Fundamentals of Medicinal Chemistry

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Library of Congress Cataloging-in-Publication Data

Thomas, Gareth, Dr.
Fundamentals of medicinal chemistry / Gareth Thomas.
p. cm.
Includes bibliographical references and index.
ISBN 0-470-84306-3 (cloth : alk. paper) ISBN 0-470-84307-1 (paper : alk. paper)
1. Pharmaceutical chemistry. I. Title.
RS403.T446 2003
615′.19 — — dc21 2003014218

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0-470 84306 3 (Hardback)
ISBN 0-470 84307 1 (Paperback)

Typeset in 11/14pt Times by Kolam Information Services Pvt. Ltd, Pondicherry, India
Printed and bound in Great Britain by Antony Rowe Ltd
This book is printed on acid-free paper responsibly manufactured from sustainable forestry, in which at least two trees are planted for each one used for paper production.

Contents

Preface

This book is written for second, and subsequent year undergraduates studying for degrees in medicinal chemistry, pharmaceutical chemistry, pharmacy, pharmacology and other related degrees. It is also intended for students whose degree courses contain a limited reference to medicinal chemistry. The text assumes that the reader has a knowledge of chemistry at level one of a university life sciences degree. The text discusses the fundamental chemical principles used for drug discovery and design. A knowledge of physiology and biology is advantageous but not essential. Appropriate relevant physiology and biology is outlined in the appendices.

Chapter 1 gives a brief review of the structures and nomenclature of the more common classes of naturally occurring compounds found in biological organisms. It is included for undergraduates who have little or no background knowledge of natural product chemistry. For students who have studied natural product chemistry it may be used as either a revision or a reference chapter. Chapter 2 attempts to give an overview of medicinal chemistry. The basic approaches used to discover and design drugs are outlined in Chapters 3–6 inclusive. Chapter 7 is intended to give the reader a taste of main line medicinal chemistry. It illustrates some of the strategies used, often within the approaches outlined in previous chapters, to design new drugs. For a more encyclopedic coverage of the discovery and design of drugs for specific conditions, the reader is referred to appropriate texts such as some of those given under *Medicinal Chemistry* in the *Selected Further Reading* section at the end of this book. Chapters 8 and 9 describe the pharmacokinetics and metabolism respectively of drugs and their effect on drug design. Chapter 10 attempts to give an introductory overview of an area that is one of the principal objectives of the medicinal chemist. For a more in depth discussion, the reader is referred to the many specialized texts that are available on organic synthesis. Drug development from the research stage to marketing the final product is briefly outlined in Chapter 11.

The approach to medicinal chemistry is kept as simple as possible. The text is supported by a set of questions at the end of each chapter. Answers, sometimes in the form of references to sections of the book, are listed separately. A list of recommended further reading, classified according to subject, is also included.

Gareth Thomas

Acknowledgements

I wish to thank all my colleagues, past and present without, whose help this book would have not been written. In particular, I would like to thank Dr. S Arkle for access to his lecture notes and Dr. J Wong for his unstinted help and advice, Dr. J Brown for again acting as a living pharmacology dictionary, Dr. P Cox for the molecular model diagrams and his patience in explaining to me the intricacies of molecular modelling and Mr. A Barrow and Dr. D Brimage for the library searches they conducted. I wish also to thank the following friends and colleagues for proof-reading chapters and supplying information: Dr. L Adams, Dr. C Alexander, Dr. L Banting, Dr. D Brown, Dr. S Campbell, Dr. B Carpenter, Mr. P Clark, Dr. P Howard, Dr. A Hunt, Mrs. W Jones, Dr. T Mason, Dr. J Mills, Dr. T Nevell, Dr. M Norris, Dr. J Smart, Professor D Thurston, Dr. G White and Mr. S Wills.

Finally, I would like to thank my wife for her support whilst I was writing the text.

Abbreviations

A	Adenine
Abe	Abequose
ACE	Angiotensin-converting enzyme
ACh	Acetyl choline
ADME	Absorption, distribution, metabolism and elimination
ADR	Adverse drug reaction
Ala	Alanine
Arg	Arginine
Asp	Aspartate
ATP	Deoxyadenosine triphosphate
dATP	Adenosine triphosphate
AUC	Area under the curve
C	Cytosine
CNS	Central nervous system
CoA	Coenzyme A
CYP-450	Cytochrome P-450 family
Cys	Cysteine
d.e.	Diastereoisometric excess
DHF	Dihydrofolic acid
DHFR	Dihydrofolate reductase
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
EC	Enzyme commission
e.e.	Enantiomeric excess
ELF	Effluent load factor
EMEA	European medicines evaluation agency
EPC	European Patent Convention
EPO	European Patent Office
E_s	Taft steric parameter

FDA	Food and drugs administration
FMO	Flavin monoxygenase
FGI	Functional group interconversion
Fmoc,	9-Fluorenylmethoxychloroformyl group
FdUMP	5-fluoro-2′-deoxyuridyline monophosphate
FUdRP	5-fluoro-2′-deoxyuridylic acid
G	Guanine
GABA	γ-Aminobutyric acid
GI	Gastrointestinal tract
Gln	Glutamine
Glu	Glutamatic acid
Gly	Glycine
GSH	Glutathione
Hb,	Haemoglobin
HbS	Sickel cell haemoglobin
His	Histidine
HIV	Human immunodeficiency disease
hnRNA	Heterogeneous nuclear RNA
Ile	Isoleucine
IV	Intravenous injection
IM	Intramuscular injection
KDO	2-Keto-3-deoxyoctanoate
LDA	Lithium diisopropylamide
LDH	Lactose dehydrogenase
Leu	Leucine
Lys	Lysine
mACh	Muscarinic cholinergic receptor
MA(A)	Market authorisation (application)
MCA	Medical control agency
Met	Methionine
Moz	4-Methoxybenzyloxychloroformyl group
MR	Molar refractivity
mRNA	messenger RNA
nACh	Nicotinic cholinergic receptor
NAD^+	Nicotinamide adenine dinucleotide (oxidised form)
NADH	Nicotinamide adenine dinucleotide (reduced form)

$NADP^+$	Nicotinamide dinucleotide phosphate (oxidised form)
NADPH	Nicotinamide dinucleotide phosphate (reduced form)
NAG	β-*N*-Acetylglucosamine
NAM	β-*N*-Acetylmuramic acid
ONs	Sequence defined oligonucleotides
P-450	Cytochrome P-450 oxidases
PABA	*p*-Aminobenzoic acid
PCT	Paten Cooperation Treaty
PG	Prostaglandin
Phe	Phenylalanine
PO	Per oral (by mouth)
pre-mRNA	Premessenger RNA
Pro	Proline
ptRNA	Primary transcript RNA
QSAR	Quantitative structural-activity relationships
RNA	Ribonucleic acid
SAM	*S*-Adenosylmethionine
SAR	*See* Structural-activity relationships
Ser	Serine
SIN-1	3-Morpholino-sydnomine
T	Thymine
THF	Tetrahydrofolic acid
Thr	Threonine
dTMP	Deoxythymidylate-5′-monophosphate
tRNA	transfer RNA
Try	Tyrosine
U	Uracil
UDP	Uridine diphosphate
UDPGA	Uridine diphosphate glucuronic acid
dUMP	Deoxyuridylate-5′-monophosphate
UdRP	Deoxyuridylic acid
Val	Valine

1 Biological Molecules

1.1 Introduction

Chemical compounds and metallic ions are the basic building blocks of all biological structures and processes that are the basis of life as we know it. Some of these naturally occuring compounds and ions (**endogenous species**) are present only in very small amounts in specific regions of the body, whilst others, such as peptides, proteins, carbohydrates, lipids and nucleic acids, are found in all parts of the body. A basic knowledge of the nomenclature and structures of these more common endogenous classes of biological molecules is essential to understanding medicinal chemistry. This chapter introduces these topics in an attempt to provide for those readers who do not have this background knowledge.

The structures of biologically active molecules usually contain more than one type of functional group. This means that the properties of these molecules are a mixture of those of each of the functional groups present plus properties characteristic of the compound. The latter are frequently due to the interaction of adjacent functional groups and/or the influence of a functional group on the carbon–hydrogen skeleton of the compound. This often involves the electronic activation of C–H bonds by adjacent functional groups.

1.2 Amino acids

1.2.1 Introduction

Simple amino acids are the basic building blocks of proteins. Their structures contain both an amino group, usually a primary amine, and a carboxylic acid. The relative positions of these groups vary, but for most naturally occurring

Fundamentals of Medicinal Chemistry, Edited by Gareth Thomas
© 2003 John Wiley & Sons, Ltd
ISBN 0 470 84306 3 (Hbk), ISBN 0 470 84307 1 (pbk)

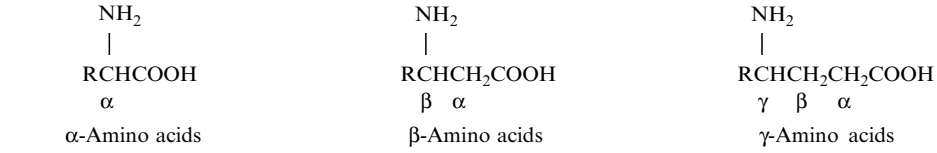


Figure 1.1 The general structural formulae of amino acids. Amino acids may be classified as α, β, γ ....etc. depending on the relative positions of the amine and carboxylic acid groups. α-Amino acids are the most common naturally occuring amino acids

compounds the amino group is attached to the same carbon as the carboxylic acid (Figure 1.1).

The structures of amino acids can also contain other functional groups besides the amine and carboxylic acid groups (Table 1.1). Methionine, for example, contains a sulphide group, whilst serine has a primary alcohol group.

Table 1.1 Examples of the names and structures of amino acids

Amino acid	Name	Symbol/letter		p*I*(25°)
$CH_3CH_2(NH_2)COOH$	Alanine	Ala	A	6.0
$NH_2\text{-}\overset{\overset{NH}{\|\|}}{C}\text{-}NHCH_2CH_2CH_2CH(NH_2)COOH$	Arginine	Arg	R	10.8
$NH_2COCH_2CH(NH_2)COOH$	Asparagine	Asn	N	5.4
$HOOCCH_2CH(NH_2)COOH$	Aspartic acid	Asp	D	3.0
$HOOCCH_2CH_2CH(NH_2)COOH$	Glutamic acid	Glu	E	3.2
$H_2NCOCH_2CH_2CH(NH_2)COOH$	Glutamine	Gln	Q	5.7
$CH_2(NH_2)COOH$	Glycine	Gly	G	6.0
	Histidine	His	H	7.6
$CH_3CH_2\overset{\overset{CH_3}{\|}}{C}HCH(NH_2)COOH$	Isoleucine	Ile	I	6.0
$CH_3\overset{\overset{CH_3}{\|}}{C}HCH_2CH(NH_2)COOH$	Leucine	Leu	L	5.9
$H_2NCH_2CH_2CH_2CH_2CH(NH_2)COOH$	Lysine	Lys	K	9.7
$CH_3SCH_2CH_2CH(NH_2)COOH$	Methionine	Met	M	5.7
$PhCH_2CH(NH_2)COOH$	Phenylalanine	Phe	F	5.5
	Proline	Pro	P	6.3
$CH_2OHCH(NH_2)COOH$	Serine	Ser	S	5.7
$CH_3\overset{\overset{CH_3}{\|}}{C}HCH(NH_2)COOH$	Valine	Val	V	6.0

The nature of the side chains of amino acids determines the hydrophobic (water hating) and hydrophilic (water loving) nature of the amino acid. Amino acids with hydrophobic side chains will be less soluble in water than those with hydrophilic side chains. The hydrophobic/hydrophilic nature of the side chains of amino acids has a considerable influence on the conformation adopted by a peptide or protein in aqueous solution. Furthermore, the hydrophobic/hydrophilic balance of the groups in a molecule will have a considerable effect on the ease of its passage through membranes (Appendix 5).

1.2.2 Structure

All solid amino acids exist as dipolar ions known as zwitterions (Figure 1.2(a)). In aqueous solution the structure of amino acids are dependent on the pH of the solution (Figure 1.2(b)). The pH at which an aqueous solution of an amino acid is electrically neutral is known as the **isoelectric point (pI)** of the amino acid (Table 1.1). Isoelectric point values vary with temperature. They are used in the design of electrophoretic and chromatographic analytical methods for amino acids.

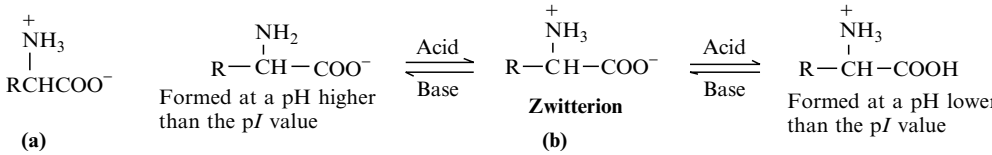


Figure 1.2 (a) The general structural formula of the zwitterions of amino acids. (b) The structures of amino acids in acidic and basic aqueous solutions

1.2.3 Nomenclature

Amino acids are normally known by their trivial names (Table 1.1). In peptide and protein structures their structures are indicated by either three letter groups or single letters (Table 1.1, and Figure 1.7). Amino acids such as ornithine and citrulline, which are not found in naturally occuring peptides and proteins, do not have an allocated three or single letter code (Figure 1.3).

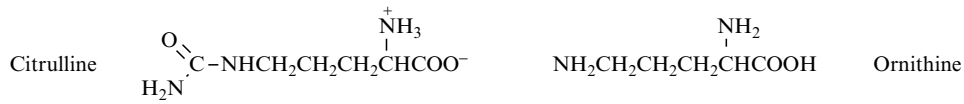


Figure 1.3 Ornithine and citrulline

Most amino acids, with the notable exception of glycine, are optically active. Their configurations are usually indicated by the D/L system (Figure 1.4) rather than the R/S system. Most naturally occuring amino acids have an L configuration but there are some important exceptions. For example, some bacteria also possess D-amino acids. This is important in the development of some antibacterial drugs.

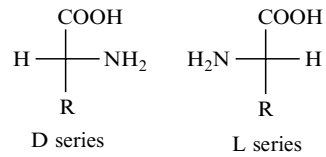


Figure 1.4 The D/L configurations of amino acids. Note that the carboxylic acid group must be drawn at the top and the R group at the bottom of the Fischer projection. Stereogenetic centres in the R group do not affect the D/L assignment

1.3 Peptides and proteins

Peptides and proteins have a wide variety of roles in the human body (Table 1.2). They consist of amino acid residues linked together by **amide functional groups** (Figure 1.5(a)), which in peptides and proteins are referred to as **peptide links** (Figure 1.5(c)). The amide group has a rigid flat structure. The lone pair of its nitrogen atom is able to interact with the π electrons of the carbonyl group.

Table 1.2 Examples of some of the biological functions of proteins

Function	Notes
Structural	These proteins provide strength and elasticity to, for example, bone (collagen), hair (α-keratins) and connective tissue (elastin).
Enzymes	This is the largest class of proteins. Almost all steps in biological reactions are catalysed by enzymes.
Regulatory	These are proteins that control the physiological activity of other proteins. Insulin, for example, regulates glucose metabolism in mammals.
Transport	These transport specific compounds from one part of the body to another haemoglobin transports carbon dioxide too and oxygen from the lungs. Cell membranes contain proteins that are responsible for the transport of species from one side of the membrane to the other.
Storage	These provide a store of substances required by the body. For example, the protein ferritin acts as an iron store for the body.
Protective	These proteins that protect the body. Some form part of the bodies immune system defending the body against foreign molecules and bacteria. Others, such as the blood clotting agents thrombin and fibrinogen, prevent loss of blood when a blood vessel is damaged.

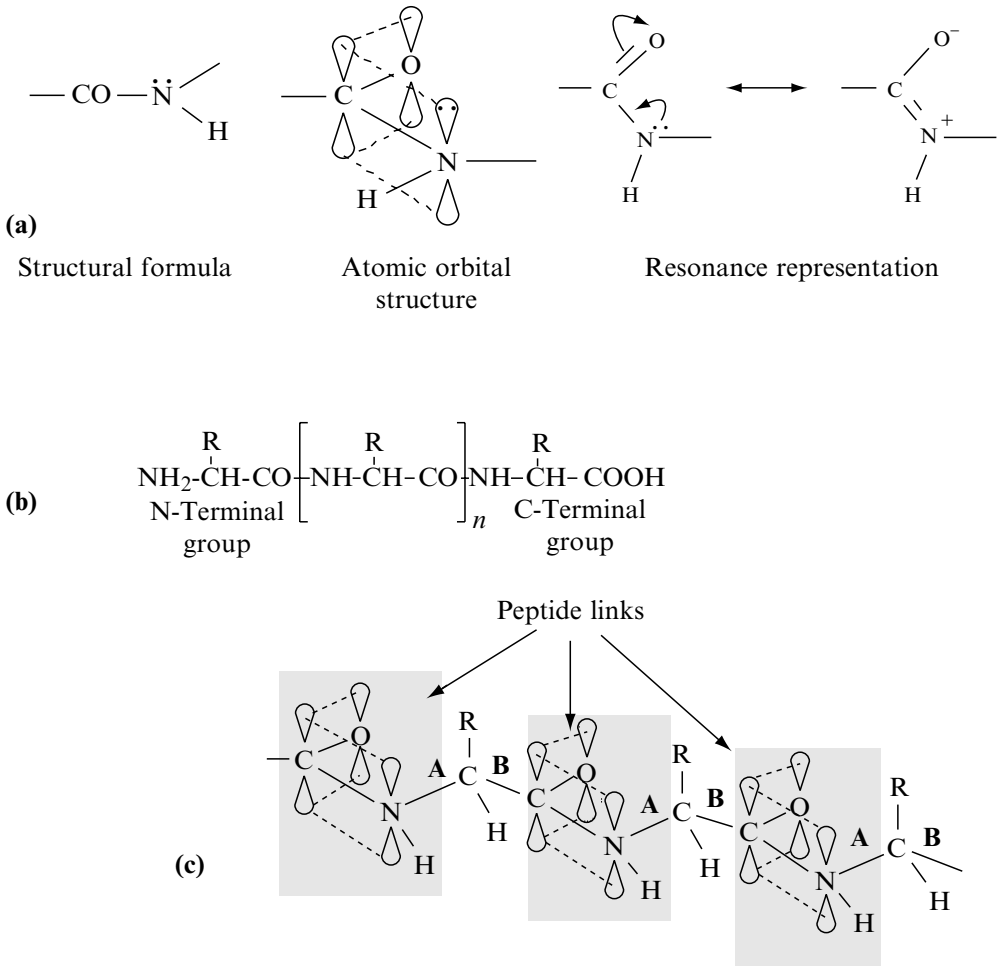


Figure 1.5 (a) The structure of the amide functional group. (b) The general structure of simple peptides. (c) The peptide link is planar and has a rigid conjugated structure. Changes in conformation can occur about bonds A and B. Adapted from G Thomas, *Chemistry for Pharmacy and the Life Sciences including Pharmacology and Biomedical Science*, 1996, published by Prentice Hall, a Pearson Education Company

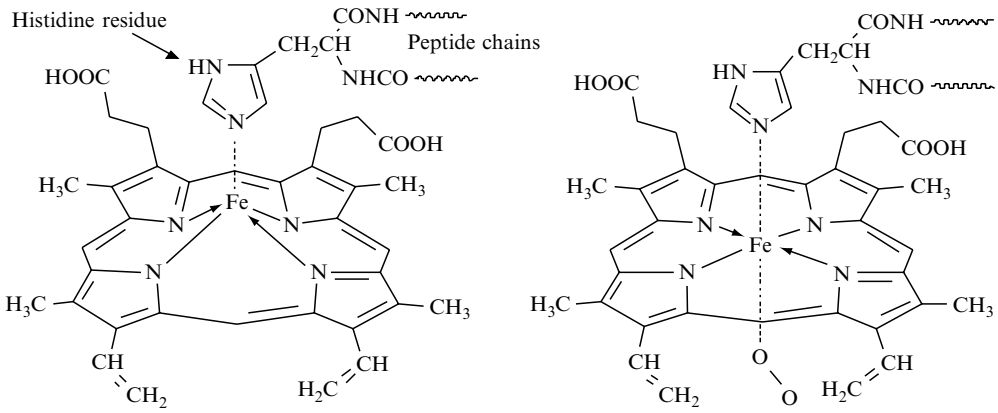
This electron delocalization is explained by p orbital overlap and is usually shown by the use of resonance structures (Figure 1.5(a)).

The term **peptide** is normally used for compounds that contain small numbers of amino acid residues whilst the term **polypeptide** is loosely used for larger compounds with relative molecular mass (RMM) values greater than about 500 or more. **Proteins** are more complex polypeptides with RMM values usually greater than 2000. They are classified as **simple** when their structures contain

only amino acid residues and **conjugated** when other residues besides those of amino acids occur as integral parts of their structures. For example, haemoglobin is a conjugated protein because its structure contains a haem residue (Figure 1.6). These non-amino-acid residues are known as **prosthetic groups** when they are involved in the biological activity of the molecule. Conjugated proteins are classified according to the chemical nature of their non-amino-acid component. For example, glycoproteins contain a carbohydrate residue, haemoproteins a haem group and lipoproteins a lipid residue.

1.3.1 Structure

The structures of peptides and proteins are very varied. They basically consist of chains of amino acid residues (Figures 1.5(b), 1.5(c) and 1.7). These chains may be branched due to the presence of multi-basic or acidic amino acid residues in the chain (Figure 1.7(d)). In addition, bridges (cross links) may be formed between different sections of the same chain or different chains. Cysteine residues, for example, are responsible for the S–S bridges between the two peptide chains that form the structure of insulin (Figure 1.7(e)). The basic structure of peptides and proteins is twisted into a conformation (time dependent overall shape) characteristic of that peptide or protein. These conformations are dependent on both the nature of their biological environment as well as their chemical structures. The ability of peptides and proteins to carry out their biological functions is normally dependent on this conformation. Any changes to any part of the structure of a



(**a**) Deoxy-haemoglobin (deoxy-Hb)

(**b**) Oxy-haemoglobin (oxy-Hb)

Figure 1.6 The structure of the haem residue in deoxy- and oxy-haemoglobins. In deoxy-Hb the bonding of the iron is pyramidal whilst in oxy-Hb it is octahedral

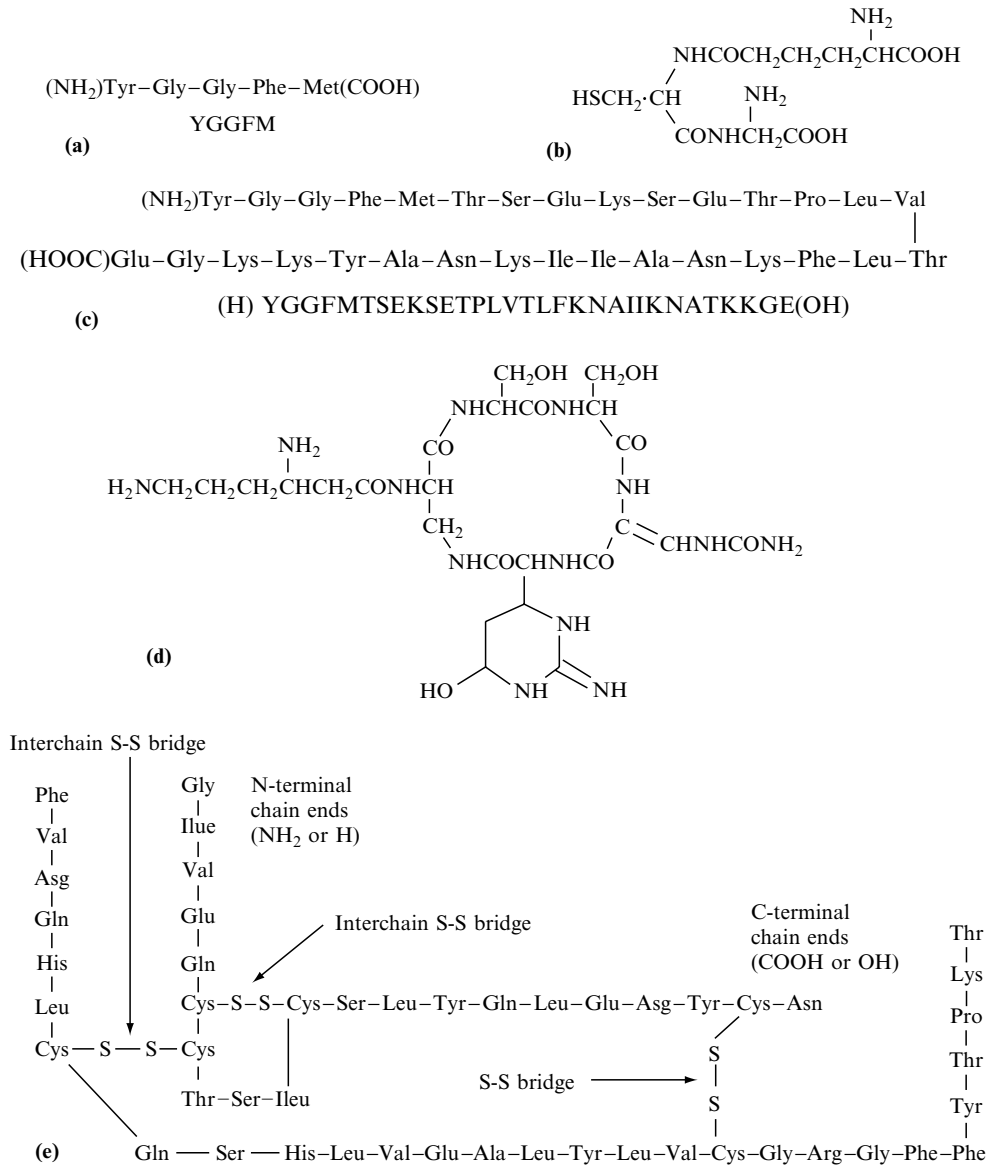


Figure 1.7 Representations of the primary structures of peptides. Two systems of abreviations are used to represent primary structures. The single letter system is used for computer programs. In both systems the N-terminus of the peptide chain is usually drawn on the left-hand side of the structure. (a) Met-enkephalin. This pentapeptide occurs in human brain tissue. (b) Glutathione, an important constituent of all cells, where it is involved in a number of biological processes. (c) β-Endorphin. This endogenous peptide has opiate activity and is believed to be produced in the body to counter pain. (d) Viomycin, a polypeptide antibiotic produced by *Streptomyces griseoverticillatus* var. *tuberacticus*. The presence of the dibasic 2,3-diaminoproanoic acid residue produces the chain branching. (e) Insulin, the hormone that is responsible for controlling glucose metabolism

peptide or protein will either change or destroy the compound's biological activity. For example, sickle-cell anaemia (Appendix 1) is caused by the replacement of a glutamine residue by a valine residue structure of haemoglobin.

Proteins are often referred to as **globular** and **fibrous proteins** according to their conformation. Globular proteins are usually soluble in water, whilst fibrous proteins are usually insoluble. The complex nature of their structures has resulted in the use of a sub-classification, sometimes referred to as **the order of protein structures**. This classification divides the structure into into primary, secondary, tertiary and quaternary orders of structures.

The **primary protein structure** of peptides and proteins is the sequence of amino acid residues in the molecule (Figure. 1.7).

Secondary protein structures are the local regular and random conformations assumed by sections of the peptide chains found in the structures of peptides and proteins. The main regular conformations found in the secondary structures of proteins are the α-helix, the β-pleated sheet and the triple helix (Figure 1.8). These and other random conformations are believed to be mainly due to intramolecular hydrogen bonding between different sections of the peptide chain.

The **tertiary protein structure** is the overall shape of the molecule. Tertiary structures are often formed by the peptide chain folding back on itself. These folded structures are stabilized by S–S bridges, hydrogen bonding, salt bridges (Figure 1.9(a)) and van der Waals' forces within the peptide chain and also with molecules in the peptide's environment. They are also influenced by hydrophobic interactions between the peptide chain and its environment. Hydrophobic interaction is thought to be mainly responsible for the folded shape of the β-peptide chain of human haemoglobin (Figure 1.9(b)). In this structure the hydrophilic groups of the peptide chain are on the outer surface of the folded structure.

Quaternary protein structures are the three dimensional protein structures formed by the noncovalent associations of a number of individual peptides and polypeptide molecules. These individual peptide and polypeptide molecules are known as subunits. They may or may not be the same. Haemoglobin, for example, consists of four subunits, two α- and two β-units held together by hydrogen bonds and salt bridges.

The structures of peptides and proteins usually contain numerous amino and carboxylic acid groups. Consequently, water soluble proteins in aqueous solution can form differently charged structures and zwitterions depending on the pH of the solution (see 1.2.2). The pH at which the latter occurs is known as the isoelectric point (pI) of the protein (Table 1.3). The nature of the charge on the structures of peptides and proteins has a considerable effect on their solubility

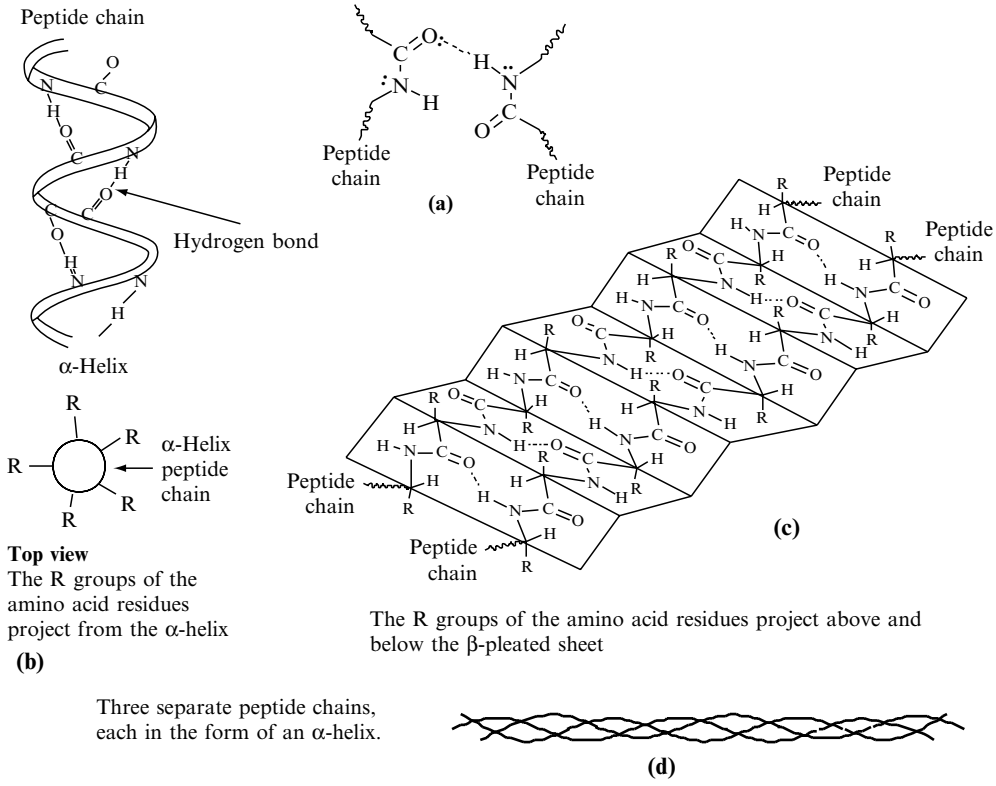


Figure 1.8 The secondary structures of proteins. (a) Hydrogen bonding between peptide links. The conjugated lone pair of the amide nitrogen atom is not available to form hydrogen bonds. (b) The α-helix. The peptide chain is largely held in this shape by intramolecular hydrogen bonds. (c) β-Pleated sheets are formed by hydrogen bonding between neighbouring peptide chains. Antiparallel β-sheets (shown) have the peptide chains running in opposite directions. Parallel β-sheet (not shown) have the peptide chains running in the same direction. Silk fibroin has a high proportion of antiparallel β-pleated sheets. (d) The triple helix in which the three peptide chains are largely held together by hydrogen bonding. For example, the basis of the structure of the fibrous protein collagen which occurs in skin, teeth and bones, consists of three chains of the polypeptide tropocollagen in the form of a triple helix. This forms a cable like structure known as a *protofibril*. Reproduced from G Thomas, *Chemistry for Pharmacy and the Life Sciences including Pharmacology and Biomedical Science*, 1996, by permission of Prentice Hall, a Pearson Education Company

and biological activity. For example, the water solubility of a protein is usually at a minimum at its isoelectric point whilst the charge on a protein may affect the ease of transport of a protein through a plasma membrane (see Appendix 5). It is also important in electrophoretic and chromatographic methods of protein analysis.

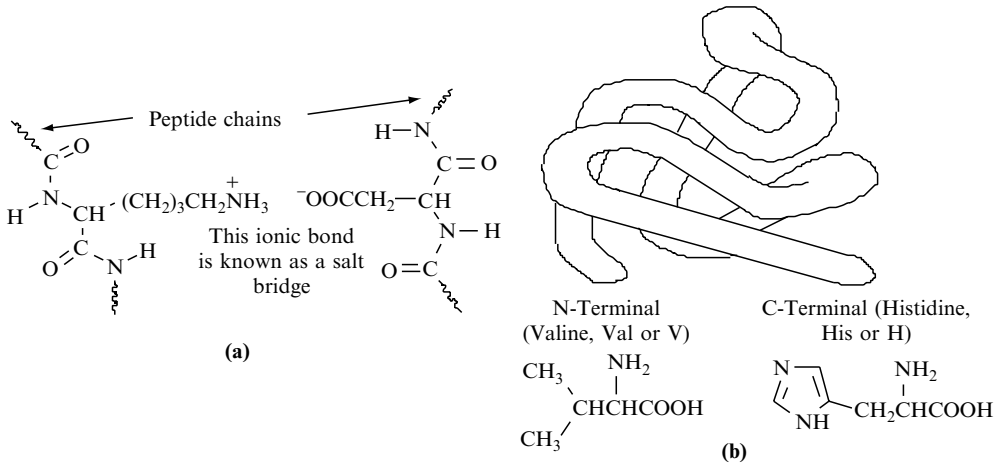


Figure 1.9 (a) A salt bridge. This is essentially an ionic bond. (b) The folded structure of a β-haemoglobin polypeptide chain. Reproduced from G Thomas, *Chemistry for Pharmacy and the Life Sciences including Pharmacology and Biomedical Science*, 1996, by permission of Prentice Hall, a Pearson Education Company

Table 1.3 Examples of the p*I* values of proteins (various sources)

Protein	p*I* (25°)	Protein	p*I* (25°)	Protein	p*I* (25°)
Cytochrome c (horse)	10.6	γ-Globulin (human)	6.6	Lysozyme (hen)	11.0
Fibrinogen (human)	5.5	Histone (bovine)	10.8	Ribonuclease A (bovine)	9.4
Haemoglobin A (human)	7.1	Insulin (human)	5.4	Serum albumin (human)	4.9

1.4 Carbohydrates

Carbohydrates, or sugars as they are commonly known, are classified as monosaccharides, oligosaccharides and polysaccharides. **Monosaccharides** are either polyhydroxyaldehydes (**aldoses**) or polyhydroxyketones (**ketoses**), which are not converted to any simpler polyhydroxyaldehydes and polyhydroxyketones respectively under aqueous hydrolysis conditions. Carbohydrates also include compounds such as glucosamine (Figure 1.10), whose structures contain amino groups as well as hydroxy groups. These compounds are known as **amino sugars**. However, not all polyhydroxyaldehydes and ketones are classified as carbohydrates.

Monosaccharides are classified according to the total number of carbon atoms in their structure. For example, an aldohexose is a monosaccharide that contains a total of six carbon atoms including that of the aldehyde in its structure. Similarly, a ketopentose has five carbons in its structure including the one in the keto group. **Oligosaccharides** are carbohydrates that yield from two to about nine monosaccharide molecules when one molecule of the oligosaccharide is hydrolysed. Small oligosaccharides are often classified according to the number of monosaccharide residues contained in their structures. For example, disaccharides and trisaccharides contain two and three monosaccharide residues respectively whilst **polysaccharides** yield larger numbers of monosaccharide molecules per polysaccharide molecule on hydrolysis. All types of carbohydrate occur widely in the human body. They exhibit a wide variety of biological functions but in particular act as major energy sources for the body.

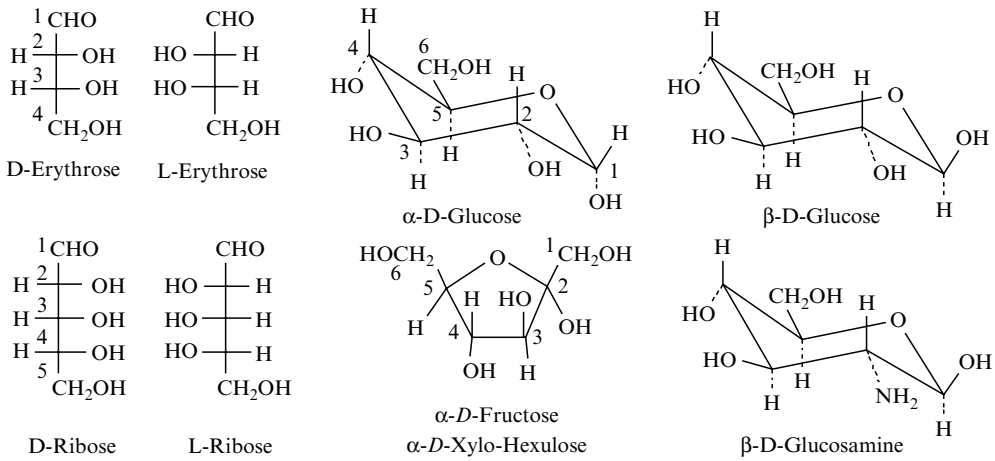


Figure 1.10 Examples of the cyclic and straight chain structures of monosaccharides. The carbon of the carbonyl group has the lowest locant

1.4.1 The structure of monosaccharides

Monosaccharides can exist as either straight chain or cyclic structures (Figure 1.10). Those with five or more carbon atoms usually assume either a five (**furanose**) or six (**pyranose**) membered ring structure. These cyclic structures are formed by an internal nucleophilic addition between a suitably positioned hydroxy group in the molecule and the carbonyl group (Figure 1.11). It results in the formation of the corresponding cyclic hemiacetal or hemiketal. The rings of these cyclic products exist in their normal conformations. For example, six

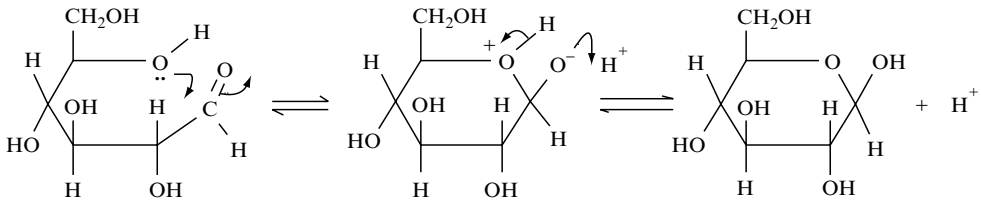


Figure 1.11 The cyclization of the *straight chain* form of glucose to form the β-hemiacetal cyclic form of the molecule

membered rings usually occur as chair conformations whilst five membered rings exist as envelope conformations.

This internal nucleophilic addition introduces a new chiral centre into the molecule. The carbon of the new centre is known as the **anomeric carbon** and the two new stereoisomers formed are referred to as **anomers**. The isomer where the new hydroxy group and the CH_2OH are on opposite sides of the plane of the ring is known as the alpha (α) anomer. Conversely, the isomer with the new hydroxy group and terminal CH_2OH on the same side of the plane of the ring is known as the beta (β) anomer (Figure 1.12).

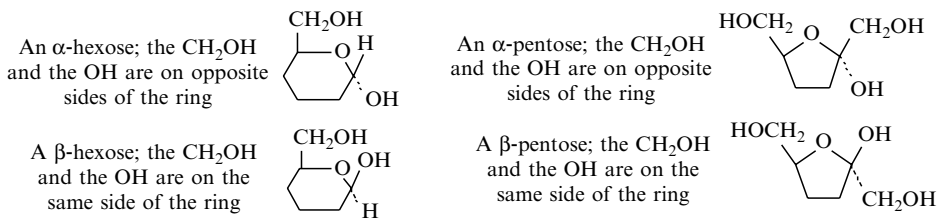


Figure 1.12 The α- and β-anomers of monosaccharides drawn using the Haworth convention. In this convention solid lines represent bonds above the plane of the ring whilst dotted lines are used to indicate bonds below the plane of the ring. Reproduced from G Thomas, *Chemistry for Pharmacy and the Life Sciences including Pharmacology and Biomedical Science*, 1996, by permission of Prentice Hall, a Pearson Education Company

In many cases pure α- and β-anomers may be obtained by using appropriate isolation techniques. For example, crystallization of D-glucose from ethanol yields α-D-glucose $[\alpha]_D$ +112.2° whilst crystallization from aqueous ethanol produces β-D-glucose $[\alpha]_D$ +18.7°. In the solid state these forms are stable and do not interconvert. However, in aqueous solution these cyclic structures can form equilibrium mixtures with the corresponding straight chain form (Figure 1.13). The change in optical rotation due to the conversion of either the pure α- or pure β-anomer of a monosaccharide into an equilibrium mixture of both forms in aqueous solution is known as **mutarotation** (Figure 1.13).