steadily evolving into increasingly descriptive, empirical studies of larger and larger macromolecular assemblies, structures and interacting molecular networks. The molecular increasingly gives ground to the cellular. In contrast, chemical biology is about chemistry-trained graduates and researchers taking a fundamental interest in the way biology works. Consequently, the focus is on the molecular and the quantitative, where molecular properties are investigated, studied and then gradually linked to macromolecular and cellular behaviour where possible. This is a fundamentally 'bottom-up' approach to understanding biology in keeping with the chemist's natural enthusiasm and appreciation for molecular structure and behaviour first and foremost.

This textbook has been produced with the third/fourth year graduate student and young researcher in mind, namely those who have a solid background in chemical principles and are ready to apply and grow their chemical knowledge to suit a future degree or career interest in chemical biology. In preparing this textbook our objective has not been to try and cover everything currently seen as chemical biology, but instead to ask ourselves what topics and themes should be described as the essentials of chemical biology and how should these be presented in a way most appropriate and appealing for those of a chemical rather than a biological orientation. In doing this, we concluded that the true essentials of chemical biology are represented by the structure, characterisation and measurable behaviour of the main biological macromolecules and macromolecular lipid assemblies found in all cells of all organisms. We have also concluded that the activities of small molecules in biology for respiration and primary and secondary metabolism should not be included in the essentials of chemical biology except where they feature as protein prosthetic groups or otherwise modify macromolecule behaviour. In our view, simple metabolism and metabolite interconversions are the stuff

of biochemistry, whilst fascination with secondary metabolism, secondary metabolites and their interconversions has been the traditional preserve of bio-organic chemistry (a subset of organic chemistry).

Hence, in our textbook we begin with structure (Chapter 1) and synthesis (Chapters 2 and 3), then consider how structure is determined (Chapters 4–6), followed by a consideration of dynamic behaviour and molecular interactions (Chapters 7–9), concluding with molecular evolution and thoughts on the origins of life, quintessentially from the chemistry point of view (Chapter 10). Armed with such essentials, we hope that readers will then be ready to think about and then tackle any problem of their chosen interest at the chemistry–biology and/or chemistry–medicine interfaces, after a little more detailed and specific reading of course. Foremost, we hope that our textbook will provide a valuable tool for chemical biology students and researchers to open the door and step through into the extraordinary world of biology without feeling that they must leave their chemical principles behind them!

Andrew Miller
Julian Tanner

Glossary of physical terms

Chapter 1			
Potential energy	V	J	[kg m^2 s^{-2}]
Electrical point charge	q_n	C	
Vacuum permittivity	ε_0	F m^{-1}or C^2 m^{-1} J^{-1}	[C^2 kg^{-1}m^{-3} s^2]
Permittivity of medium	ε	F m^{-1}or C^2 m^{-1} J^{-1}	[C^2 kg^{-1}m^{-3} s^2]
Distance between (charge/nuclear) centres	r	m	
(Electric) dipole moment	μ_n	C m	
Polarisability volume	α'_n	m^3(Å^3, cm^3)	
Ionisation energies	I_n	J	[kg m^2 s^{-2}]
J is Joule; F is Farad; C is Coulomb	μ_{ind} or μ_{ind}	C m	
Chapter 4			
(Time dependent) induced dipole moment			
(Time dependent) electronic polarisability	α (ν_v)	C m^2 V^{-1}	
(Oscillating) electric field (of light)	?(ν_v)	V m^{-1}	
Absorbance	A or A (λ)	arbitrary units	
Optical density	OD (λ)	arbitrary units	
Pathlength (optical)	l	cm	
Extinction coefficient	ε??? or gε (λ)	l mol^{-1} cm^{-1}	
Biological macromolecular concentration	c_M	mol l^{-1}	
Wavelength	λ	nm	
Molecular weight (of protein)	M_p	D or kD	[g mol^{-1}]
Molecular weight (of nucleotide)	M_{nt}	D or kD	[g mol^{-1}]
Concentration (of nucleotide)	c_{nt}	mol l^{-1}	
Differential absorbance	ΔA(λ),	arbitrary units	

Essentials of Chemical Biology Andrew Miller and Julian Tanner

Differential molar extinction coefficient	$\Delta\varepsilon(\lambda)$,	l mol^{-1} cm^{-1}	
Ellipticity	$\theta(\lambda)$	deg	
Molar ellipticity	$[\theta(\lambda)]$	deg l mol^{-1} cm^{-1}	
Vibrational frequency of light	ν_v	s^{-1}	
(Equilibrium) electric field (of light)	$?_0$	V m^{-1}	
Equilibrium polarisability component	$\alpha_0(\nu_v)$	C m^2 V^{-1}	
Nuclear oscillation component	$\alpha_R(\nu_R)$	C m^2 V^{-1}	
Frequency of vibrational modes (molecular)	ν_R	s^{-1}	
Frequency of emitted light	ν_{em}	s^{-1}	
Planck's constant	h	J s or N m s	[kg m^2 s^{-1}]
Speed of light	c	m s^{-1}	
Radiative lifetime (fluorescence)	τ_R s		
Radiative lifetime (phosphorescence)	$\tau_{R,Phor}$s		
Rate of spontaneous emission (fluorescence)	k_Fs^{-1}		
Rate of internal conversion (fluorescence)	k_{IC}s^{-1}		
Rate of intersystem crossing (fluorescence)	k_{IS}s^{-1}		
Rate of quenching (fluorescence)	k_qs^{-1}		
Fluorescence intensity (no **Q**)	I_{em} or F_0	arbitrary units	
Fluorescence intensity (in presence of **Q**)	F	arbitrary units	
FÖrster length	R_0m		
Interfluorophore distance	R_Fm		
Fluorescence quantum yield	ϕ_F		
Fluorescence quantum yield (of donor, **D**)	ϕ_D		
Refractive index	$?_R$		
X-ray absorption coefficient	μ_{ab} m^{-1}		
Incident intensity (of X-ray)	I_{x0}	arbitrary units	
Transmitted intensity (of X-rays)	I_x	arbitrary units	
V is Volt (J C^{-1}); D is Daltons and kD kiloDaltons	J	J s rad^{-1}	[kg rad s^{-1}]

Chapter 5

(Nuclear) angular momentum			
Gyromagnetic ratio	γ	rad s^{-1} T^{-1}	
Magnetic moment (z-axis)	μ_z	J T^{-1} or A m^2	
Nuclear magneton	μ_NJ T^{-1}		

Nuclear g-factor	g_I		
Charge (of an electron)	e C		
Mass (of proton)	$m_p$kg		
Applied magnetic field	B_zT or N m^{-1}A^{-1}		
Lamor (precession) frequency	ν_Ls^{-1}		
Planck's constant	h J s	[kg m^2 s^{-1}]	
	$h/2\pi$	J s rad^{-1}	[kg rad s^{-1}]
Coupling constant	J	s^{-1}(Hz)	
Boltzmann constant	k	J K^{-1}	[kg m^2 s^{-2} K^{-1}]
(Absolute) temperature	T	K	
(Scalar) longitudinal relaxation time constant	T_1	s	
Transverse relaxation time constant	T_2	s	
Longitudinal magnetisation – polarisation	$?_z(?)$		
Transverse magnetisation – coherence	$?_y(?)$		
Spectral line width (half peak intensity)	$\Delta\nu_{L,1/2}$	s^{-1}(Hz)	
(Electron) angular momentum	J_e	J s rad^{-1}	[kg rad s^{-1}]
Electron gyromagnetic ratio	γ_e	rad s^{-1} T^{-1}	
Electron magnetic moment	$\mu_z{}^e$ 7	J T^{-1}	
Bohr magneton	μ_B	J T^{-1}	
g-factor	g_e		
Mass (of an electron)	m_e	kg	
rad is radians (2π); T is Tesla; A is ampere (C s^{-1})	d_{hkl}	Å	

Chapter 6

Distance between lattice planes			
Scattering length	b_{X-ray}	cm	
Distance of resolvable separation - resolution	d_R	Å	
Planck's constant	h	J s	[kg m^2 s^{-1}]
Charge (of an electron)	e C		
Electrical potential difference (in Field Emission gun)	Φ	V or ?g?^{tx}	[kg m^2 s^{-2}C^{-1}]
Mass (of an electron)	m_e	kg	
Maximum particle size	D	m	
Büttiker-Landauer tunnelling time	τ^{BL}	s	
Variable (z-axis) barrier dimension	s_z	m	
Barrier crossing constant	Φ	m^{-1}	
Piezo electric bar changes in length	Δl_p	m	
(Piezo electric biomorph) displacement	Δx_p	m	

(Piezo electric) potential difference	U_p	V or ?g?^{tx}	[kg m^2 s^{-2}C^{-1}]
(Piezo electric) coefficient	d_{31}	m V^{-1}or C N^{-1}	[C s^2 m^{-1} kg^{-1}]
Tunnelling current	I_TA		
Van-der-Waals interactions (tip to surface)	$F_{VDW}(d_z)$	N	[kg m s^{-2}]
Hamaker constant	H	N m or J	[kg m^2 s^{-2}]
Distance (z-axis)	d_z	m	
Radius of tip above surface	R_z	m	
Surface-to-tip interaction forces	F_{ST}	N	[kg m s^{-2}]
Spring constant	c_{ST}	N m^{-1}	[kg s^{-2}]
Youngs Modulus	E_M	Pa or N m^{-2}	[kg m^{-1} s^{-2}]
Pa is Pascal (N m^{-2})	V_h	cm^{3}or m^3	
Chapter 7			
Hydrated volume			
Macromolecular molecular weight	M_{MM}	D or kD	[g mol^{-1}]
Avogadro's number	N_0	mol^{-1}	
Macromolecular partial specific volume	V_{MM}	cm^3 g^{-1}	
Hydration level	Δ		
Coefficient of translational frictional force	$f_{trans,sph}$	kg s^{-1}or g s^{-1}	
Spherical macromolecular radius	r_{sph}	cm or m	
Viscosity	η	Pa s or N m^{-2} s	[kg m^{-1} s^{-1}, g cm^{-1} s^{-1}]
Coefficient of rotational frictional force	$f_{rot,sph}$	kg m^2 s^{-1} or g cm^2 s^{-1}	
Spherical macromolecular volume	V_{sph}	m^3 or cm^3	
General coefficient of translational frictional force	f_{trans}	kg s^{-1}or g s^{-1}	
General coefficient of rotational frictional force	f_{rot}	kg m^2 s^{-1} or g cm^2 s^{-1}	
Macromolecular flux	J_{MM} mol m^{-2} s^{-1}	kg m^{-2} s^{-1} or g cm^{-2} s^{-1}	
Macromolecular concentration	C_{MM}	kg m^{-3}or g cm^{-3} mol m^{-3}	
Average macromolecular velocity	$\langle v_{MM} \rangle$	m s^{-1} or cm s^{-1}	
Macromolecular diffusion coefficient	D_{MM}	m^2 s^{-1} or cm^2 s^{-1}	
Boltzmann constant	k	J K^{-1}	[kg m^2 s^{-2} K^{-1}]
Debye length	r_D	m	
Ionic strength	?	mol m^{-3} or mol kg^{-1} M (mol l^{-1})	
Permittivity of medium	ε	F m^{-1}or C^2 m^{-1} J^{-1}	[C^2 kg^{-1}m^{-3} s^2]
Association constant	K_a	M^{-1}	

Dissociation constant	K_d	M	
Moles (of ligand) bound per mole (of receptor)	B	(Mol fraction)	
Total molar quantity (of ligand) bound (to receptor)	m_{RL}	mol	
Total molar quantity (of ligand) added	m_{L0}	mol	
Total system volume	V_{tot}	m^3, dm^3 (l), cm^3	
Chemical potential of species i μ_i	$J mol^{-1}$	$[kg\ m^2\ s^{-2}\ mol^{-1}]$	
Concentration of species i	c_i	M ($mol\ l^{-1}$)	
Molar gas constant	R	$J\ K^{-1}\ mol^{-1}$	$[kg\ m^2\ s^{-2}\ K^{-1}\ mol^{-1}]$
Standard free energy change	ΔG^0	$J\ mol^{-1}$, $kJ\ mol^{-1}$	$[kg\ m^2\ s^{-2}\ mol^{-1}]$
Standard enthalpy change	ΔH^0	$J\ mol^{-1}$, $kJ\ mol^{-1}$	$[kg\ m^2\ s^{-2}\ mol^{-1}]$
Standard entropy change	ΔS^0	$J\ mol^{-1}K^{-1}$	$[kg\ m^2\ s^{-2}\ mol^{-1}K^{-1}]$
(Exchangeable) heat energy	?	J	$[kg\ m^2\ s^{-2}]$
(Fractional) change in enthalpy	dH	J	
Electric field	E_e	$V\ m^{-1}$or $J\ C^{-1}\ m^{-1}$	$[kg\ m\ s^{-2}\ C^{-1}]$
Electrophoretic velocity	v_e	$m\ s^{-1}$	
Electrophoretic mobility	μ_e	$m^2\ V^{-1}\ s^{-1}$	$[C\ s\ kg^{-1}]$
Apparent electophoretic mobility	μ_a	$m^2\ V^{-1}\ s^{-1}$	$[C\ s\ kg^{-1}]$
EOFelectophoretic mobility	μ_{EOF}	$m^2\ V^{-1}\ s^{-1}$	$[C\ s\ kg^{-1}]$
Time to detector	t_e	s	
Effective length (of capillary)	l_e	m	
Total length (of apparatus)	L_e	m	
Applied potential difference	$?_e$	V or $J\ C^{-1}$	$[kg\ m^2\ s^{-2}\ C^{-1}]$
Rate of association (complex formation) (***on***-rate)	k_{ass}	$M^{-1}s^{-1}$	
Rate of dissociation (complex) (***off***-rate)	k_{diss}	s^{-1}	
Resonant angle	Y_t	arc s	
Concentration dependent ***on***-rate (complex formation)	k_{on}	s^{-1}	
Chapter 8	ν	$M\ s^{-1}$	$[mol\ l^{-1}\ s^{-1}]$
Initial rate of (biocatalysis)			
Initial substrate concentration	[S]	M	$[mol\ l^{-1}]$
Unimolecular rate constant for mechanism step **n**	k_n	s^{-1}	
Bimolecular rate constant for mechanism step **n**	k_n	$M^{-1}\ s^{-1}$	$[l\ mol^{-1}\ s^{-1}]$
Michaelis constant	K_m	M	$[mol\ l^{-1}]$
Equilibrium dissociation constant for **ES** complex	K_s	M	$[mol\ l^{-1}]$

Catalytic rate constant (when [S] ≫ K_m)	k_{cat}	s^{-1}	
Maximum initial rate (when [S] ≫ K_m)	V_{max}	$M\ s^{-1}$	$[mol\ l^{-1}\ s^{-1}]$
Catalytic rate constant (whenK_m ≫ [S])	k_{cat}/K_m	$M^{-1}\ s^{-1}$	$[l\ mol^{-1}\ s^{-1}]$
Inhibitor equilibrium dissociation constant	K_I	M	$[mol\ l^{-1}]$
Base equilibrium ionization constant	$K_d{}^B$	M	$[mol\ l^{-1}]$
Acid equilibrium ionization constant	$K_d{}^A$	M	$[mol\ l^{-1}]$
Saddle-point vibration frequency	$\nu_{??}$	s^{-1}	
Transition state forward decomposition rate constant	$k_c{}^{\ddagger}$	s^{-1}	
Quasi-equilibrium association constant	$K_c{}^{\ddagger}$.	M^{-1}	
Forward rate constant	k_p	$M^{-1}s^{-1}$	
Partition function for molecular population	$z\ q^z$		
Boltzmann constant	k	$J\ K^{-1}$	$[kg\ m^2\ s^{-2}\ K^{-1}]$
Transition state-ground state energy difference	E_0	J	$[kg\ m^2\ s^{-2}]$
Planck's constant	h	J s	$[kg\ m^2\ s^{-1}]$
Standard free energy (of activation)	$\Delta G_0{}^{\ddagger}$	$kJmol^{-1}$	$[kg\ m^2\ s^{-2}mol^{-1}]$
Free energy (of activation) (from **E** and **S**)	$\Delta G_{ES}{}^{\ddagger}$	$kJmol^{-1}$	$[kg\ m^2\ s^{-2}mol^{-1}]$
Free energy (of activation) (from **ES** complex)	$\Delta G_T{}^{\ddagger}$	$kJmol^{-1}$	$[kg\ m^2\ s^{-2}mol^{-1}]$
Free energy (of association) of (**E** and **S**)	$\Delta G_S\ kJmol^{-1}$	$[kg\ m^2\ s^{-2}mol^{-1}]$	
Molar gas constant	R	$J\ K^{-1}mol^{-1}$	$[kg\ m^2\ s^{-2}\ K^{-1}mol^{-1}]$
Rate constant for electron transfer	k_{ET}	s^{-1}	
Equilibrium association constant (for **D** and **A**)	$K_{a,DA}$	M^{-1}	$[l\ mol^{-1}]$
Edge to edge distance (between **D** and **A**)	R_{ET}	m	
Beta value	β_{ET}	m^{-1}	
Chapter 9			
Unitary charge of an ion	z		
Accelerating electrostatic potential	$?_z$	V or $J\ C^{-1}$	$[kg\ m^2\ s^{-2}\ C^{-1}]$
Velocity of ion travel	$\nu_?s^{-1}$		
Ion mass	**m**	D, kD (or a.m.u.)	
Time to detector	t_z	s	
Length (of field-free flight tube)	L_z	m	

Contents

1

The Structures of Biological Macromolecules and Lipid Assemblies

1.1 General introduction

All living organisms are comprised of cells that may vary considerably in terms of size, shape and appearance; in complex multicellular organisms, many cells are organised into diverse, functional organs to perform a collective function (Figure 1.1). In spite of their wide morphological diversity, all cells of all living organisms, wherever they are located, are comprised of **proteins**, **carbohydrates**, **nucleic acids** and **lipid assemblies**. These together give a cell form and function. To know and understand the chemistry of these biological macromolecules is to comprehend the basic infrastructure not only of a cell but also of living organisms. In functional terms, macromolecular lipid assemblies provide for compartmentalisation in the form of membrane barriers, which not only define the 'outer limits' of each cell but also divide up the intracellular environment into different organelles or functional zones (Figure 1.2). Membrane barriers are fluidic and lack rigidity, so proteins provide a supporting and scaffolding function not only in the main fluid bulk of the cell, known as the **cytosol**, but also within organelles. Within the **nucleus**, proteins also provide a nucleic acid packaging function in order to restrain and constrain spectacular quantities of nucleic acids within the nuclear volume. Everywhere in any cell, proteins also perform other individualised functions in outer membranes (as pores or receptors for example), in organelle membranes (as selective transporters, redox acceptors or energy transducers), in the cytosol or organelle volumes (as enzyme catalysts, molecular chaperones or 'communication and control' centres) and in the nucleus (as regulators and transcribers of the genetic code). The extraordinary variety

Essentials of Chemical Biology Andrew Miller and Julian Tanner

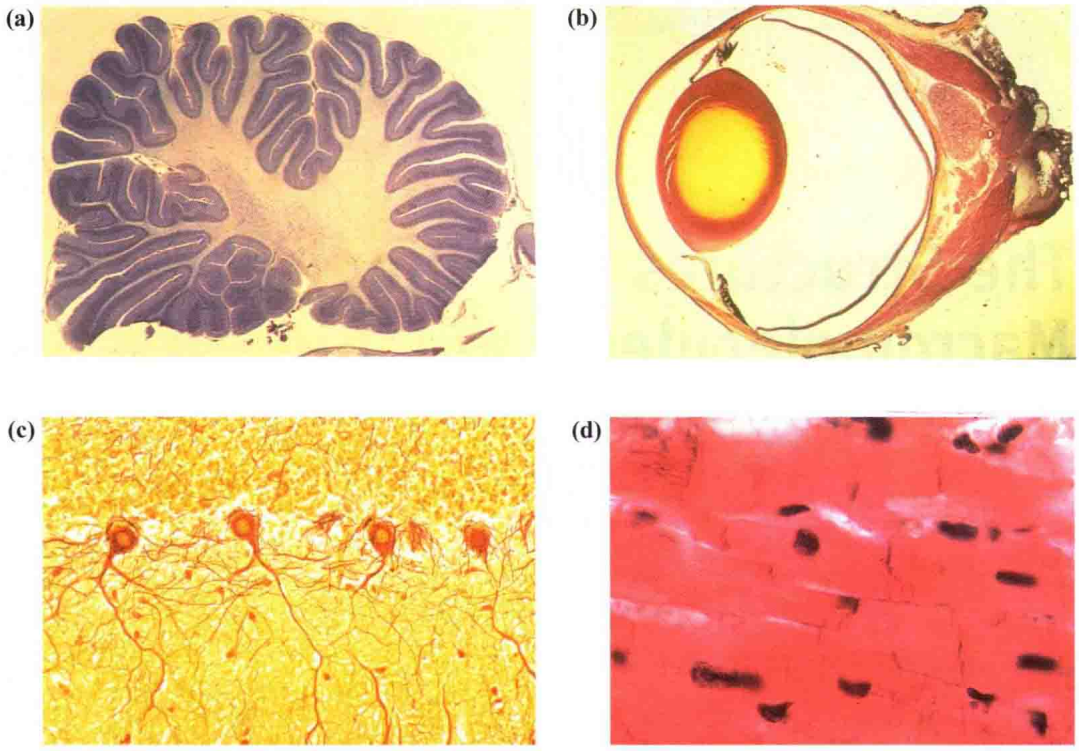

Figure 1.1 Organs and Cells. (a) cross section of mammalian brain showing the complex surface folds. There are an incalculable number of cells that make up the mammalian brain; **(b) cross section of mammalian eye ball** in which the lens is made of proteins controlled in function by peripheral muscles. There is an enormous morphological and functional diversity between cells required for muscle control, light reception, and signal transduction along the optic nerve; **(c) cross section of mammalian neurological tissue** illustrating the neuron cell bodies with complex axonal/dendritic processes surrounded by support cells all of a wide range of size, shape, structure and function; **(d) cross section of mammalian heart tissue** showing clusters of muscle fibres (single cell myocytes) that make up the heart wall. Myocytes are multinucleate with a very different shape, composition and function to neurological cells (all illustrations from Philip Harris Ltd, Weston Super Mare, UK).

of protein functions and the 'workhorse'-like nature of proteins in biology has made them endlessly fascinating to biochemists and now to chemical biologists alike.

Nucleic acids are found in two main classes, namely **deoxyribonucleic acid** (**DNA**) and **ribonucleic acid** (**RNA**). DNA is largely restricted to the nucleus and harbours genetic information that defines the composition and structure of cells and even the multicellular organisation of complex organisms, reaching even beyond this to influence organism behaviour as well. DNA molecules are partly segmented into **genes** that contain coding information for protein structures, but also into many other delineations associated with control over gene use. In fact, the level and sophistication of this control may well be the primary determinant of complexity in multicellular organisms: the more extensive and sophisticated the level of control, the more sophisticated and complex the multicellular organism. By contrast, RNA's most important role is in shuttling information from the nucleus to the cytosol. The primary function of RNA equates to the processing of genetic information from the DNA storage