Michel Fleck · Aram M. Petrosyan

Salts of Amino Acids

Crystallization, Structure and Properties

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Michel Fleck
Institute of Mineralogy
and Crystallography
University of Vienna
Vienna, Austria

Aram M. Petrosyan
National Academy of Sciences
of Armenia
Yerevan, Armenia

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Preface

On asking somebody what they are made of, the reply frequently heard is 'mostly water'. Although this statement is definitely correct, it is only the boring background material, so to say, on a par with the answer 'air' when asked what you have in your home. The really interesting stuff is there in smaller percentages, as for example carbohydrates, lipids, and proteins (in the case of our body). The first two of these three groups certainly fulfill important functions, but mostly structural ones. The actual machinery of every living cell consists almost completely of proteins. Therefore, it is no surprise to learn that the only building instructions written in our genetic make-up, i.e. the DNA, are those for proteins. But where are the instructions for the assembly of carbohydrates, lipids, and other material of our body, when there is DNA – and DNA only – to contain information? The answer is obvious: DNA codes for proteins, and these do everything else, such as all disassembling, rearranging, combining, constructing and every other conceivable chemical procedure to manufacture or alter lipids, carbohydrates, steroids, etc.

This brief illustration is supposed not only to show the importance of proteins, but also the vast diversity of functions of these molecules. And as form follows function, the variety of forms is similarly vast. This results from the way proteins are built: As encoded in the DNA, a chain of amino acids is constructed, and as a consequence of the chemical properties of these buildings units, the originally linear protein folds into a highly complex, three dimensional object. Thus, the multitude of protein structures arises simply from the structural variety of amino acids.

Consequently, it is no wonder that proteins and amino acids have been intensively studied by scientists ever since the necessary methods have become available. Besides this avalanche of material produced on biological, biochemical and chemical aspects of proteins and amino acids, there has been a much smaller community of researchers developing and studying compounds of amino acids. These materials, which exist in the solid state at ambient conditions, crystallize in a wide variety of forms and symmetries, display an equally wide range of interesting chemical and physical properties and have therefore become a topic very actively

researched recently. As there is no comprehensive work on the entirety of these species so far, we feel that this book should prove an overview and insight for all students, teachers and scientists involved in the study of amino acid compounds.

Vienna, Austria — Michel Fleck
Yerevan, Armenia — Aram M. Petrosyan

Contents

1 Introduction 1
1.1 What Are Amino Acids? 1
1.2 Naming Amino Acids 6
1.3 Configuration: Chirality and Optical Activity 9
1.4 Conformation: Molecular Shape and Stability 13
1.5 Cations, Anion, Zwitterions 14
1.6 Concluding Remarks 17
References 18

2 Amino Acid Structures 21
2.1 Introducing Remarks 22
2.2 Solubility and Crystal Growth 22
2.3 Amino Acid Structures 25
2.3.1 Glycine 27
2.3.2 Alanine 32
2.3.3 Valine 38
2.3.4 Leucine 39
2.3.5 Isoleucine 41
2.3.6 Proline 42
2.3.7 Methionine 43
2.3.8 Phenylalanine 44
2.3.9 Tryptophan 45
2.3.10 Serine 46
2.3.11 Threonine 49
2.3.12 Cysteine 50
2.3.13 Asparagine 52
2.3.14 Glutamine 55
2.3.15 Aspartic Acid 56
2.3.16 Glutamic Acid 57
2.3.17 Tyrosine 58
2.3.18 Histidine 59

2.3.19 Lysine . . . 60
2.3.20 Arginine . . . 61
2.3.21 Nonstandard Amino Acids . . . 64
2.4 Summary . . . 70
References . . . 72

3 Compounds of Amino Acids as Anions . . . 83
3.1 Introducing Remarks . . . 84
3.2 Glycine . . . 90
3.3 Alanine . . . 93
3.4 Valine, Leucine, and Isoleucine . . . 99
3.5 Proline, Methionine, Phenylalanine, and Tryptophan . . . 102
3.6 Serine and Threonine . . . 107
3.7 Cysteine . . . 109
3.8 Asparagine, Glutamine, Aspartic Acid, and Glutamic Acid . . . 112
3.9 Tyrosine, Histidine, Lysine, and Arginine . . . 121
3.10 Nonstandard Amino Acids . . . 125
3.11 Concluding Remarks . . . 127
References . . . 127

4 Compounds of Amino Acids and Neutral Salts . . . 139
4.1 Introducing Remarks . . . 139
4.2 Glycine . . . 140
4.2.1 Glycine Metal Halogenides . . . 140
4.2.2 Glycine Metal Perchlorates . . . 147
4.2.3 Other Glycine Salts . . . 149
4.3 Alanine . . . 152
4.4 Valine, Leucine, and Isoleucine . . . 156
4.5 Proline, Methionine, Phenylalanine, and Tryptophan . . . 160
4.6 Serine, Threonine, and Cysteine . . . 167
4.7 Asparagine, Glutamine, Aspartic Acid, and Glutamic Acid . . . 169
4.8 Tyrosine, Histidine, Lysine, and Arginine . . . 173
4.9 β-Alanine . . . 175
4.10 Betaine . . . 177
4.11 Other Nonstandard Amino Acids . . . 185
4.12 Concluding Remarks . . . 190
References . . . 193

5 Reactions of Amino Acids with Acids . . . 207
5.1 Simple Salts . . . 207
5.1.1 Salts of Glycine . . . 207
5.1.2 Salts of Sarcosine . . . 217
5.1.3 Salts of Dimethylglycine (DMG) . . . 223
5.1.4 Salts of Betaine . . . 223
5.1.5 Salts of α-Alanine . . . 231
5.1.6 Salts of β-Alanine . . . 240

5.1.7 Salts of Phenylalanine 245
5.1.8 Salts of Serine 249
5.1.9 Salts of Threonine 257
5.1.10 Salts of Tyrosine 261
5.1.11 Salts of Cysteine 263
5.1.12 Salts of Methionine 267
5.1.13 Salts of Valine 272
5.1.14 Salts of Leucine 281
5.1.15 Salts of Isoleucine 286
5.1.16 Salts of Proline 288
5.1.17 Salts of Tryptophan 293
5.1.18 Salts of Asparagine and Aspartic Acid 297
5.1.19 Salts of Glutamine and Glutamic Acid 302
5.1.20 Salts of Ornithine 305
5.1.21 Salts of Lysine 310
5.1.22 Salts of Arginine 337
5.1.23 Salts of Histidine 379
5.1.24 Adducts of Amino Acids with Inorganic and Organic Acids 425
5.2 Salts of Amino Acids with Dimeric Cations 432
5.2.1 Salts with (A. . .A^+) Type Dimeric Cations 432
5.2.2 Salts with (A^+. . .A^+) Type Dimeric Cations 477
5.2.3 Salts of Amino Acids with (A^+. . .A^{2+}) Type Dimeric Cations 480
5.3 Mixed Salts of Amino Acids with Different Anions and Cations 481
5.3.1 Introductory Notes 481
5.3.2 Mixed Salts of Amino Acids with Different Anions 485
5.3.3 Concluding Remarks 509
References 520

Index 573

Chapter 1
Introduction

Abstract Within this chapter, the fundamental properties of amino acids are presented. The basic chemical features of amino acids are the ubiquitous amino and acid groups; the residue of the molecule is usually referred to as side chain. Of an infinite number of conceivable amino acids, twenty (plus a few more or less frequent) members are found in proteins of living beings and thus play a crucial role in the chemistry of life. From a chemical point of view, the chirality of most amino acids is an important feature, which is discussed in regard with the nomenclature systems conventionally employed. Chirality is related with symmetry, both of the molecule and the crystal structure of amino acids (or their salts). Moreover, the chemical flexibility of amino acids, both in terms of symmetry and in terms of their amphoteric nature, is reviewed, thus forming the frame of reference for the following chapters which deal with the actual amino acid salts.

Keywords Amino acids • Standard amino acids • Non-standard amino acids • Nomenclature • Configuration • Chirality • Optical activity • Enantiomer • Racemate • Conformation • Torsion angle • Cations • Anions • Zwitterions

1.1 What Are Amino Acids?

Chemically speaking, amino acids compose just one among many families of organic compounds. Any organic molecule possessing at least one amino and one acid group belongs to this family (Fig. 1.1). Generally, this means any hydrocarbon chain, possibly branched, with or without other functional groups, aromatic rings, or any other imaginable organic structure. Consequently, it is clear the number of amino acids conceivable is infinite.

Nevertheless, the number "20" is found in many lists of amino acids. This of course results from the fact that amino acids are probably the most important molecules for biological functions, and every living cell on the planet has been believed to use the same set of these 20 standard amino acids (Fig. 1.2) to

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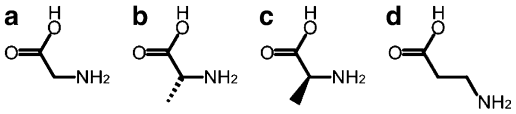

Fig. 1.1 *Simple amino acids*. Glycine, the simplest amino acid, has the minimal requirements of amino acids: one acid and one amino group (**a**). With an additional methyl group, the resulting amino acid is alanine, which exists in three forms: D-α-alanine (**b**) and L-α-alanine (**c**) are enantiomers, whereas in third isomer, β-alanine (**d**) has the amino group bonded to the C3 atom

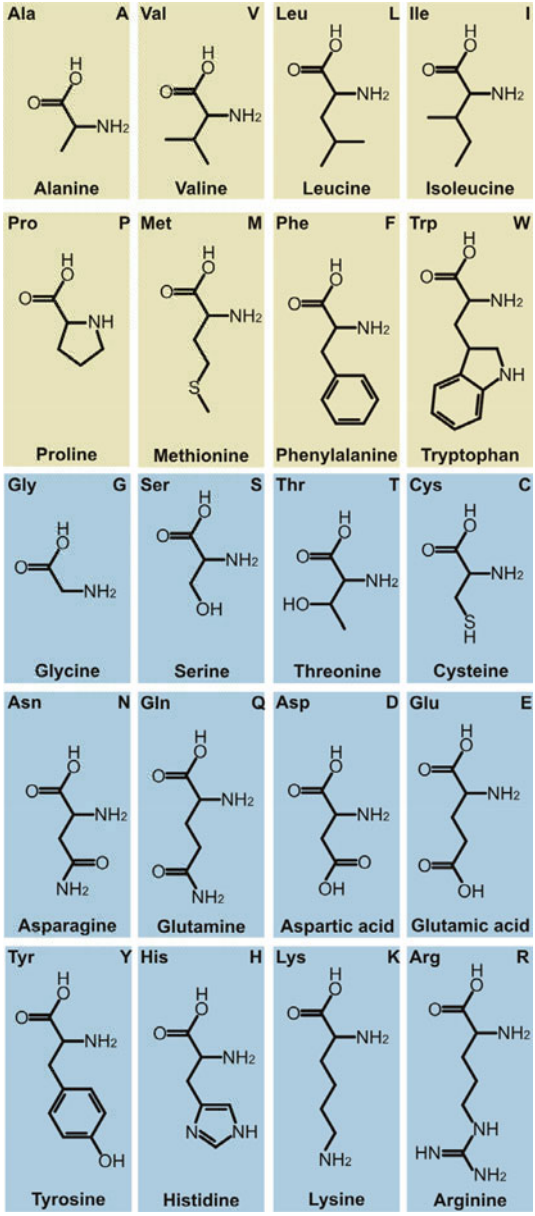

Fig. 1.2 *The twenty standard amino acids. Yellow* represents unpolar, *blue* polar amino acids, although there is a smooth transition (as, e.g., from Gly to Ala to Val, etc.). Note that apart from the ubiquitous amino and acid groups, there are two (Asp and Glu) with a further acid group (so-called acidic amino acids) as well as three (His, Lys, Arg) with a further amino group (so-called basic amino acids). All amino acids are shown in their neutral state, i.e., with no acidic deprotonation or basic protonation. This does not represent the actual state of any amino acid (neither in solution nor solid state), as protonation or deprotonation (or both) occurs – depending on the pH (see Sect. 1.4)

manufacture their proteins. There has been much active discussion on a possible extension of this list since the 1980s, when it has been found that there is another amino acid used in protein production, namely, selenocysteine, which retains a special status (see box below). Posttranslational alterations are frequent, however, so more than 120 amino acids are found in proteins and more than three times as many have been known to occur in other, nonprotein functions in living cells (Wagner and Musso 1983). Presently, it is assumed that there are more than 500 amino acids in nature (Gutiérrez-Preciado et al. 2010).

Although the standard amino acids are listed in most textbooks on organic chemistry and molecular biology, one rarely finds an explanation why exactly these 20 out of an infinite number of amino acids constitute the biological machinery of every cell. In 1981, Weber and Miller presented a detailed analysis of possible reasons, including aspects such as stability, steric reasons, frequency in the primordial soup, etc. Most importantly, the ability to form a strong but flexible chain, with the possibility of reversible lateral bonding, is a main prerequisite for the construction of proteins. Weber and Miller reckon that if life were to develop on another planet, about three fourths of the standard amino acids would be the same as on earth.

Selenocysteine: The 21st Amino Acid?

In the 1980s, it was discovered that the geneticist's model bacterium *Escherichia coli* uses selenocysteine in its protein synthesis. This amino acid is coded by one of the STOP codons, namely, UGA. Additional research found that selenocysteine is incorporated in proteins in the same way as all the other standard amino acids and that this amino acid does not appear in *E. coli* only, but in many animals and even humans (Günzler et al. 1984). Culminating with a paper in Nature (Söil 1988), many scientists happily heralded selenocysteine as the "21st amino acid."

This excitement has deflated since, as it has been found that selenocysteine has several differences in regard with the standard amino acids (apart from the fact that it contains selenium). First, it does not possess its own code in the DNA, but is rather coded by a STOP codon, followed by a so-called selenocysteine insertion sequence (SECIS). Second, it is not ubiquitous but synthesized on demand, as it is highly reactive and thus not easily stored in cells. In fact, selenocysteine attaches to its tRNA as a serine molecule, which then is processed into selenocysteine before being used in protein assembly.

The main reason why this amino acid is not regarded as part of the standard set is the fact that it is not universal in nature, as are the other 20 amino acids. Although ubiquitous in animals (including humans), it does not occur in every domain of life. Only about one sixth of the bacteria and archaea sampled genetically produce selenocysteine, and in higher plants and fungi, this amino acid has not been found at all. Therefore, this 21st amino acid is not considered as part of the standard set (Longtin 2004).

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Among the many other amino acids that have been found in nature, another one has been considered as an addition to the standard set (Krzycki 2005): pyrrolysine, an amino acid that methanogenic archaea utilize in the methane metabolism and encode via the codon UAG (usually another STOP codon). As pyrrolysine is even less ubiquitous than selenocysteine, this amino acid is also not generally accepted as an addition to the standard 20.

Whatever the reason for their success, there is one feature all standard amino acids have in common: They all are α-amino acids (the nomenclature of amino acid is described in Sect. 1.2). This appears to have been a major advantage in the chemical evolution of proteins, as it allows the formation of the well-known peptide chain, with the peptide bonds along the backbone and the side chains facing outward, thus facilitating the establishment of different types of intrachain bonds, which in turn make the diversity and flexibility of protein structures possible (Weber and Miller 1981).

Nevertheless, other amino acids exist in nature (presumably they were even present in the primordial soup) and play important roles in our biochemistry. Many of these species are not α-amino acids. Maybe the best known example is γ-aminobutyric acid (GABA, Fig. 1.3), which is the main inhibitory neurotransmitter in the central nervous system of all mammals, including us humans. Another prominent non-α-amino acid is β-alanine (Fig. 1.1d), which is a constituent of vitamin B5 (pantothenic acid) as well as the antioxidants carnosine and anserine that are ubiquitous in mammal muscle tissue (Zapp and Wilson 1938). Some more examples are presented in Sect. 1.2.

Amino Acids and Proteins

As said above, amino acids are the monomers that constitute proteins – the macromolecules that make up the majority of biological machinery in every living cell, from bacteria to human beings. This immense diversity in functionality (proteins do not only act as enzymes, there are also structural proteins, motile proteins, protective proteins, transport proteins, membrane proteins, etc.; see Gutteridge and Thornton 2005) has two main reasons: Firstly, amino acids themselves differ structurally (and thus chemically) from one another via the differences of their side chains. Secondly, amino acids bond to each other by a condensation reaction, forming an amide bond, which is more specifically called peptide bond. Units of two amino acids are thus referred to as dipeptides; molecules made from three amino acids are called tripeptides, etc. Such short units are generally referred to as oligopeptides, larger chains as polypeptides, although there is no strict boundary. Larger units still are proteins, although again there is no sharp boundary. In fact, it is not the length of the chain that defines the protein, but

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the structure that arises from the folding of the chain (consequently, the term polypeptide is often used to indicate a linear chain of amino acids, whereas a protein is a polypeptide that is folded).

This folding results in the actual protein structure and follows from the sequence of amino acids as defined in the genes of living beings. In fact, the genetic code defines so-called codons of three "letters" of the DNA, i.e., three of the bases forming the genetic information within the double helix. A complicated biological process, protein synthesis, is responsible for the formation of the peptide chain in the correct sequence: DNA is copied onto messenger RNA (or mRNA for short), which is moved to the ribosomes (in higher organisms, some additional editing of the RNA occurs before). In the ribosomes, mRNA is brought in contact with amino acids mounted on short RNA strands, so-called transfer RNA (or tRNA). Sterically constrained within the ribosome, two amino acids are positioned close enough to each other so that the condensation reaction occurs. As the mRNA moves through the ribosome, one amino acid after another is added, resulting in a peptide chain. As stated above, the chain has to fold correctly so that it becomes an actual protein. For small proteins, this folding happens by itself; larger chains need help from so-called chaperones, proteins themselves, which assist in correct folding.

The structure of a protein is hierarchical: The peptide chain (i.e., the primary structure) folds locally to helices or sheets simply by hydrogen bonds (α-helices or β-sheets, the secondary structure). These parts again fold up to create the actual protein structure (or tertiary structure), stabilized by nonlocal interactions. These are commonly hydrophobic interactions, hydrogen bonds, ionic bonds, covalent bonds (disulfide bridges between two cysteine side chains), or additional modifications of the amino acids that occur after the synthesis of the chains. Frequently, a functional biological unit does not comprise one lone protein, but an aggregation of more than one protein, interlocked in the so-called quaternary structure. For instance, collagen, the main structural protein of connective tissue in animals, is an arrangement of three protein strands or immunoglobulins (antibodies) consisting of four protein parts.

As the folding of proteins is governed by many parameters, the prediction of the actual structure from the primary sequence is not trivial. As protein molecules are enormous, the structure with the minimal energy cannot be simply calculated, only estimated. As Bohannon (2009) states, there are "more ways to fold a protein than there are atoms in the universe." Funnily, a group of innovative scientists devised an online computer game called *FoldIt*, where players all over the world can engage in protein structure prediction, as they compete and collaborate to optimize energy of a given sequence (Cooper et al. 2010). As it turned out, the community of online players was able to solve problems much more efficiently than expert scientist or computer algorithms could.

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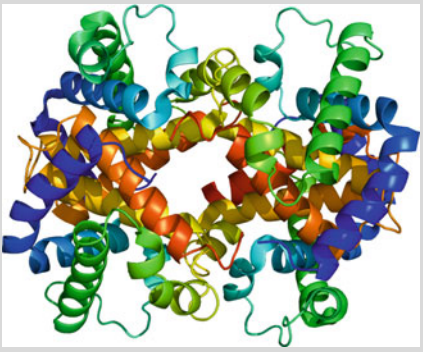
Apart from prediction or molecular modeling, experimental determination of protein structures is a challenging task for crystallographers. Not only are proteins huge molecules, the crystallization of suitable samples is not as straightforward as for smaller molecules (especially membrane proteins turned out to be hard to crystallize). Still, research in this area has blossomed over the last years and is still growing (for an overview of Protein Crystallography, see Drenth 2007, and references therein).



1.2 Naming Amino Acids

Since there is a large – theoretically an infinite – number of amino acids, several rules have been devised to deal with amino acid nomenclature (besides the standard IUPAC regulations). Apart from the fact that the most common amino acids have trivial names[1] (see Fig. 1.2), there are principles for the formation of semisystematic names as well as atom labeling systems for designating locants on amino acids (IUPAC 1979, 1983).

The employment of semisystematic names applies to substituted standard amino acids and works on the same general principles used for all organic molecules, i.e., the name of the substituent group is attached to the trivial name of the amino acid, whereas the position of the substituent is designated as specified below (e.g., 5-nitrohistidine).

Nevertheless, there are several trivial names in use for other common amino acids, mostly derivatives of standard amino acids, but also some other simple

[1] The etymological background of the trivial names is explained in the respective parts of Chap. 2.

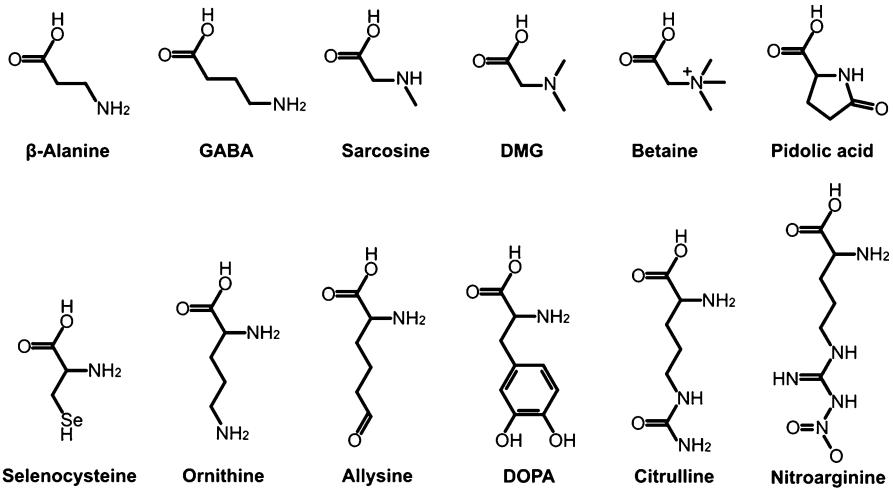


Fig. 1.3 *Some common amino acids beyond the standard twenty*. Only the first two examples are β- and γ-amino acids, namely, β-alanine and γ-aminobutyric acid (GABA). The rest are α-amino acids, as the standard twenty. Together with N-methylglycine (sarcosine), N-dimethylglycine, and N-trimethylglycine (betaine), β-alanine and GABA are examples of non-chiral amino acids. Note also that the structure for betaine is actually the cationic form, betainium (this issue is explained in Sect. 1.4). All other examples shown here are optically active α-amino acids. Pidolic acid (pyroglutamic acid or 5-oxoproline), a derivate of proline, is found in some proteins, as, e.g., bacteriorhodopsin. The aforementioned selenocysteine is the Se analog of cysteine, ornithine appears in the metabolism of urea, as a product of arginine. Allysine is a lysine derivate that plays a vital role as part of structural proteins (e.g., collagen or elastin) and therefore of our connective tissue. DOPA (3,4-dihydroxyphenylalanine) is produced from tyrosine, and acts as precursor for many important hormones and neurotransmitters, such as dopamine, adrenaline, or noradrenalin. Citrulline, as ornithine, is another part of the urea cycle and was first isolated in water melons (Citrullus lanatus, hence the name). Nitroarginine is another derivate of arginine (as is citrulline). In biological systems, all the optically active amino acids referred to here are L-forms (see Sect. 1.3)

examples. Some of these names, along with the semisystematic ones and the formulae, are shown in Fig. 1.3. Moreover, there are several instances which can be regarded as combinations of two standard amino acids. One prominent example is cystine, which is a disulfide of two cysteine moieties (as found in the keratin of our hair). Likewise, lanthionine is a thioester of two alanine residues (and also is found in hair, or wool, where it was first discovered).

As far as atom labeling is concerned, two alternative systems are employed: The atoms are either numbered according to the normal chemical system for designating locants, i.e., starting with the carboxylate carbon atom as C1, or by the utilization of Greek letters, starting with the C2 atom as α (Fig. 1.4). The latter system is of importance not only for defining possible additional substituent positions but to characterize the position of the eponymous amino group: As said above, the standard twenty amino acids have the amino group adjacent to the carboxylic

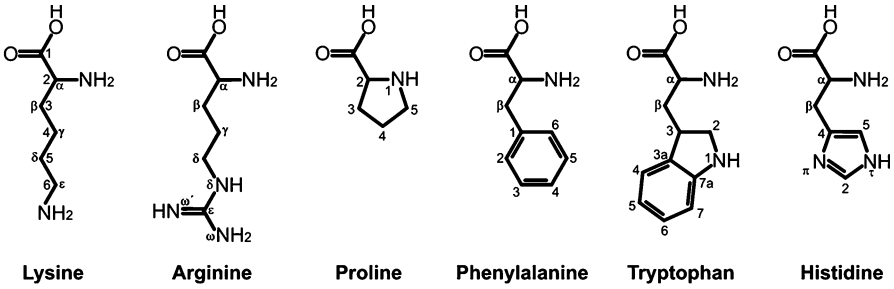


Fig. 1.4 *Atom labeling in amino acids*, shown exemplary for lysine (as a straight-chain amino acid), arginine (heteroatoms are labeled as the preceding carbon atom, equivalent side chains are denoted with the same letter), proline (numbered as in pyrrolidine), phenylalanine and tryptophan (numbered as aromatic ring systems), and histidine (the N-atoms in the imidazole ring are denoted by "pro" (near) and "tele" (far)). Detailed regulations on amino acid labeling are given by the IUPAC (1983)

acid group, i.e., in α position. Therefore, they are all referred to as α-amino acids. Likewise, there are β-amino acids, γ-amino acids, etc.

This system used for designating positions is simple for aliphatic, straight-chain amino acids. When heteroatoms, branching, aliphatic or aromatic cycles, etc. are present, the rules are somewhat more complicated. Some examples for designating locants are shown in Fig. 1.4. For the complete rules, the reader is referred to the details given by the IUPAC (1983).[2]

For the standard amino acids, two specific abbreviations are commonly used, namely, a three- and a one-letter symbol for each amino acid (Fig. 1.2). For general purposes, only the three-letter-symbol is used, the employment of the one-letter-symbol should be restricted to denote long amino acid sequences, i.e., when discussing primary structures of proteins. In this book, we will use the three-letter-symbol only.

[2] The numbering of atoms within an amino acid molecule should be done following the rules set by the IUPAC (1983). In acyclic amino acids, the carbon atoms are numbered as follows:

The C atom of the carboxyl group next to the C atom which carries the amino group is C-1, the rest follows consequently. As an alternative, Greek letters can be used, where the C-2 atom is designated α. Although the IUPAC recommend the numbers, not the Greek letters, the terms "α-amino acids" or "α-carbon atom" are frequently used in the literature.

Heteroatoms are given the same number as the carbon atom to which they are attached. The nitrogen atom of the "α-amino group" would thus be N-2. When identical side chains occur, such as in valine or leucine, they are given the same number, one with an apostrophe. In said examples, these methyl atoms are thus labeled C-4 and C-4' (valine) and C-5 and C-5' (leucine). In arginine, where the terminal amino groups are formally different (see scheme in Fig. 1.4) but in fact identical due to resonance, this system is also employed.

Amino acids with rings are numbered along the rules of the systematic nomenclature of rings; for rings with heteroatoms, the numbering scheme of the mother compound is used (see scheme for Pro, Phe, Trp, His in Fig. 1.4).

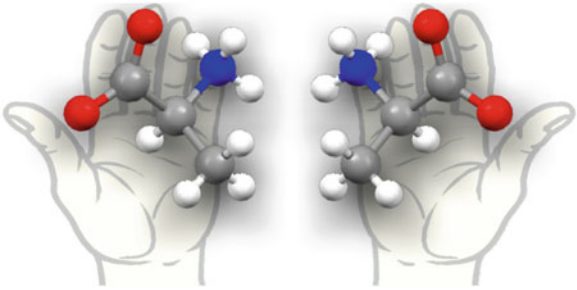


Fig. 1.5 *Chirality in amino acids*. Most amino acids are chiral, i.e., they exist in "left-handed" L- and "right-handed" D-form. These two molecules of opposing chirality are enantiomers; a mixture of both is called a racemate

1.3 Configuration: Chirality and Optical Activity

There is one puzzling fact in the question of the standard amino acids that scientist have pondered for decades: The issue of chirality. Apart from glycine, all of the standard twenty are chiral, i.e., they possess (at least) one carbon atom with four different substituents. Thus they exist in two enantiomers, commonly referred to as left- and right-handed (or L- and D-forms, respectively, Fig. 1.5; for nomenclature of chiral molecules see box below). This alone would not make a puzzle, but all biological systems employ L-amino acids, and L-amino acids nearly exclusively. So far, no reason for this has been found, as chemically both enantiomers are equivalent (only reactions with other chiral systems can distinguish between L- and D-form). Ideas have been proposed, such as simply the random development of L-forms as the first system capable of self-reproduction – a feature conserved by evolution. Another theory discusses the idea that circular polarized light from a quickly rotating star destroyed D-amino acids and thus promoted the other enantiomers (Flores et al. 1977; Bailey et al. 1998). One more possibility is the influence of meteorites, which is based on the fact that analysis of the Murchison meteorite (which contains amino acids) found an excess of L-enantiomers (Cronin and Pizzarello 1997).

D-/L- and *R*-/S-Nomenclature

Organic chemists need to distinguish between left- and right-handed forms when dealing with chiral molecules. However, the simple terms "left handed" and "right handed" cannot be easily employed when speaking of molecules. Today, two systems are in use, the D/L- and *R*/*S*-nomenclature.

The D/L-system was devised by Emil Fischer in 1891 and employed for carbohydrates (in fact monosaccharides, i.e., sugars) and amino acids. Although possible to use for other classes of molecules, these two families are the only ones for which the D-/L-nomenclature is used today.

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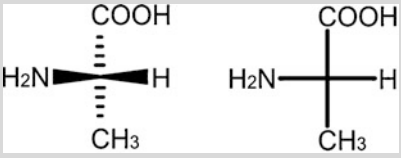
The reference species is glyceraldehyde, which was known to be optically active (see below). Arbitrarily, Fischer named the (+) dextrorotatory form D (for *dexter*) and the (−) levorotatory L (for *laevis*) – a connection which is not general, as we know today!

To decide if a chiral atom is to be defined as D or L, a molecule is viewed in the so-called Fischer projection. To do this, the following rules have to be used:

- The longest chain of carbon atoms is oriented vertically.
- The carbon atom with the highest oxidation state is located on top.
- All bonds are depicted as vertical or horizontal lines.
- Horizontal bonds project toward the viewer; vertical bonds project away from the viewer.
- If the group with the highest priority (i.e., highest oxidation state) is facing right, this form is termed D, and if facing left, it is termed L.

As an example, L-alanine is shown in Fischer projection below.



Although this system works well for sugar and amino acid molecules (as well as several other organic species), it cannot be employed generally. For instance, a molecule without a carbon chain cannot be oriented according to Fischer projection.

Thus, another nomenclature system was introduced by Cahn, Ingold, and Prelog: The so-called *R*/*S*-system (for *rectus* and *sinister*) is a method usable for any chiral molecule; it does not need a reference molecule as glyceraldehyde. To decide if a carbon atom is to be termed *R* or *S*, the following rules need to be regarded:

- The substituents of the chiral atoms are assigned priority according to their atomic number (when identical, the atomic numbers of the substituents' substituents are considered).
- The molecule is viewed so that the substituent with the lowest atomic number is facing away from the viewer.
- The remaining substituents are thus forming a circle; if their priority is ordered clockwise, the chiral atom is termed *R*, if counterclockwise, *S*.

Again, this projection is shown for L-alanine, which, in terms of this nomenclature, is called *S*-alanine.

(continued)

Although the *R*/*S*-nomenclature is the system which can be used for all chiral species, the D/L-system still persists for amino acids (and sugars) out of tradition and comparability with the amount of work published. We therefore stick to this nomenclature system within this book.

Whatever the reason, L-amino acids prevailed and proliferated – once established biochemical pathways of life on earth stuck to this enantiomer.[3] As said above, almost all amino acids in living beings exist in their L-form, as do – consequently – all proteins, and thus all cellular machinery. Nevertheless, over the last decades, some remarkable exceptions have been discovered: D-amino acids were found in the toxin of the platypus (Torres et al. 2002), D-aspartic acid was found to be a neurotransmitter, not only in mammals but also in mollusks (Snyder and Kim 2000; D'Aniello et al. 2011 and references therein). In bacteria, D-alanine and D-glutamine are found in the peptidoglycan cell wall, D-methionine, and D-leucine and other amino acids are used for regulatory signals (Cava et al. 2011). Perhaps most curious is the effect of the D-amino acids found in the toxin of the South American tree frog *Phyllomedusa bicolor*: A certain indigenous people in Peru, the Matsés, employ the frogs' poison for a specific ritual, where they burn their own chests in order to apply an extract gained from the frogs' skin. Severe diarrhea results, followed by a short blackout. When the hunters come to, they experience sharpened senses and the feeling of invulnerability, a hallucination based on the D-amino acid within the drug (Jilek et al. 2005). A brief but concise overview of the role of D-amino acids in animal peptides is given by Jilek and Kreil (2008). Recently, Kantrowitz et al. (2010) reported that D-serine might be utilized for medical treatment of schizophrenia, as this D-amino acid plays a crucial role in the human brain and was found to be deficient in brains of people suffering from schizophrenia.

This spatial difference between molecules of opposite chirality is called *configuration*, in contrast to the term conformation (see below). A very important feature of chiral materials is the fact that they are optically active, i.e., they alter the plane

[3] One might wonder why a small excess of one form resulted in chiral biochemistry, as the other enantiomer would still be present, only in lower quantities. In other words, how come the chemical machinery of proteins is chiral at all? What prevented the development of achiral proteins, i.e., proteins made of amino acids of both chiralities? It was found that homochirality is necessary for the origin of life. Peptides of both L- and D- amino acids cannot fold into bioactive configurations, as, for instance, the α-helix (Bada 1996). Proteins from D- or L-amino acids work equally well, but proteins from racemates do not form effective enzymes.

of polarization of light as it passes through a solution or crystal of this compound (see box below). It has to be noted that a molecule with only one chiral center is always chiral, whereas molecules with an even number of chiral atoms can be achiral. How is this possible? If a molecule has two chiral atoms at opposite ends, mirror symmetry between these ends can exist, therefore canceling out optical activity, as well as chirality of the molecule itself. The most famous example is mesotartaric acid, which in contrast to L- or D-tartaric acid is not optically active.

When synthesized from achiral precursors, the resulting amino acid can assume both configurations, as they are equal to all energetic and chemical purposes. Consequently, such a reaction produces a mixture of D- and L-enantiomers in a 1:1 ratio, a so-called *racemate*. Clearly, a solution containing such a racemic mixture is not optically active, as both enantiomers are present and the effect is canceled out. When growing crystals of such a mixture, it is possible to produce enantiopure crystals (e.g., distinct D- and L-crystals) by adding the respective chiral seeds (in fact, this represents one method of racemic resolution, i.e., the separation of a racemate into its optically active components). A small fraction of racemates (approximately between 5 and 10 %, Jacques et al. 1981) spontaneously crystallize as conglomerates of enantiopure crystals, whereas the majority forms racemic or DL-crystals.

Optical Activity

When plane-polarized light passes through a chiral medium – be it a solution or a crystal – the plane of polarization is altered by a certain value. The degree of alteration is specific for the material (in liquids the concentration must be known, of course) and is usually called the specific rotation α, given as the angle of rotation observed when passing through a solution of a sample with the concentration of 1 g/ml and a path length of 10 cm. If the polarization plane is rotated clockwise (when looking into the light), the compound is labeled (+) or dextrorotatory, if counterclockwise, it is labeled (−) or levorotatory. This is not to be confused with the chirality of the molecule itself, as there is no correlation between configuration and rotational behavior. For instance, out of the 19 optically active standard l-amino acids (glycine is not chiral), 9 are dextrorotatory.

Physically speaking, it is of course not true to say that the plane of polarization is rotated – just as it is not true to assume that photons bounce back off a surface when reflected or are slowed down when passing through matter. In fact, photons do not pass through a medium at all; rather, they are absorbed and reemitted all the time as they interact with matter. Usually, this reemission does not alter the plane of polarization, as the incoming photon's *E*-vector produces oscillations in the atom in the same direction. Consequently, the reemitted photon's *E*-vector direction is unchanged, only the propagation of light is delayed by this process. This delay is, of course, described by the refractive index of the material.

(continued)

In the case of optically active materials, we need to take into account the fact that any plane-polarized light can be described as an interference of left-handed and right-handed circularly polarized light. In optically active material, the delay of reemission is different for left-handed and right-handed circularly polarized light. Still, the interference of both does produce plane-polarized light, although the *E*-vector of the emerging photon has a different direction than the original one. In other words, optical activity is a kind of birefringence: The material has two different refractive indices – for both kinds of circularly polarized light.

The configuration of the molecules has an important impact on molecular and crystal symmetry: As said above, chirality rules out mirror or inversion symmetry (as these symmetry operations invert the chirality of a system and would therefore cancel it). Likewise, if a crystal comprises only one enantiomer of a given species, this crystal cannot possess inversion or mirror symmetry and is therefore necessarily non-centrosymmetric. Racemates or DL-crystals, on the other hand, can very well possess these inversion symmetries, as the respective L- and D-molecules in the crystal are frequently related to each other via mirror planes or inversion centers. This feature will be reflected strongly in the following chapters.

This might appear to be a trivial point. In fact, the symmetry of a crystal is of supreme importance as it correlates with the symmetry of all physical effects. More precisely, the symmetry elements of any physical property of a given crystal must include all symmetry elements of the point group of this crystal (Neumann's principle). This implies that certain effects are possible only in special point groups. Probably the most prominent examples are effects like piezoelectricity (see pp. 28, 32, 38, 72,144, 234, 238, 252, 304, 332, 343f, 351f, 387), which cannot occur in centrosymmetric crystals. Thus, the question of chirality and crystal symmetry is not only an issue of crystallography but also of possible physical applications. Therefore, as most amino acids are chiral, they are possible candidates for all effects that require non-centrosymmetric crystals.

1.4 Conformation: Molecular Shape and Stability

Regrettably, the term configuration is often confused with the term *conformation*, which basically describes the shape of the molecule. In other words, the various conformations of a molecule represent all conceivable shapes of this molecule that are possible due to free rotation around covalent single bonds. Thus, the conformation of a molecule may alter constantly (as it does in liquid or gas phase simply because of thermal motion) and can be "frozen" when incorporated in a crystal lattice. In contrast, the configuration cannot be changed by simple rotation around a bond. In order to change the configuration (from L- to D- or vice versa) a chemical

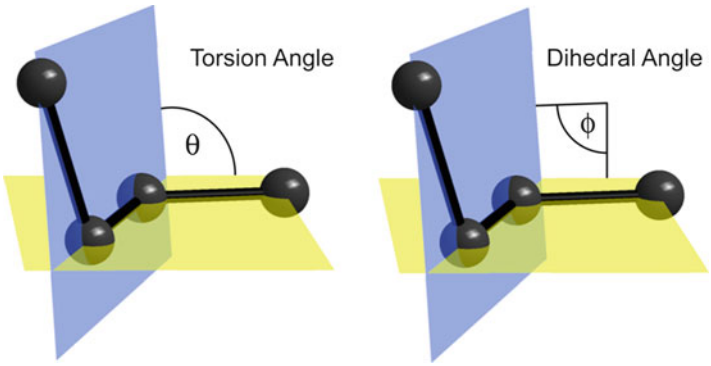


Fig. 1.6 *Torsion and dihedral angle*. When describing conformations of molecules, torsion angles are usually given – representing the angle between the planes through atoms. Alternatively, the angles between the orthogonal vectors of the planes can be given. In this case the term dihedral angle should be used to avoid confusion

reaction has to take place, i.e., bonds must be broken and formed again (McNaught and Wilkinson 1997).

The fact that a molecule may assume any conformation just by rotation about its bonds suggests that all conformations are energetically equal and therefore equally probable. This is not the case. Steric reasons are responsible for different energy levels of different conformations (Mo et al. 2004), although other reasons have been proposed earlier (Weinhold 2001, 2003).

As the rotation around single bonds is continuous, any conformation is possible. Consequently, a precise description of the conformation can be presented by the value of the torsion angle or the dihedral angle (these two terms are sometimes confused, see Fig. 1.6 for definition).

Nevertheless, some conformations are more likely (i.e., energetically favorable) than others, depending on shapes and dimensions of all parts of the molecule. For hydrocarbon chains, some conformations occur frequently and have therefore been given specific names (Fig. 1.7). In the solid state, only these favorable conformations are found.

1.5 Cations, Anion, Zwitterions

Apart from the structural flexibility of amino acids due to their conformational freedom, there is another way in which amino acids can adapt to a given chemical environment: As amphoteric species, amino acids can act as both acids and bases. Thus, they can donate or accept protons (i.e., form anions or cations), or even both at the same time. In this case, the acid proton is formally transferred to the amino group, thus turning the truly neutral molecule into a zwitterion (actually an

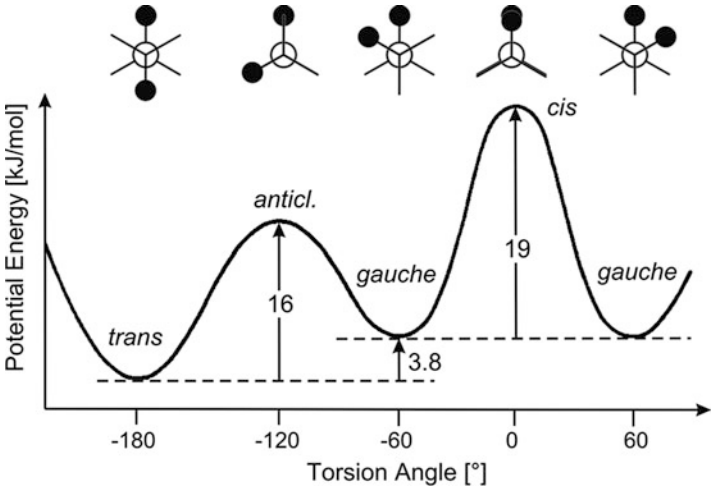


Fig. 1.7 *Conformations of n-butane*, shown as a correlation of torsion angle and potential energy. The molecule is shown on *top*, viewed along the C2–C3 bond (Newman projection), with the terminal methyl groups depicted as black circles. Depending on the relative position of the terminal methyl groups and the hydrogen atoms, staggered conformations are energetically favored in contrast to eclipsed conformations. When the methyl groups are located on opposite ends ("trans"), the potential energy is at a minimum. Another local minimum is found for the "gauche" conformation, at torsion angles of ±60° (McMurry 2007)

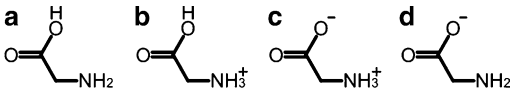


Fig. 1.8 *Protonation and deprotonation of amino acids*. As shown exemplary for glycine, the truly neutral form (**a**) is a very rare one. In solution, the true form is determined by the pH, in solid state by the other ions or molecules present in the crystal. At low, medium, or high values of the pH, the amino acid is a cation (**b**), zwitterion (**c**), or anion (**d**). As usual for cations or anions, the amino acids in these states are named with the conventional endings (-ium or -ate, respectively). Thus, the protonated glycine moiety (**b**) is referred to as a glycinium cation; the deprotonated form (**d**) is called glycinate anion

intramolecular acid–base-reaction, Fig. 1.8). In total, a zwitterion is still neutral, although it distinctly carries a positive and negative charge each (therefore, zwitterions are sometimes referred to as "inner salts"). This zwitterionic state is in fact a very common one: In solution, only a very minor fraction of all amino acid molecules exists in the truly neutral form. Only from an environment of noble gases, amino acids in the non-ionized form can be obtained.

Of course, the pH value of the solution plays a crucial role in determining the state of the amino acid: When below the acid dissociation constant pKa of the amino group (e.g., 9.6 for glycine), this group is protonated; thus, the amino acid carries a positive charge. At values over the pKa of the carboxylic acid group (e.g., 2.34 for glycine), this group is deprotonated, resulting in a negative charge. If the pH is between these

Table 1.1 *Acid dissociation constants (pKa) and isoelectric points (pI) of common amino acids* (Pogliani 1992). Some amino acids have side chains with acidic/basic properties; for these groups the pKa value is also given (in case of bases, the value corresponds to the conjugate acid)

Amino acid	pKa ($-NH^{3+}$)	pKa (−COOH)	pKa (side chain)	pI
Glycine	9.6	2.34		5.97
Alanine	9.69	2.35		6.02
Valine	9.62	2.32		5.97
Leucine	9.60	2.36		5.98
Isoleucine	9.68	2.36		6.02
Phenylalanine	9.13	1.83		5.48
Tryptophan	9.39	2.38		5.88
Tyrosine	9.11	2.20	10.07 (−OH)	5.65
Histidine	9.17	1.82	6.0 (imidazolium)	7.58
Serine	9.15	2.21		5.68
Threonine	10.43	2.63		6.53
Methionine	9.21	2.28		5.75
Cysteine	10.78	1.71	8.33 (−SH)	5.02
Aspartic acid	9.82	2.09	3.86 (−COOH)	2.87
Glutamic acid	9.67	2.19	4.25 (−COOH)	3.22
Asparagine	8.08	2.02		5.41
Glutamine	9.13	2.17		5.65
Lysine	8.95	2.18	10.53 ($-NH_3^+$)	9.74
Arginine	9.04	2.17	12.48 ($-NH_3^+$)	10.76
Proline	10.60	1.99		6.30

two values, both effects occur simultaneously, which means the amino acid is a zwitterion, with opposite charges at the amino and carboxylate groups.

In a solution of a medium pH, there is a dynamic equilibrium of protonation and deprotonation of the amino acid, with the majority of the molecules in zwitterionic state, and only a small fraction in cationic or anionic state. For every amino acid, there is a pH where the amount of cations and anions exactly balances out. This equilibrium value is called the *isoelectric point* (pI). For amino acids with only the ubiquitous amino and acid group, the pI is exactly between the two pKa values, for those with additional acidic and basic side chains, all pKa values must be taken into account. The pKa as well as the pI values for the amino acids discussed in this book are given in Table 1.1.

In the structural figures shown in the previous sections, the amino acids are always depicted in the truly neutral state, although this does not represent the actual situation. In fact, the diagram as given in Fig. 1.8c, d does also not give a realistic representation, as far as the carboxylate group is concerned. More accurately, the π-electrons of the C=O bond as well as the electron of the deprotonated hydrogen atom are delocalized about the whole carboxylate group, a state well known from aromatic systems and commonly referred to as *mesomeric effect* or *resonance effect*. As the electrons are delocalized, the formal difference between single C–O and double C=O bonds disappear in the molecule. This is clearly expressed in the bond lengths found in crystalline state, as shown for several instances in the following chapters.

1.6 Concluding Remarks

As demonstrated in this chapter, amino acids show – despite the common structural features – a very high degree of diversity. This diversity will become even more apparent in the following chapters, where the pure amino acids as well as their salts are discussed in some details. Several interesting, structural, physical, and chemical aspects will be presented, along with some indications on possible applications of amino acid salts. Although most of the properties that allow exploitation as materials with physical, technical, chemical, or pharmaceutical value occur in salts, mostly in solid state, there has been an interesting finding on amino acids in a curious state: Recently, Fukumoto et al. (2005) reported the synthesis of ionic liquids from 20 natural amino acids (for the utilization of ionic liquids, see box below). Within this paper, the authors showed that amino acid ionic liquids were able to dissolve native amino acids under anhydrous conditions and are themselves soluble in organic solvents (e.g., chloroform). This finding is but one which shows the versatility of amino acids – another unexpected discovery of amino acid properties made nearly 200 years after the first report of a member of this family.

Ionic Liquids

Although ionic liquids have been known for over a century, their real impact on science has been made when Wilkes and Zaworotko (1992) presented ionic liquids with weakly coordinating anions (as PF_6^- and BF_4^-), which have made a wide range of applications possible. Ionic liquids are generally salts with a low melting point, i.e., liquid at more or less ambient conditions. Thus, they are powerful solvents that have made the leap from laboratory to industry (Plechkova and Seddon 2008), both in the chemical and pharmaceutical community. Maybe even more important seems the utilization of ionic liquids as promising solvents for cellulose. As the most abundant chemical on earth, cellulose is part of every kind of plant tissue harvested and yet hard to process chemically. Dissolving cellulose at ambient conditions might be a chance to develop biofuel on a basis that does not compete with food production (Ohno and Fukaya 2009). Another very promising application of ionic liquids is their use as short-time energy storage medium. This is of importance in connection with the increasing development of photovoltaics: As it is necessary to absorb excess energy (e.g., in sunshine) which has to be released later (e.g., at night), there is heavy demand for materials that can store energy reversibly. Ionic liquids with a high liquid-phase temperature range are possible candidates for this application. An overview of physical and chemical properties of ionic liquids is given by Zhang et al. (2009).

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Chapter 2
Amino Acid Structures

Abstract Although this book deals with salts of amino acids, this chapter discusses the structures of pristine amino acids, since these molecular structures are also found in salts, and factors as solubility and conditions of crystal growth are important for the synthesis of amino acid salts as well as the pure form. In this context, the impact of minimal changes in conditions (such as impurities) on the growth of amino acid crystals is noted. The structural variation is very high, as not only amino acids differ from each other, but many amino acids exist in more than one form. This refers to the fact that enantiopure crystals can be grown as well as racemates (so-called DL-amino acids). Moreover, often more than one hydration state is found: Anhydrous forms are common, but many amino acids form hydrated crystals. For some amino acids (e.g., glycine, proline, methionine), more than one polymorph of the same hydration state is found. Some of these polymorphs form at ambient condition, often due to minuscule changes in conditions. For others, variation in temperature and pressure has been found to be the cause of the formation of different polymorphs. High-pressure data are available for some amino acids (e.g., alanine, serine, cysteine). Most amino acids are found to form a so-called head-to-tail motif, where acid and amino groups connect to form infinite chains. In some of the larger, nonpolar amino acids, a bilayer pattern is found, where polar groups of opposing molecules face each other, forming a layer, with the hydrophobic side chain facing outward (this motif is found in phenylalanine, methionine, leucine, or isoleucine). Not all amino acids crystallize readily, as is proved by the crystal structure of L-arginine, which could be determined only very recently, and that of lysine, which could not be solved at all to date. In addition to the standard 20, some nonstandard amino acids are discussed. Finally, notes on remarkable physical effects (such as piezoelectric data) or possible applications (as for instance the interactions of amino acids with carbon nanotubes) are presented.

Keywords Amino acid structures • Solubility • Crystal growth • Hydrophobicity • Polymorphs • Non-ambient conditions • Head-to-tail motif • Polar amino acids • Nonpolar amino acids • Physical properties

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