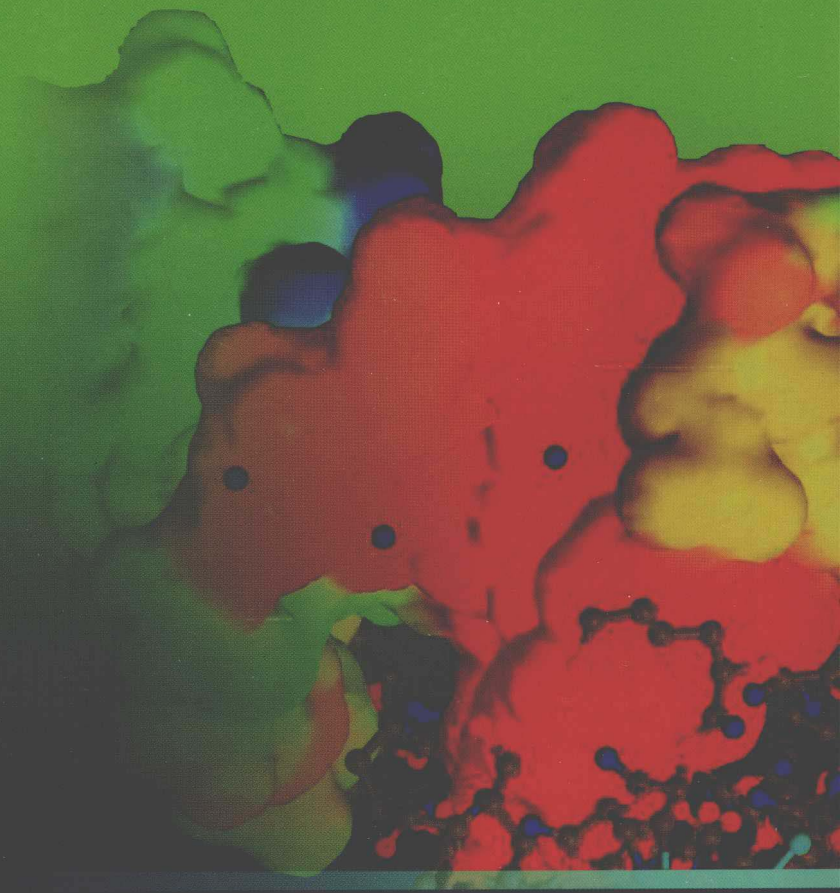
医学教育改革系列教材

Biochemistry

Chief Editors Wei Ding Hongti Jia



高等教育出版社
HIGHER EDUCATION PRESS

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高等教育出版社·北京
HIGHER EDUCATION PRESS　BEIJING

图书在版编目（CIP）数据

生物化学 = Biochemistry：英文 / 丁卫，贾弘禔主编. -- 北京：高等教育出版社，2012.6

ISBN 978-7-04-034339-7

Ⅰ.①生… Ⅱ.①丁…②贾… Ⅲ.①生物化学－高等学校－教材－英文 Ⅳ.①Q5

中国版本图书馆 CIP 数据核字（2012）第 061737 号

总 策 划 林金安 吴雪梅 席 雁

策划编辑 瞿德竑 责任编辑 瞿德竑 封面设计 张 楠 责任印制 毛斯璐

出版发行	高等教育出版社	咨询电话	400－810－0598
社 址	北京市西城区德外大街 4 号	网 址	http://www.hep.edu.cn
邮政编码	100120		http://www.hep.com.cn
印 刷	北京中科印刷有限公司	网上订购	http://www.landraco.com
开 本	889mm×1194mm 1/16		http://www.landraco.com.cn
印 张	11.5	版 次	2012 年 6 月第 1 版
字 数	340 千字	印 次	2012 年 6 月第 1 次印刷
购书热线	010－58581118	定 价	26.00 元

物 料 号 34339－00

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Foreword

Global developments in medicine and health shape trends in medical education. And in China education reform has become an important focus as the country strives to meet the basic requirements for developing a medical education system that meets international standards. Significant medical developments abroad are now being incorporated into the education of both domestic and international medical students in China, which includes students from Hong Kong, Macao and Taiwan that are taught through mandarin Chinese as well as students from a variety of other regions that are taught through the English language. This latter group creates higher demands for both schools and teachers.

Unfortunately there is no consensus as to how to improve the level and quality of education for these students or even as to which English language materials should be used. Some teachers prefer to directly use original English language materials, while others make use of Chinese medical textbooks with the help of English language medical notes. The lack of consensus has emerged from the lack of English language medical textbooks based on the characteristics of modern medical education in China.

In fact, most Chinese teachers involved in medical education have already attained an adequate level of English language usage. However, English language medical textbooks that reflect the culture of the teachers would in fact make it easier for these teachers to complete the task at hand and would improve the level and quality of medical education for international students. In addition, these texts could be used to improve the English language level of the medical students taught in Chinese. This is the purpose behind the compilation and publishing of this set of English language medical education textbooks.

The editors in chief are mainly experts in medicine from Capital Medical University (CCMU). The editorial board members are mainly teachers of a variety of subjects

from CCMU. In addition, teachers with rich teaching experience in other medical schools are also called upon to help create this set of textbooks. And finally some excellent scholars are invited to participate as final arbiters for some of the materials.

The total package of English medical education textbooks includes 63 books. Each textbook conforms to five standards according to their grounding in science; adherence to a system; basic theory, concepts and skills elucidated; simplicity and practicality. This has enabled the creation of a series of English language textbooks that adheres to the characteristics and customs of Chinese medical education. The complete set of textbooks conforms to an overall design and uniform style in regards to covers, colors, and graphics. Each chapter contains learning objectives, core concepts, an introduction, a body, a summary, questions and references that together serve as a scaffold for both teachers and students.

The complete set of English language medical education textbooks is designed for teaching overseas undergraduate clinical medicine students (six years), and can also serve as reference textbooks for bilingual teaching and learning for 5-year, 7-year and 8-year programs in clinical medicine.

We would like to thank the chief arbiters, chief editors and general editors for their arduous labor in the writing of each chapter. We would also like to acknowledge all the contributors. Finally, we would like to acknowledge Higher Education Press. They have all provided valuable support during the many weekends and evening hours of work that were necessary for completing this endeavor.

President of Capital Medical University
Director of English Textbook Compiling Commission
Zhaofeng Lu
August 1st, 2011

Preface

In the past decade, medical education achieved great development in Capital Medical University, China (CCMU), serving the students coming from all parts of China and overseas. On the one hand, the growing number of foreign students at CCMU crave for English books suitable for the teaching and learning with the Chinese medical education system; on the other hand, the Chinese students are asked and eager to actively participate in the international academic exchanges nowadays. To meet the needs of both foreign and Chinese students majoring in basic and clinic medical sciences, CCMU puts forward a project to compile textbooks in English as a part of the university's developing strategy and objectives, which are "based on Beijing, embracing the nation; leading in China and recognized around the world". Thus, the textbook of biochemistry in English was prepared by the senior instructors in the Department of Biochemistry and Molecular Biology, CCMU.

As our experience, medicine students may sometimes complain about biochemistry courses with the overload of information and boring contents in lectures. Unfortunately, the nature of this course indeed decides that there are a lot to be learned and memorized. We have intentionally arranged the texts as straight forward as possible, therefore hopefully, this simple direct "focus and concise" style will be accepted by teachers and students. The first three chapters introduce to the structures, properties and functions of proteins (including enzymes) and nucleic acids. Chapters 4 to 8 are the discussion about the metabolisms of carbohydrates, lipids, amino acids and nucleotides, and of biological oxidation (the formation of ATP and water) in cells. Chapter 9 summarizes the integrated metabolic pathways of glucose, fatty acids, amino acids, and nucleotides, and emphasizes the regulation of metabolisms. Chapters 10 to 12 focus on the processes and regulation of replication, transcription and translation (genetic information transmission). Chapters 13 and 14 briefly introduce the biochemistry at the tissue level of blood and liver, providing students some examples prior to their subsequent learning of medicine in relation to clinical aspects. Unlike some other biochemical texts, this textbook does not discuss

recombinant DNA and technical issues related to molecular biology. We will leave those contents in the separate book of Molecular Biology.

Our writing of this book was encouraged and supported by the administration of teaching management, CCMU. We are grateful to the Higher Education Press, China. Most importantly, we will be more than happy to hear from readers' suggestions on improvements for the next edition.

Wei Ding
Hongti Jia
March, 2012

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Contents

Chapter 1

Molecular Compositions of Proteins

▪ Principal Points

All 20 of the α-amino acids in human proteins are "L" stereoisomers (*L*-α-amino acids). They are classified into several types on the basis of polarity and charge of R groups. Amino acids can act as either an acid or base upon environment pH. The characteristic pH, at which the net electric charge is zero, is called isoelectric point (pI). Aromatic amino acids have a maximum UV absorption (A_{280}), contributing to the spectroscopic properties of proteins.

Proteins are macromolecules composed of one or more polypeptide chains, each with a characteristic sequence of amino acids linked by peptide bonds. Peptide bond is formed by reaction between the α-amino group of one amino acid and the α-carboxyl group of another, with the elimination of a water molecule.

Primary structure of proteins is defined as the sequence of amino acid residues in a peptide chain. Secondary structure refers to particularly spatial arrangements of peptide segments, of which the most common are the forms of α-helix and β-pleated sheet. Tertiary structure is the three-dimensional folding of a polypeptide. Quaternary is described as the spatial arrangement of multiple subunits of a protein. The primary structure of a protein determines three-dimensional structure, and this in turn determines the function of the protein. A loss of three-dimensional structure sufficient to cause loss of function is referred to as denaturation.

Based on the physico-chemical properties of proteins/polypeptides, many approaches are designed to separate, determine and analyze proteins/polypeptides.

1.1 Molecular Compositions of Proteins

1.1.1 Proteins have Fundamental Importance to the Livings

The word ***protein***, derived from the Greek *proteios* meaning "of the first rank", was coined by Berzelius (1838) to emphasize the importance to life. This is because of two major reasons. First, except water, proteins are the most essential and abundant constituents of animal organisms including humans, composing about 45% of the dry weight of body. The wide distribution of proteins in the body indicates that proteins have abilities to meet the needs of the body such as the formation of tissue or cells and the maintenance of growth, renewal and repair. Second, proteins have the most diversified biological functions. Many proteins are enzymes that catalyze biochemical reactions in living cells. Some proteins have the functions of transport and storage, for example, hemoglobin transports oxygen in blood, and myoglobin carries and stores oxygen in skeletal muscle. Proteins also have structural or mechanical functions, such as actin and myosin in muscle, and actin and tublin in the cytoskeleton that maintains cell shape. Other proteins are important in multiple functions such as cell signaling, immune responses, cell adhesion, cell division, *etc.*

1.1.2 Proteins are Composed of Major and Trace Elements

Protein molecules are made of five principle or **major elements**, including carbon (C), hydrogen (H), oxygen (O), nitrogen (N), and sulfur (S). Among the major elements, nitrogen content in proteins is relatively constant; the average **nitrogen** content in proteins is about 16%. Proteins are the major source of N in biological systems, so the protein quantity can be estimated by the following equation:

Protein content in 100 g sample=N content per gram×6.25×100

The other elements present at very low levels in proteins are called **trace elements** such as phosphorus (P), iron (Fe), copper (Cu), zinc (Zn), iodine (I)... They are also essential to the function of specific protein.

1.1.3 All 20 of L-α-amino Acids have Common Structure and Specifically Chemical Properties upon R Groups

All proteins, whether from the most ancient lines of prokaryote or the most complex forms of eukaryote, are constructed from the same set of 20 **amino acids** (AAs), covalently linked together through peptide bonds. All 20 of α-amino acids are *L*-stereoisomers excepted(*L*-α-amino acids) and the building blocks used for protein synthesis in biological systems, so that they are called common or standard amino acids. In addition to these 20 amino acids, a few additional amino acids are found in low amount in specific proteins, and others are present in living organisms but not as constituents of proteins. Amino acids are often designated by either a three-letter abbreviation or a one-letter symbol (Table 1-1).

Table 1-1 Abbreviations for 20 standard amino acids

Amino acid	Three-letter abbreviation	One-letter abbreviation	Amino acid	Three-letter abbreviation	One-letter abbreviation
Alanine	Ala	A	Leucine	Leu	L
Arginine	Arg	R	Lysine	Lys	K
Asparagine	Asn	N	Methionine	Met	M
Aspartic acid	Asp	D	Phenylalanine	Phe	F
Cysteine	Cys	C	Proline	Pro	P
Glutamine	Gln	Q	Serine	Ser	S
Glutamic acid	Glu	E	Threonine	Thr	T
Glycine	Gly	G	Tryptophan	Trp	W
Histidine	His	H	Tyrosine	Tyr	Y
Isoleucine	Ile	I	Valine	Val	V

1.1.3.1 Amino acids have common structure features

All 20 of ***L*-α-amino acids** have a general structure depicted in Figure 1-1. With the exception of glycine, the amino acids are optically active compounds, in which a carboxyl group (—COOH), an amino group ($—NH_2$), a hydrogen atom, and a variable side chain (R group) bind to the asymmetric carbon (α-carbon). They differ from one another by the chemical composition of their R groups.

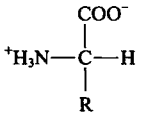
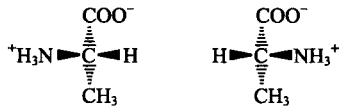


Figure 1-1 General structure of *L*-α-amino acids

Since α-amino acids have an asymmetric a-carbon atom and four different substituent groups bind to the α-carbon, all amino acids exhibit stereoisomerism except glycine. For instance, alanine has two stereoisomers (Figure 1-2). The Fischer projection of an α-amino acid is written with the NH_2 group to the right of the asymmetric carbon for the *D*-isomer, and to the left for the *L*-isomer. Almost all biological functions involving amino acids have strict requirements for *L*-isomers; however, there is limited biological use of *D*-amino acids, since they are present in some biological materials, e. g. certain bacterial cell walls and some antibiotics.



L-alanine *D*-alanine

Figure 1-2 Stereoisomers of alanine

1.1.3.2 Amino acids are zwitterions

Amino acids in solution at neutral pH exist predominantly as dipolar ions, termed **zwitterions.** In the dipolar form, the amino group is protonated ($—NH_3^+$), and the carboxyl group is deprotonated ($—COO^-$). The ionization state of an amino acid varies with pH. In acidic solution (e. g. pH = 1), the amino group is protonated ($—NH_3^+$) and the carboxyl group is not dissociated (—COOH). As the pH is raised, the carboxylic acid is the first group to give up a proton, in as much as its **pKa** is near 2. The dipolar form persists until the pH approaches 9, when the protonated amino group loses a proton. Amino acids in solution at certain pH are predominantly in dipolar form, fully ionized but without net charge (having zero net charge); the characteristic pH at which the net electric charge is zero is called **isoelectric point**, designated as **pI.** An amino acids at any pH below its pI, has a net positive charge; when at any pH above its pI, it has a net negative charge (Figure 1-3).

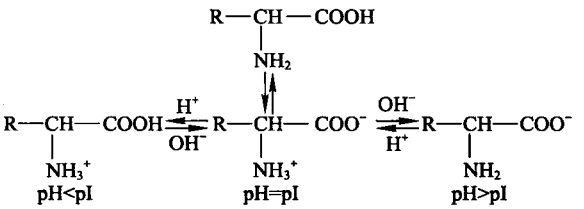


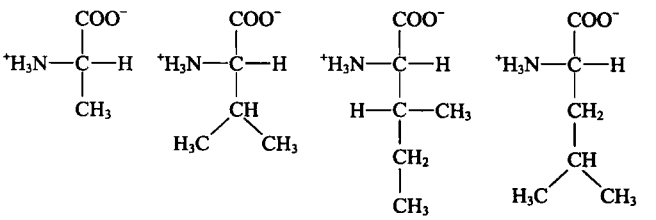
Figure 1-3 The ionization state of amino acids is altered by a change in pH

1.1.3.3 Amino acids can be classified by R group

The solubility and ionization properties of R groups are influential traits of amino acids, and collectively they contribute greatly to the native three-dimensional structures of individual polypeptides. Based on the two characteristics of R groups, the 20 amino acids are classified into four categories as follows.

Nonpolar R groups

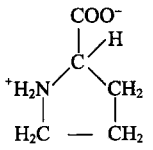
Eight of the amino acids have nonpolar side chains, thereby displaying varied degrees of hydrophobicity. Four (alanine, valine, leucine, and isoleucine) have aliphatic noncyclic R groups (Figure 1-4).



Alanine (Ala, A) Valine (Val,V) Isoleucine (Ile,I) Leucine (Leu,L)

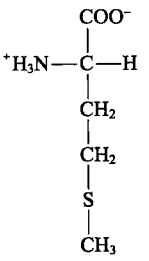
Figure 1-4 Alanine and three branched-chain amino acids have aliphatic R groups

Alanine is the least hydrophobic of the eight because of its small methyl side chain. Valine, leucine, and isoleucine are called the branched-chain amino acids because of the branching in their aliphatic R groups. The fifth "amino" acid of this group is proline (Figure 1-5), which has an aliphatic heterocyclic structure that includes both the R group and the a-nitrogen atom. Thus, proline differs from the other 19 amino acids since it is an imino acid, having an imino (=NH) rather than an amino ($—NH_2$) group.



Proline (Pro,P)

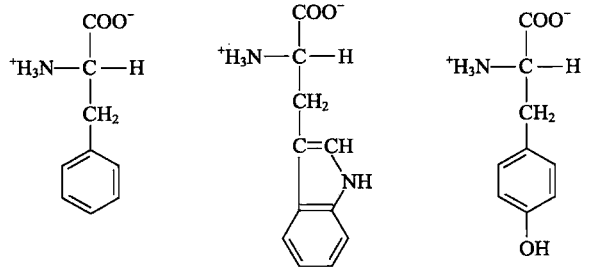
Figure 1-5 Proline is an imino acid



Methionine (Met,M)

Figure 1-6 Methionine

The sixth amino acid, methionine (Figure 1-6), has a sulfur atom in its nonpolar side chain and is one of two sulfur-containing amino acids incorporated into proteins. The remaining two amino acids, phenylalanine and tryptophan (Figure 1-7 a, b), have water-insoluble aromatic rings in their structures. Phenylalanine has a phenyl group in its side chain and tryptophan an indole group (a condensed ring composed of benzene and pyrrole); both are considered aromatic amino acids.



a. Phenylalanine (Phe, F) b. Tryptophan (Trp, W) c. Tyrosine (Tyr, Y)

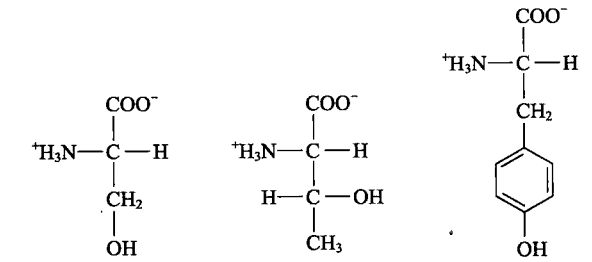
Figure 1-7 Aromatic amino acids

Polar, neutral R groups

This class contains seven amino acids which are relatively hydrophilic because of the polar functional groups in their side chains. Three amino acids (serine, threonine, and tyrosine) are hydroxylated, and the OH groups contribute to their polarity (Figure 1-8). Tyrosine, like phenylalanine and tryptophan, is also an **aromatic amino acid** (Figure 1-8 c).

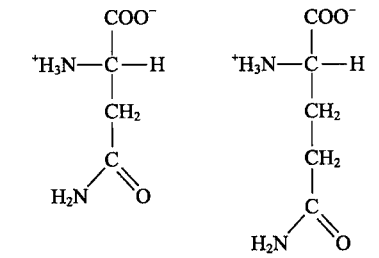
Cysteine, the other sulfur-containing amino acid, is polar because of its sulfhydryl (—SH) group. Often in protein structures, two cysteinyl residues are covalently linked to each other through oxidation of their sulfhydryl groups, producing a **disulfide bond** (—S—S—), which are particularly important in folding and stabilizing some proteins.

Asparagine and glutamine (Figure 1-9) are derived from aspartic acid and glutamic acid, and each has a polar amide group in its side chain.



a. Serine (Ser, S) b. Threonine (Thr, T) c. Tyrosine (Tyr, Y)

Figure 1-8 Three hydroxylated amino acids

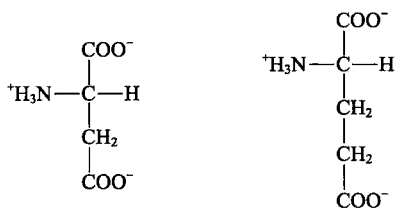


Asparagine (Asn, N) Glutamine (Gln, Q)

Figure 1-9 Two amino acids with amide groups

Negatively charged (acidic) polar R groups

Both aspartic acid and glutamic acid have a second carboxyl group, which is fully ionized (negatively charged) at physiological pH (Figure 1-10). Both are referred to as **acidic amino acids** because they donate H^+ when placed in solution.

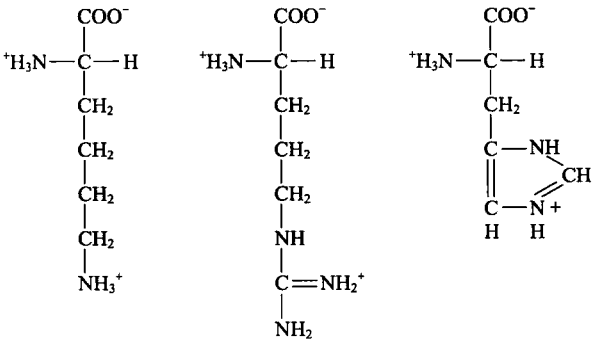


Aspartic acid (Asp, D) Glutamic acid (Glu, E)

Figure 1-10 Two acidic amino acids

Positively charged (basic) polar R groups

Lysine and arginine, two of the three **basic amino acids** (Figure 1-11), have R groups that are positively charged at physiological pH. Ionic charges are provided by protonation of the amino group of the ε-carbon of lysine and of the guanidinium group of arginine. The third basic amino acid, histidine has an imidazolium R group with a p*K*a value of 6.0 and, therefore, is less than 10 per cent protonated at pH 7. Of the 20 amino acids, histidine is the only one whose isoelectric point of about 7.6 is near physiological pH.



Lysine (Lys, K) Arginine (Arg, R) Histidine (His, H)

Figure 1-11 Basic amino acids

1.1.4 Amino Acids can be Joined by Peptide Bonds to Form Peptides

1.1.4.1 Amino acids can form peptides

Most importantly, amino acids can be joined by peptide bounds to form peptides. Two amino acids react through the α-NH_2 group of one amino acid and the α-COO^- group of another to yield a dipeptide and a water molecule (Figure 1-12). The substituted linkage between an α-NH_2 group of one amino acid and an α-COO^- group of another, with the elimination of the elements of water, is termed **peptide bond**. The structure of two or more amino acids covalently joined by peptide bonds is called **peptide** (chain), such as dipeptide, tripeptide, **oligopeptides** (a few amino acids are joined) and **polypeptides** (many amino acids joined). An amino acid unit of a polypeptide is called an (amino acid) **residue**. In a polypeptide structure, the two terminal amino acid residues are the only ones that possess a free α-NH_3^+ or α-COO^- group. The terminal residue with a free α-NH_3^+ group is called the **amino-terminal** or N-terminal residue. The **carboxyl-terminal** or C terminal residue has a free α-COO^- group and is at the other terminus of the polypeptide. In biological systems, polypeptides are synthesized from the amino terminus to the carboxyl terminus, and the generally accepted convention is to write the amino acid sequence of a polypeptide from left to right, starting with the N-terminal residue (Figure 1-13). Although the terms "polypeptide" and "protein" are sometimes used interchangeably, a peptide has lower and a protein has higher molecular weights.

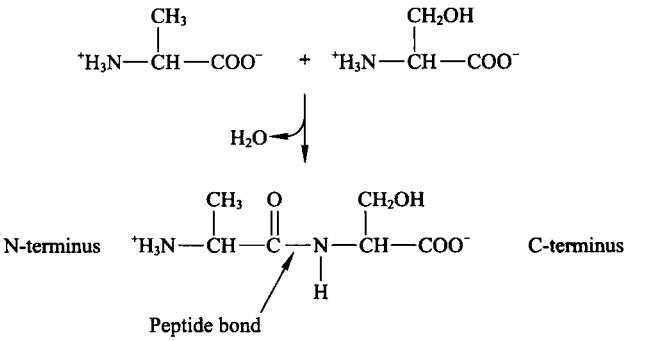


Figure 1-12 Formation of a dipeptide

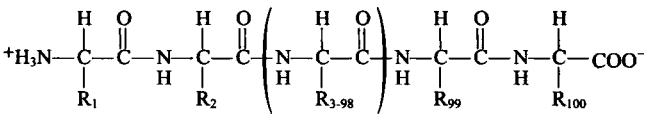
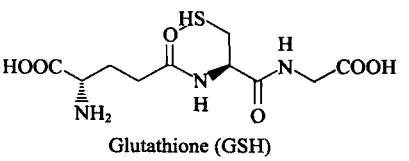


Figure 1-13 Basic structural features of a polypeptide containing 100 amino acid residues

1.1.4.2 Peptides may have biological activities

There are many functional peptides in human body. Naturally occurring peptides range in length from two to many thousands of amino acid residues. Even the smallest peptides can play important physiological role. For example, a number of vertebrate hormones are small peptides. These include oxytocin (nine amino acid residues), which is secreted by the posterior pituitary and stimulates uterine contractions; bradykinin (nine residues), which inhibits inflammation of tissues; and thyrotropin-releasing factor (three residues), which is formed in the hypothalamus and stimulates the release of another hormone. **Glutathione (GSH)** is one of the most important biologically active peptides. Glutathione is a tripeptide containing an unusual peptide linkage between the amine group of cysteine and the carboxyl group of the glutamate side chain (Figure 1-14). Glutathione is also an antioxidant protecting of cells against free radicals or peroxide.



Glutathione (GSH)

Figure 1-14 Glutathione is a tripeptide