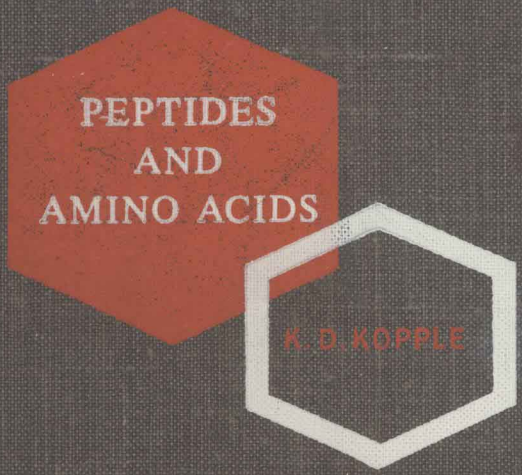
PEPTIDES AND AMINO ACIDS



K. D. KOPPLE

PEPTIDES AND AMINO ACIDS

KENNETH D. KOPPLE ILLINOIS INSTITUTE OF TECHNOLOGY

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PEPTIDES AND AMINO ACIDS

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PEPTIDES AND AMINO ACIDS

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▪ EDITOR'S FOREWORD

UNDERGRADUATE EDUCATION in chemistry is in the midst of a major revolution. Sophisticated material, including extensive treatments of current research problems, is increasingly being introduced into college chemistry courses. In organic chemistry, this trend is apparent in the new "elementary" textbooks. However, it has become clear that a single text, no matter how sophisticated, is not the best medium for presenting glimpses of advanced material in addition to the necessary basic chemistry. A spirit of critical evaluation of the evidence is essential in an advanced presentation, while "basic" material must apparently be presented in a relatively dogmatic fashion.

Accordingly, we have instituted a series of short monographs intended as supplements to a first-year organic text; they may, of course, be used either concurrently or subsequently. It is our hope that teachers of beginning organic chemistry courses will supplement the usual text with one or more of these intermediate level monographs and that they may find use in secondary courses as well. In general, the books are designed to be read independently by the interested student and to lead him into the current research literature. It is hoped that they will serve their intended educational purpose and will help the student to recognize organic chemistry as the vital and exciting field it is.

We welcome any comments or suggestions about the series.

RONALD BRESLOW

New York, New York
December, 1964

PREFACE

LIKE OTHER SPECIALIZED TOPICS in organic chemistry, peptide chemistry is treated only briefly in undergraduate courses and texts. To satisfy any deeper interest, students must jump from general organic texts to specialized review articles and the research literature. This brief book is intended to bridge that gap. It will thereby, I hope, reduce the activation barrier for entry into this increasingly exciting field.

While retaining the outlook of an organic chemist, I have tried to provide a survey that includes some of the biological and physical chemical aspects of the study of peptides, so that the over-all significance of the area is apparent. This attempt, coupled with limitations on space, has precluded coverage of individual topics in the depth that would warrant citation of the original literature; the references given at the end of each chapter are to recent detailed reviews, although individual papers are cited in a few cases.

I would like to express my appreciation to Professor Murray Goodman and to Mr. Edward A. Dratz, whose comments on the manuscript have led to clearer presentation. The responsibility for the choice of material is, of course, mine.

K. D. KOPPLE

Chicago, Illinois
July 1965

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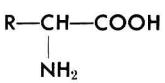
1

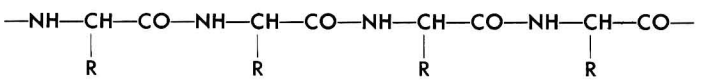
INTRODUCTION

THREE KINDS of organic polymers are elaborated by living organisms. These substances, often called *biopolymers*, perform vital functions. *Nucleic acids* store and copy information necessary for replication of an organism. *Proteins* function as structural materials, act in the biological conversion of chemical to mechanical energy, and catalyze and direct the chemical reactions necessary for growth and maintenance of the living state. *Polysaccharides* serve as structural materials and reservoirs of fuel.

The term protein (derived from the Greek, *proteios*, meaning prime) was appropriately applied, in 1838, to a group of complex nitrogen-containing substances found in plant and animal tissue. At the beginning of the present century, it was recognized that proteins are composed of α-amino carboxylic acids:



combined, by biological processes resulting in the elimination of water, to form polyamides:



The term *peptide bond* was applied to the amide link between amino acid residues, and molecules composed of α-amino acids so linked are called *peptides*. (The word protein refers to naturally occurring peptides containing more than about 50 amino acid residues in a single molecule.)

Although the molecular backbone of a protein is composed of the same repeating unit, —N—C—CO—, the side chains attached to the saturated carbon atom of each unit vary. Nature has chosen these side chains from a limited number, about 20. Since proteins are generally composed of hundreds of amino acid residues, these 20 building blocks may be arrayed in an infinite number of combinations, each defining a molecule with a particular set of chemical and physical properties. Thus, proteins can be generated with specific tailoring to the biological functions they perform.

In recent years, chemical and biological studies of proteins and related substances have begun to show some details of the dependence of biological function on chemical structure. This has come about through development of chemical and physical methods for determining the structure and chemical reactivity of proteins, and through continued improvement of the synthetic techniques by which protein-like model substances can be rationally prepared. It is the purpose of the following pages to provide an introduction to this chemistry.

In the succeeding chapters, we shall discuss, first, the organic chemistry of the protein building blocks, the amino acids (Chapter 2), then the chemical methods by which these substances can be linked to form peptides (Chapter 3). Many physiologically active peptides, such as hormones and antibiotics, are synthetically accessible. Synthesis serves as a check on proposed structures and as a means for producing potentially useful structural variations. Synthetic peptides are also useful for study of some of the properties of proteins.

In Chapter 4 we discuss the manner in which amino acid sequence and other covalent features of proteins are uncovered. Determination of peptide sequence is now a common, if arduous, procedure, and the order of amino acids in any protein can be determined if enough of it can be isolated in a state of high purity. However, knowledge of the covalent structure alone by no means explains the physical and chemical properties of a peptide. A variety of noncovalent interactions among the peptide backbone, the various side chains, and the environment contribute to the establishment of a

favored three-dimensional structure. This is discussed in Chapter 5.

In Chapter 6 are cited some examples of areas in which there is a growing knowledge of the relationship between chemical structure of peptides and their biological function.

Synthesis of large peptides and determination of protein structure would not be possible without effective methods for separating amino acid and peptide mixtures into their components. These techniques are presented in the Appendix.

References

The two works listed contain excellent and detailed surveys of most of the topics outlined in succeeding pages.

J. P. Greenstein and M. Winitz, *Chemistry of the Amino Acids,* (3 vols), Wiley, New York, 1961.

H. Neurath (ed.), *The Proteins,* 2nd ed., Vols. I and II, Academic Press, New York, 1963, 1964.

2

α–AMINO ACIDS

2–1 Occurrence

IN PRINCIPLE, the term *amino acid* could be used to refer to any compound containing an amino group and an acidic function. In practice, the words are most often used with reference to the amino acids that have received most intensive study: α-amino carboxylic acids isolated from natural sources. Well over 100 of these have been isolated and identified, but only 20 are obtained upon hydrolysis of typical proteins.

The 20 α-amino acids that are the building blocks of proteins are listed in the first part of Table 2–1. Most of them contain primary amino groups. All but glycine contain at least one asymmetrically substituted atom, the α-carbon, and occur naturally in optically active form. Residues of most occur in all proteins, although hydroxylysine and hydroxyproline appear only in collagen, which is the major protein of skin, bone, tendon, and other connective tissue. Aspartic and glutamic acids, common constituents of all proteins, often appear as the amides asparagine and glutamine. Cystine and cysteine, because of their ready interconvertibility by oxidation-reduction, are considered derivatives of the same substance; cystine is the form usually isolated. Table 2–2 indicates the amino acid composition of several representative proteins from animal sources.

TABLE 2–1 ■

Naturally Occurring α-Amino Acids

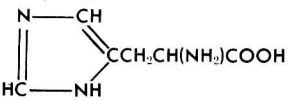
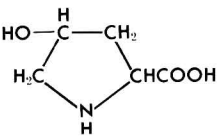
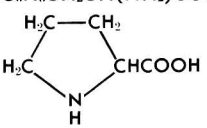
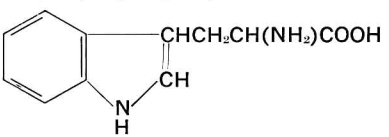
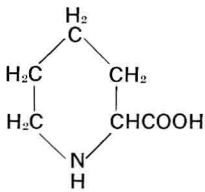
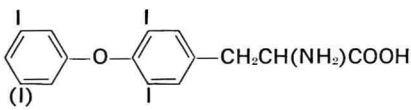
Name	Structural formula	Abbreviation
	Protein Building Blocks	
Alanine	$CH_3CH(NH_2)COOH$	Ala
Arginine	$HN{=}C(NH_2)NH(CH_2)_3CH(NH_2)COOH$	Arg
Aspartic acid	$HO{-}COCH_2CH(NH_2)COOH$	Asp
(Asparagine)	$(H_2N{-})$	$Asp(NH_2)$
Cysteine	$HSCH_2CH(NH_2)COOH$	Cys
(Cystine)	$(SCH_2CH(NH_2)COOH)_2$	Cys | Cys
Glutamic acid	$HO{-}COCH_2CH_2CH(NH_2)COOH$	Glu
(Glutamine)	$(H_2N{-})$	$Glu(NH_2)$
Glycine	$CH_2(NH_2)COOH$	Gly
Histidine		His
Hydroxylysine	$H_2NCH_2CH(OH)CH_2CH_2CH(NH_2)COOH$	Hylys
Hydroxyproline		Hypro
Isoleucine	$C_2H_5CH(CH_3)CH(NH_2)COOH$	Ile
Leucine	$(CH_3)_2CHCH_2CH(NH_2)COOH$	Leu
Lysine	$H_2N(CH_2)_4CH(NH_2)COOH$	Lys
Methionine	$CH_3SCH_2CH_2CH(NH_2)COOH$	Met
Phenylalanine	$C_6H_5CH_2CH(NH_2)COOH$	Phe
Proline		Pro
Serine	$HOCH_2CH(NH_2)COOH$	Ser
Threonine	$CH_3CH(OH)CH(NH_2)COOH$	Thr
Tryptophan		Try
Tyrosine	$p\text{-}HOC_6H_5CH_2CH(NH_2)COOH$	Tyr
Valine	$(CH_3)_2CHCH(NH_2)COOH$	Val

TABLE 2–1 (*Continued*)

Name	Structural formula	Abbreviation
	Important Nonprotein Amino Acids	
α-Aminoadipic acid	$HOCO(CH_2)_3CH(NH_2)COOH$	Higher plants, antibiotics
α,γ-Diaminobutyric acid	$H_2NCH_2CH_2CH(NH_2)COOH$	Antibiotics
Ornithine	$H_2N(CH_2)_3CH(NH_2)COOH$	Widespread
Pipecolic acid		Higher plants
Sarcosine	CH_3NHCH_2COOH	Widespread
Triiodothyronine (Thyroxine)		Thyroid hormones

Of the proteins listed, keratin and myosin are fibrous proteins, keratin the protein of hair and wool, and myosin the major protein of muscle. Serum albumin has a composition representative of soluble proteins.

The natural α-amino acids are colorless, stable, high-melting solids. Most are soluble in water, at least to some extent, and are not soluble in common organic solvents. The amino acids of protein are obtained from protein hydrolyzates; they do not occur in high concentration uncombined. Because cystine and tyrosine are only sparingly soluble in water, they are readily isolated, but separation of other amino acids in pure form requires special techniques. All the amino acids listed in Table 2–1 have been synthesized, most by several different routes.

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