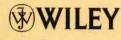
Essentials of

Chemical Biology

Structure and Dynamics of Biological Macromolecules



Andrew Miller and Julian Tanner





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

X PREFACE

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	$oldsymbol{q}_{ m n}$	C	
Vacuum permittivity	ε_0	$F m^{-1} or C^2 m^{-1} J^{-1}$	
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	$\mu_{ m n}$	C m	
Polarisability volume	$oldsymbol{lpha}_{\mathrm{n}}^{\epsilon}$	$\mathrm{m}^3(\mathrm{\AA}^3,\mathrm{cm}^3)$	
Ionisation energies	$oldsymbol{I}_{ m n}$	J	$[kg m^2 s^{-2}]$
J is Joule; F is Farad; C is Coulomb	$oldsymbol{\mu}_{ ext{ind}}$ or $oldsymbol{\mu}_{ ext{ind}}$	C m	
Chapter 4			
(Time dependent) induced dipole			
moment			
(Time dependent) electronic polarisability	$\alpha \; (oldsymbol{ u}_{ m v})$	$C m^2 V^{-1}$	
(Oscillating) electric field (of light)	?($\nu_{ m v}$)	$V m^{-1}$	
Absorbance	$A ext{ or } A (\lambda)$	arbitrary units	
Optical density	$OD(\lambda)$	arbitrary units	
Pathlength (optical)	1	cm	
Extinction coefficient	$\varepsilon_{???}$ or g ε (λ)	$1 \mathrm{mol^{-1} cm^{-1}}$	
Biological macromolecular concentration	$c_{ m M}$	$\text{mol } l^{-1}$	
Wavelength	λ	nm	
Molecular weight (of protein)	$M_{ m p}$	D or kD	$[g \text{ mol}^{-1}]$
Molecular weight (of nucleotide)	$M_{ m nt}$	D or kD	$[g \text{ mol}^{-1}]$
Concentration (of nucleotide)	$c_{ m nt}$	$\text{mol } l^{-1}$	
Differential absorbance	$\Delta A(\lambda)$,	arbitrary units	

Differential molar extinction coefficient	$\Delta \varepsilon(\lambda)$,	$1\mathrm{mol^{-1}cm^{-1}}$	
Ellipticity	$\theta(\lambda)$	deg	
Molar ellipticity	$[\theta(\lambda)]$	deg l mol ⁻¹ cm ⁻¹	
Vibrational frequency of light	$ u_{\rm v}$	s^{-1}	
(Equilibrium) electric field (of light)	? 0	$\rm V~m^{-1}$	
Equilibrium polarisability component	$lpha_0(u_{ ext{ iny v}})$	$C m^2 V^{-1}$	
Nuclear oscillation component	$lpha_{ ext{R}}(u_{ ext{R}})$	$C m^2 V^{-1}$	
Frequency of vibrational modes (molecular)	$oldsymbol{ u}_{ m R}$	s^{-1}	
Frequency of emitted light	$oldsymbol{ u}_{ m em}$	s^{-1}	
Planck's constant	h	Js or Nms	$[kg m^2 s^{-1}]$
Speed of light	C	$\mathrm{m}\;\mathrm{s}^{-1}$	
Radiative lifetime (fluorescence)	$ au_{ m R}$ s		
Radiative lifetime	$oldsymbol{ au}_{ ext{R,Phor}}$ s		
(phosphorescence)			
Rate of spontaneous emission	$k_{\rm F} {\rm s}^{-1}$		
(fluorescence)			
Rate of internal conversion	$k_{\rm IC}$ s ⁻¹		
(fluorescence)	. 1		
Rate of intersystem crossing (fluorescence)	$k_{\rm IS}$ s ⁻¹		
Rate of quenching (fluorescence)	$k_{\rm q}$ s ⁻¹		
Fluorescence intensity (no Q)	$I_{ m em}$ or F_0	arbitrary units	
Fluorescence intensity (in presence of Q)	F	arbitrary units	
FÖrster length	R_0 m		
Interfluorophore distance	$R_{\rm F}$ m		
Fluorescence quantum yield	$\phi_{ extsf{F}}$		
Fluorescence quantum yield (of donor, D)	$\phi_{ m D}$		
Refractive index	? R		
X-ray absorption coefficient	$\mu_{\rm ab}~{ m m}^{-1}$		
Incident intensity (of X-ray)	$I_{ m x0}$	arbitrary units	
Transmitted intensity (of X-rays)	$I_{\scriptscriptstyle m X}$	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	$\mu_{ m N}$ J T $^{-1}$		

The state of the s			
Nuclear g-factor	g_{I}		
Charge (of an electron)	e C		
Mass (of proton)	$m_{\rm p}$ kg		
Applied magnetic field	$B_z T$ or N m ⁻¹ A ⁻¹		
Lamor (precession) frequency	$\nu_{\rm L} { m s}^{-1}$		
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	$s^{-1}(Hz)$	[RS rad 5]
Boltzmann constant	, k	$J K^{-1}$	$[kg m^2 s^{-2} K^{-1}]$
(Absolute) temperature	T	K	[Kg III 5 K]
(Scalar) longitudinal relaxation	T_1	S	
time constant	11	3	
Transverse relaxation time constar	. + T		
	-	S	
Longitudinal magnetisation –	? _z (?)		
polarisation	2 (2)		
Transverse magnetisation –	? _y (?)		
coherence	A	-1/TT)	
Spectral line width (half peak	$oldsymbol{\Delta}oldsymbol{ u}_{ ext{L,1/2}}$	$s^{-1}(Hz)$	
intensity)		1=1	rı 1 —11
(Electron) angular momentum	$J_{ m e}$	J s rad ⁻¹	$[kg rad s^{-1}]$
Electron gyromagnetic ratio	$\gamma_{\rm e}$	rad $s^{-1} T^{-1}$	
Electron magnetic moment	μ_z^e 7	$J T^{-1}$	
Bohr magneton	$\mu_{ ext{B}}$	$ m J~T^{-1}$	
g-factor	$g_{\rm e}$		
Mass (of an electron)	$m_{\rm e}$	kg	
rad is radians (2π) ; T is Tesla; A is	$oldsymbol{d}_{ ext{hkl}}$	Å	
ampere ($C s^{-1}$)			
Chapter 6			
Distance between lattice planes			
Scattering length	$\boldsymbol{b}_{\mathrm{X-ray}}$	cm	
Distance of resolvable separation -		Å	
resolution	r K	7.1	
Planck's constant	h	J s	$[kg m^2 s^{-1}]$
Charge (of an electron)	e C	, 0	[RS III 0]
Electrical potential difference (in	Φ	V or ?g?tx	$[kg m^2 s^{-2}C^{-1}]$
Field Emission gun)	-	, 01 .8.	[Kg III 5 C]
Mass (of an electron)	$m_{\rm e}$	kg	
Maximum particle size	D	m	
Büttiker-Landauer tunnelling time			
Variable (z-axis) barrier dimension		S	
	n s_z Φ	m m^{-1}	
Barrier crossing constant			
Piezo electric bar changes in lengt	L.	m	
(Piezo electric biomorph)	$\Delta x_{ m p}$	m	
displacement			

(Piezo electric) potential difference	U_{p}	V or ?g?tx	$[kg m^2 s^{-2}C^{-1}]$
(Piezo electric) coefficient	d_{31}	$\mathrm{m}\mathrm{V}^{-1}\mathrm{or}\mathrm{C}\mathrm{N}^{-1}$	$[C s^2 m^{-1} kg^{-1}]$
Tunnelling current	$I_{\mathrm{T}}A$	-1-	
Van-der-Waals interactions (tip to surface)	$F_{ m VDW}(d_{ m z})$	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	$R_{\rm z}$	m	
Surface-to-tip interaction forces	$F_{ m ST}$	N	$[kg m s^{-2}]$
Spring constant	c_{ST}	$N m^{-1}$	$[kg s^{-2}]$
Youngs Modulus	$E_{ m M}$	Pa or N m^{-2}	$[kg m^{-1} s^{-2}]$
Pa is Pascal (N m ⁻²)	$oldsymbol{V}_{ m h}$	cm ³ or m ³	
Chapter 7			
Hydrated volume	17	D 1D	1-11
Macromolecular molecular weight	$M_{ m MM}$	D or kD	$[g \text{ mol}^{-1}]$
Avogadro's number	N_0	mol^{-1}	
Macromolecular partial specific volume	$V_{ m MM}$	$cm^3 g^{-1}$	
Hydration level	Δ		
Coefficient of translational frictional force	$f_{ m trans,sph}$	$kg s^{-1} or g s^{-1}$	
Spherical macromolecular radius	$r_{ m sph}$	cm or m	
Viscosity	η^{i}	Pa s or N m ⁻² s	[kg m ⁻¹ s ⁻¹ , g cm ⁻¹ s ⁻¹
Coefficient of rotational frictional force	$f_{ m rot,sph}$	$kg m^2 s^{-1}$ or $g cm^2 s^{-1}$	
Spherical macromolecular volume	$V_{ m sph}$	m ³ or cm ³	
General coefficient of translational	$f_{ m trans}$	$kg s^{-1} or g s^{-1}$	
frictional force	Juans	-88-	
General coefficient of rotational frictional force	$f_{ m rot}$	$kg m^2 s^{-1}$ or $g cm^2 s^{-1}$	
Macromolecular flux	$J_{ m MM}$	$kg m^{-2} s^{-1} or g cm^{-2} s^{-1}$	
	$mol m^{-2} s^{-1}$		
Macromolecular concentration	$C_{\rm MM}$	$kg m^{-3} or g cm^{-3}$ mol m ⁻³	
Average macromolecular velocity	$\langle v_{\rm MM} \rangle$	$m s^{-1} or cm s^{-1}$	
Macromolecular diffusion coefficient	$D_{\rm MM}$	$m^2 s^{-1} \text{ or cm}^2 s^{-1}$	
Boltzmann constant	k	$J K^{-1}$	$[kg m^2 s^{-2} K^{-1}]$
Debye length			[Kg III 5 K]
	<i>r</i> _D	m mal m ⁻³ or mal ka ⁻¹	
Ionic strength	?	mol m ⁻³ or mol kg ⁻¹	
Dommittivity of an alice	1	$M \text{ (mol } l^{-1})$	[C2 Inn=1 -3 -2]
Permittivity of medium	ε	$F m^{-1} \text{ or } C^2 m^{-1} J^{-1}$	$[C^2 kg^{-1}m^{-3} s^2]$
Association constant	$-K_a$	M^{-1}	

Dissociation constant Moles (of ligand) bound per mole	$oldsymbol{K}_{ m d}$	M (Mol fraction)	
(of receptor)		And the state of t	
Total molar quantity (of ligand) bound (to receptor)	$m_{ m RL}$	mol	
Total molar quantity (of ligand) added	$m{m}_{ m L0}$	mol	
Total system volume	$oldsymbol{V}_{ m tot}$	m ³ , dm ³ (l), cm ³	
Chemical potential of species $i\mu_i$	$J \text{mol}^{-1}$	$[kg m^2 s^{-2} mol^{-1}]$	
Concentration of species i	$c_{\rm i}$	$M \pmod{l^{-1}}$	
Molar gas constant	R	$J K^{-1} \text{ mol}^{-1}$	$[kg m^2 s^{-2} K^{-1} mol^{-1}]$
Standard free energy change	ΔG^0	$J \text{ mol}^{-1}$, $kJ \text{ mol}^{-1}$	$[kg m^2 s^{-2} mol^{-1}]$
Standard enthalpy change	$oldsymbol{\Delta} oldsymbol{H}^0$	$J \text{ mol}^{-1}$, $kJ \text{ mol}^{-1}$	$[kg m^2 s^{-2} mol^{-1}]$
Standard entropy change	ΔS^0	$J \text{ mol}^{-1} K^{-1}$	$[kg m^2 s^{-2} mol^{-1} K^{-1}]$
(Exchangeable) heat energy	?	J	$[kg m^2 s^{-2}]$
(Fractional) change in enthalpy	dH	J	
Electric field	$E_{\rm e}$	$V m^{-1} or J C^{-1} m^{-1}$	$[kg m s^{-2} C^{-1}]$
Electrophoretic velocity	$\nu_{\rm e}$	$\mathrm{m}\;\mathrm{s}^{-1}$	
Electrophoretic mobility	$\mu_{ m e}$	$m^2 V^{-1} s^{-1}$	$[C s kg^{-1}]$
Apparent electophoretic mobility	μ_{a}	$m^2 V^{-1} s^{-1}$	$[C s kg^{-1}]$
EOFelectophoretic mobility	$\mu_{ ext{EOF}}$	$m^2 V^{-1} s^{-1}$	$[C s kg^{-1}]$
Time to detector	$t_{\rm e}$	S	
Effective length (of capillary)	$l_{\rm e}$	m	
Total length (of apparatus)	$L_{ m e}$	m	
Applied potential difference	? e	V or J C^{-1}	$[kg m^2 s^{-2} C^{-1}]$
Rate of association (complex formation) (<i>on</i> -rate)	$\mathbf{k}_{\mathrm{ass}}$	$M^{-1}s^{-1}$	
Rate of dissociation (complex) (<i>off</i> -rate)	$m{k}_{ m diss}$	s^{-1}	
Resonant angle	Y_{t}	arc s	
Concentration dependent <i>on</i> -rate (complex formation)	$k_{\rm on}$	s^{-1}	
Chapter 8	ν	$\mathrm{M}~\mathrm{s}^{-1}$	$[\text{mol } l^{-1} s^{-1}]$
Initial rate of (biocatalysis)			
Initial substrate concentration	[S]	M	$[\text{mol } l^{-1}]$
Unimolecular rate constant for mechanism step n	$\boldsymbol{k}_{\mathrm{n}}$	s^{-1}	
Bimolecular rate constant for mechanism step n	$\boldsymbol{k}_{\mathrm{n}}$	$M^{-1} s^{-1}$	$[1 \text{mol}^{-1} \text{s}^{-1}]$
Michaelis constant	K_{m}	M	$[\text{mol } l^{-1}]$
Equilibrium dissociation constant	$K_{\rm s}$	M	$[\text{mol } l^{-1}]$
for ES complex			*

Catalytic rate constant (when $[S] \gg K_m$)	$k_{\rm cat}$	s^{-1}	
Maximum initial rate (when $[S] \gg K_m$)	$V_{ m max}$	${\rm M}~{\rm s}^{-1}$	$[\text{mol } l^{-1} \ s^{-1}]$
Catalytic rate constant (when $K_{\rm m} \gg [S]$)	$m{k}_{ m cat}/m{K}_{ m m}$	$M^{-1} s^{-1}$	$[1 \text{ mol}^{-1} \text{ s}^{-1}]$
Inhibitor equilibrium dissociation constant	$K_{\rm I}$	M	$[\operatorname{mol} l^{-1}]$
Base equilibrium ionization constant	$oldsymbol{K_{ m d}}^B$	M	$[\operatorname{mol} l^{-1}]$
Acid equilibrium ionization constant	$K_{\mathrm{d}}{}^{A}$	M	$[\operatorname{mol} l^{-1}]$
Saddle-point vibration frequency	V??	s^{-1}	
Transition state forward	$k_{\rm c}^{\ \ \dagger}$	s^{-1}	
decomposition rate constant			
Quasi-equilibrium association constant	K_c^{\ddagger} .	M^{-1}	
Forward rate constant	$k_{ m p}$	$M^{-1}s^{-1}$	
Partition function for molecular population	$\mathbf{z} \mathbf{q}^z$		
Boltzmann constant	k	$\rm J~K^{-1}$	$[kg m^2 s^{-2} K^{-1}]$
Transition state-ground state	E_0	I	$[kg m^2 s^{-2}]$
energy difference	· ·	,	
Planck's constant	h	Js	$[kg m^2 s^{-1}]$
Standard free energy (of activation)	$\boldsymbol{\Delta G_0}^{\ddagger}$	kJmol ⁻¹	$[kg m^2 s^{-2} mol^{-1}]$
Free energy (of activation) (from E	$\Delta G_{\rm ES}^{\ddagger}$	kJmol ⁻¹	$[kg m^2 s^{-2} mol^{-1}]$
and S)	15	,	[-0]
Free energy (of activation) (from	$\Delta G_{\mathrm{T}}^{\ddagger}$	$kJmol^{-1}$	$[kg m^2 s^{-2} mol^{-1}]$
ES complex)	_		
Free energy (of association) of (E and S)	$\Delta G_{\rm S}$ kJmol ⁻¹	$[kg m^2 s^{-2} mol^{-1}]$	
Molar gas constant	R	$J K^{-1} \text{mol}^{-1}$	$[kg m^2 s^{-2} K^{-1} mol^{-1}]$
Rate constant for electron transfer	$k_{ m ET}$	s^{-1}	
Equilibrium association constant (for D and A)	$K_{a,DA}$	M^{-1}	$[1 \mathrm{mol}^{-1}]$
Edge to edge distance (between D and A)	$R_{ m ET}$	m	
Beta value	$oldsymbol{eta}_{ ext{ET}}$	m^{-1}	
Chapter 9	7 2.2		
Unitary charge of an ion	z		
Accelerating electrostatic potential	? _z	$V \text{ or } J C^{-1}$	$[kg m^2 s^{-2} C^{-1}]$
Velocity of ion travel	$v_{?}s^{-1}$		
Ion mass	m	D, kD (or a.m.u.)	
Time to detector	$t_{\rm z}$	S	
Length (of field-free flight tube)	$L_{\rm z}$	m	

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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

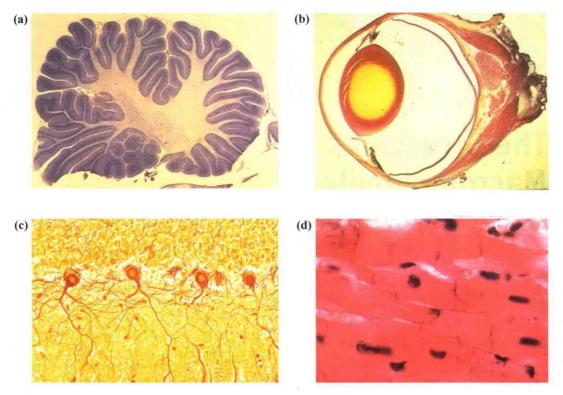


Figure 1.1 Organs and Cells. (a) cross section of mammalian brain showing the complex surface folds. There are an incalculable number of cells that make up the mammalian brain; (b) cross section of mammalian eye ball in which the lens is made of proteins controlled in function by peripheral muscles. 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