Amino acid networks

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The large range of hydrophobicities and water solubilities of α-amino acids, together with the general accessibility of the L (natural) and D (synthetic) enantiomers, makes them ideal candidates for the development of supramolecular networks in crystals, in bulk water and on solid surfaces. In crystal and co-crystal structures of L- and DL- amino acids, amino acid co-crystals and dipeptides, one already finds many useful combinations and obtains definite clues to useful intermolecular interactions. In amphiphilic bilayers and bolaamphiphilic monolayers of amino acid derivatives, crystalline α-networks can also be realized in noncovalent fibers and fiber assemblies. β-Networks presumably depend on some ordering of the fibers on solid subphases or can be made by a stepwise assembly of appropriate amino acids on solid subphases.

We are interested in the synkinesis of noncovalent assemblies of uniform width in the 0.5–50 nm range and elongations in the μm or longer range on solid surfaces, such as gold, silicon or polymers. We intend to use such assemblies as matrices for the formation of hydrophilic or hydrophobic 'crests' in stiff membrane structures. If such membranes have been formed and covalently bound to the solid subphases,[1,2] one may then also melt the crests away and replace them by rivers (Fig. 1).

Alpha- and β-networks of adjustable widths are ideal candidates for such purposes and α-amino acids provide the most promising starting materials, because they provide a large range of hydrophobicities and side-chain reactivities as well as chirality. Furthermore, one may also envisage rigid monolayers of redox-active amino acids coupled to monolayers of photoactive dyes. In this short overview, we shall discuss a few crystal structures of hydrophobic and hydrophilic α-L-amino acids and racemates, some amino acid co-crystals and, finally, dipeptides. It will be shown that specific pairing can be enforced in 3D crystals and that linear chains as well as sheets found in crystals can also be realized in synthetic lipids with amino acid headgroups. In an outlook, we discuss possible multilayers on solid surfaces and their functionalization, which have not been realized so far.

Crystals

Almost all amino acids form chains and nets of head-to-tail-arranged zwitterions in crystals. The only exception so far is the α form of L-glutamic acid in which a three-dimensional network of hydrogen bridges is built (see Fig. 2*a*). The molecules are connected *via* hydrogen bridges between the ammonium and all of the carboxylate groups, leading to a regular layer arrangement.

In the hydrophobic amino acids the monolayers pack up to form a bilayer assembly, in which a side-chain to side-chain-linking connects the hydrophobic edges of the planes by van der Waals forces. Valine,[4,5] leucine,[6,7] isoleucine,[8] D-alloisoleucine[9] and methionine[10] appear in two different conformations within one crystal of the pure enantiomer, and in only one in the racemate, as shown in Fig. 3 for L-leucine and DL-leucine. Single layers always contain only the L- or D-configured molecules; the mutual orientation of the layers is also different in the L and DL crystals. Thus, side-chains only influence the stacking of the layers: the symmetric side-chain of valine packs linearly back-to-back. Leucine and isoleucine side-chains pack in an asymmetric manner. Accordingly, chiral effects are prominent only in the latter: the racemates of leucine and isoleucine are less soluble by a factor of about three when compared to the pure enantiomers; in the case of valine the enantiomeric mixture is even slightly more soluble than the pure compounds. The lengths and arrangements of the hydrogen bridges do not change. Table 1 summarizes some physical properties of bilayer-forming amino acids. It shows that racemates may be less soluble than the pure enantiomers (Leu, Ile) or more soluble (Val); hydrogen bond patterns are more regular in the racemates. L-Norleucine[10] and DL-norleucine[11] appear in only one conformation in either of the crystals, but the β-network of the hydrogen bonds and its dimensions are the same as in the β-branched amino acids.

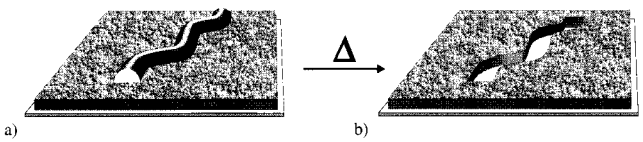


Fig. 1 (*a*) Formation of 'crests' after sedimentation of synkinetic nanostructures and subsequent self-assembly of stiff membrane structures. (*b*) The nanostructures may be melted away to leave 'rivers'

Hydrophilic amino acids form crystals in which the molecular interactions lead to a monolayer arrangement. In the β form of glutamic acid[12] (Fig. 2*b*), for example, alternating arrangements of the side-chains appear. Hydrogen bonds between the amino acid groupings of adjacent layers occur only in L-serine and L-alanine. The intralayer hydrogen bonds are slightly longer, having lengths of 2.86 and 2.92 Å, than the ones in the hydrophobic amino acids (see Table 1). In most cases the functional groups of the side-chains build hydrogen bonds with the amino acid groups in a lateral arrangement. In our example the carboxyl group accepts one such bond from the ammonium group and donates one to the α-carboxylate. The latter bond measures 2.54 Å and thus is very short. Such strong interactions disturb the linearity of the amino acid chains and lead to a bent fishbone-like pattern of the side-chains, *e.g.* L-serine monohydrate,[13] DL-serine,[13,14] L-threonine,[15] L-allothreonine,[16] L-tyrosine,[17] DL-tyrosine,[18] *etc.* Curvature is thus predetermined.

Differences between the L and the DL forms of hydrophilic amino acids show a greater variety than those in the hydrophobic ones. Anhydrous DL-glutamic acid[19] forms double layers with pairs of molecules of opposite chirality (Fig. 2*c*). In

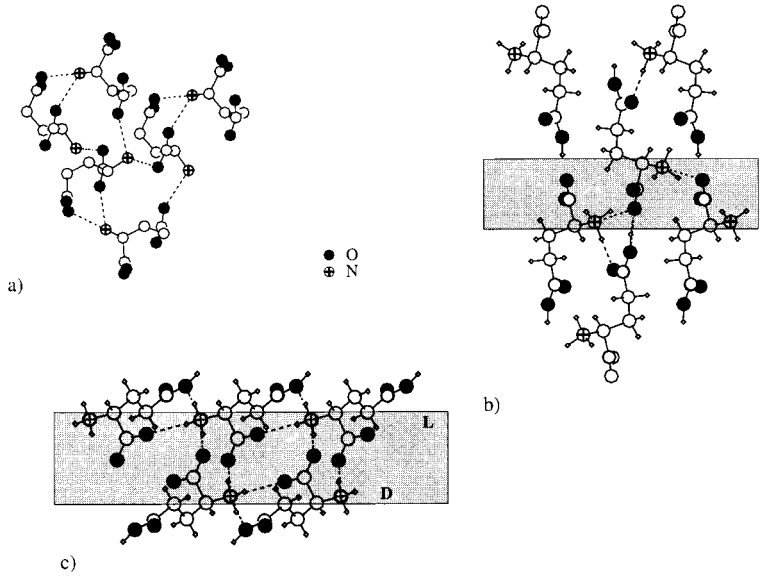


Fig. 2 (*a*) 3D network of the α form and (*b*) monolayer structure of the β form of L-glutamic acid; (*c*) bilayer of anhydrous DL-glutamic acid. The gray boxes show the hydrogen-bonded amino acid groupings. The interactions of the side-chain carboxyl group clearly lead to distortions of the linear arrangement in (*b*) and (*c*)

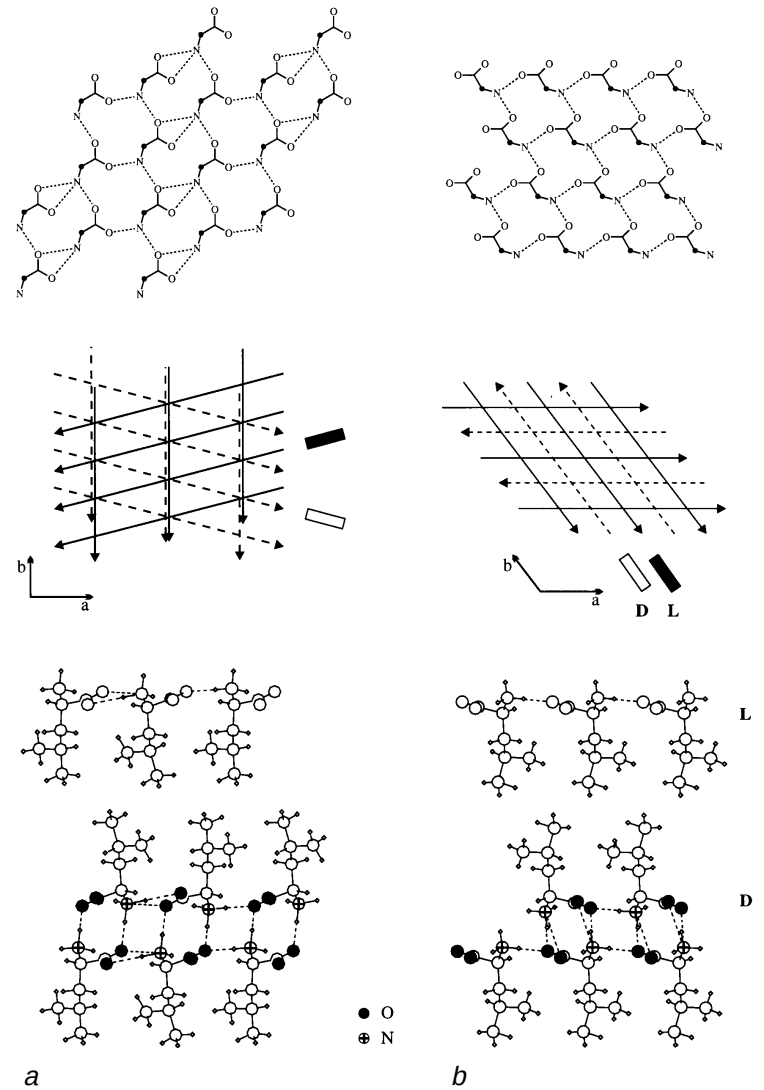


Fig. 3 (*top*) β-Network of the amino acid grouping of a monolayer, (*middle*) top plane view of the layer arrangement and (*bottom*) side elevation of the double layer of the crystals of the hydrophobic amino acids represented by (*a*) L-leucine and (*b*) DL-leucine. In the top plane view the dotted lines represent the hydrogen bridge chains of the lower layer. The arrows indicate the direction from NH_3^+ to COO^-; points of intersection correspond to the positions of the molecules; boxes show the orientation of the C—COO bond (see *top*)

Table 1 Physical properties and hydrogen bond lengths of the aliphatic amino acids

Compound	mp/°C	Solubility/ g kg^{-1} (at 20 °C)	Density/g cm^{-3}		Length of hydrogen bridges/Å		
			D_m	D_{calc}	Intralayer		Interlayer
L-Val	315	56.5	1.263	1.261	2.917/3.067[a]	2.797	2.779
					2.869		2.859
DL-Val	298 d	68.1	1.22	1.24	2.748	2.891	2.953
L-Leu	293-5	23.74	1.14	1.16	2.992/3.087[a]	2.795	2.756
					2.893		2.759
DL-Leu	293-5	9.39	1.29	1.285	2.717	2.880	2.924/3.013[a]
L-Ile	285.6	33.6	1.202	1.196	2.993/3.028[a]	2.813	2.794
					2.812		2.844
DL-Ile		21.23			2.88		2.95
L-Nle			1.136	1.134	2.813	2.799	2.792
DL-Nle		10.71		1.171	2.837	2.813	2.775

[a] Bifurcated hydrogen bridge

the case of DL-alanine[20,21] and DL-tyrosine[17,18] the single layers consist of L and D enantiomers. L-Serine monohydrate and DL-serine, where the layers again contain either L or D molecules, are very similar in their structures.

Crystals of the basic amino acids lysine and ornithine have only been obtained as salts. The molecules are aligned in chains with the usual head-to-tail arrangement. In L-lysine hydrochloride dihydrate (Fig. 4) these chains lie side-by-side to form planes.* The chloride ions and the water molecules are positioned between the amino acid group and the ω-ammonium group. The intrachain distance of the ammonium to carboxylate hydrogen bond is 2.789 Å. Adjacent planes are oriented to obtain interactions of the ω-ammonium with the α-carboxylate groups; the length of this hydrogen bond is 2.791 Å. The DL compound of lysine hydrochloride crystallizes in planes, in which racemic pairs of molecules are arranged in a head-to-tail manner. Chloride anions are sandwiched between the planes.

The most unusual interactions occur in the basic amino acid arginine (Fig. 5). The strongly basic guanidyl group leads to a zwitterionic state where only the guanidyl group is protonated but not the amino group.[23] Instead of the usual peptide-like arrangement one therefore observes head-to-tail-arranged cyclic dimers. The guanidyl group donates two hydrogen atoms to the amino acid function of its neighbour. The columns are connected *via* hydrogen bonds between the α-carboxylate and the guanidyl group in one direction and separated by four water molecules in the other one.

In the diphenylalanine monoformate and di-L-leucine hydrochloride structures the molecules form pairs *via* a short hydrogen bond between a protonated and a deprotonated carboxyl group. These pairs again build up layers with formate or chloride ions, positioned between the ammonium groups. The overall crystal structures are similar to the bilayer structures of the hydrophobic amino acids.

There are a few examples of crystal structures of molecular complexes between two different amino acids. It turns out that in combinations of two hydrophobic amino acids, phenylalanine is an ideal partner in co-crystals. Furthermore, combinations of a basic amino acid with an acidic one or ascorbic acid are favourable for crystallization.

L-Phenylalanine forms crystals only with the D-configured enantiomer of valine.[26] The crystal structure of this complex (Fig. 6) is built up just like the crystals of DL-valine, except for the difference in the side-chains of the L-phenylalanine layers. Experiments with DL-valine, DL-leucine and DL-isoleucine together with L-phenylalanine[27] show that the same kind of chiral discrimination always occurs: pseudo racemates are

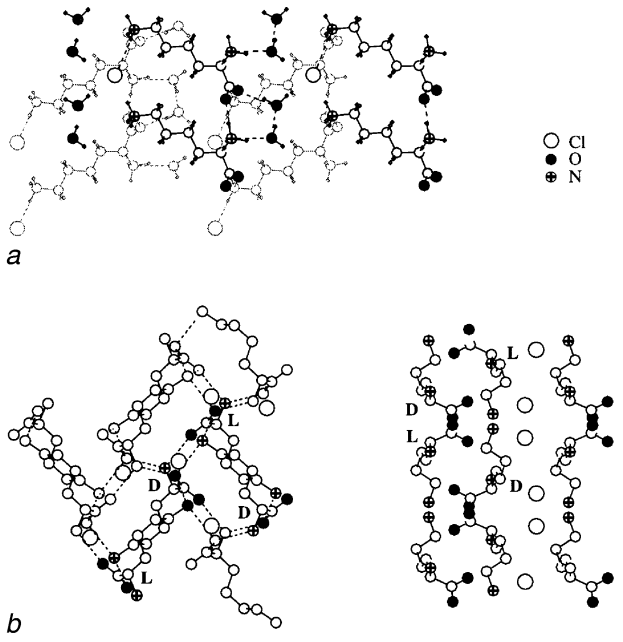


Fig. 4 (*a*) L-Lysine hydrochloride dihydrate represents an α-network made of monolayers in a herringbone arrangement with large spacings within one layer. (*b*) Top and side views of the planes of DL-lysine hydrochloride, composed of head-to-tail-arranged molecule pairs building a β-network

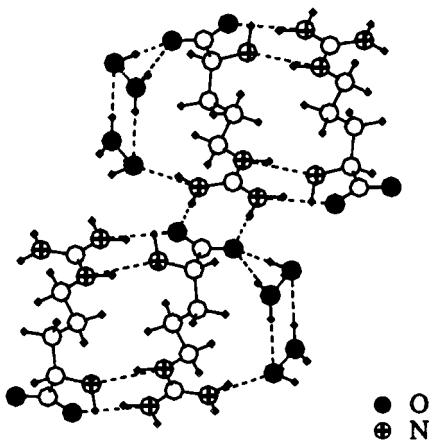


Fig. 5 L-Arginine dihydrate crystals are made of columns of head-to-tail-arranged pairs

* We use the word plane to point out that the side-chains lie within the layer's orientation in contrast to the mono- and bilayers, where the side-chains are perpendicular to it.

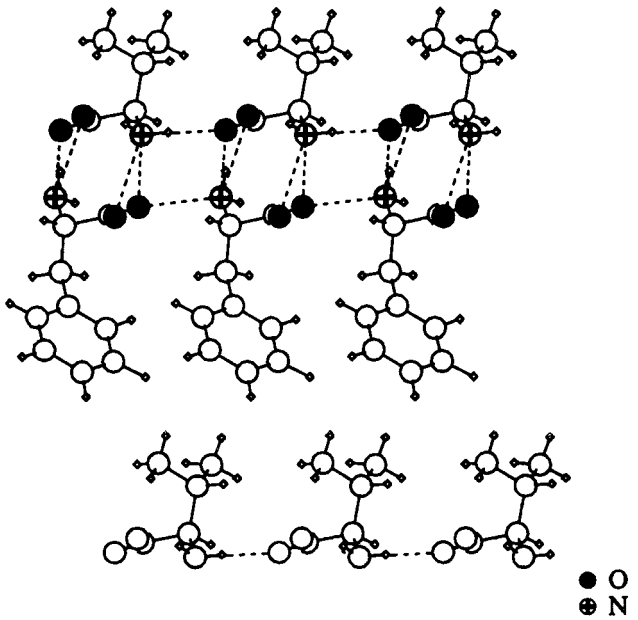
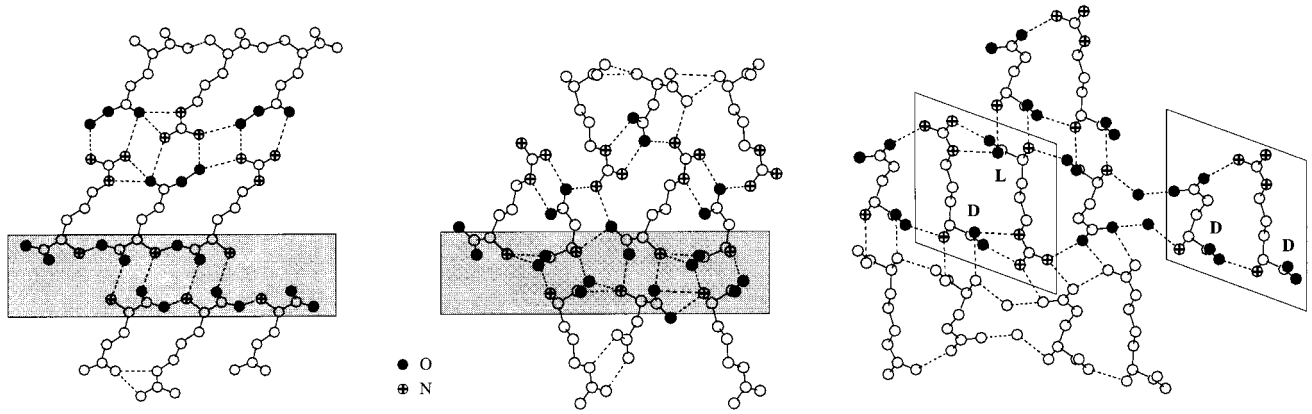


Fig. 6 L-Phenylalanine D-valine complex, a tail-to-tail bilayer

formed. Side-chain structures are thus less determinant for co-crystallization processes than the pseudo mirror image stereochemistry and the overall hydrophobic character of the amino acid. This effect is reminiscent of the chiral bilayer effect observed in membrane structures.[2]

Instructive examples of crystalline complexes composed of basic and acidic amino acids are the arginine pairs with aspartic acid or glutamic acid. All combinations of chiral mixtures, namely LL, L D and LD LD, have been reported for this group. Here again, the strongly basic guanidyl group manages to build all the five possible hydrogen bridges in each structure. This leads to very complicated arrangements in both LL complexes (L-Arg : L-Asp[28] and L-Arg : L-Glu[29]), each containing a specific interaction of the guanidyl group with the α- or the β-carboxylate, respectively. Surprisingly, the structures of the L D mixtures (L-Arg : D-Asp[30] and L-Arg : D-Glu[30,31]) are constructed of alternating L-arginine and D-aspartic or D-glutamic acid layers. In the LD LD complexes of LD-Arg : LD-Asp[32] one can observe successions of alternating amino acids of the same chirality, which are arranged head-to-tail. In LD-Arg : LD-Glu,[32] on the other hand, pairs of like molecules with different chirality or *vice versa* are found. In these arrangements, basic and acidic molecules as well as D and L enantiomers are both brought into the closest possible proximity, obviously the tightest possible packing. The same arrangement is found in some of the racemic crystals of the hydrophilic amino acids. A comparison of side-chain interactions in both the L D structures reveals remarkable differences arising from even-odd effects. The glutamic acid side-chain is connected with the guanidyl group of an arginine molecule in the next layer of its complex (Fig. 7*a*), leading to a fully extended side-chain conformation for both molecules. The length of the glutamate side-chain and the mutual orientation of the guanidyl and ω-carboxylate groups allow perfectly linear arrangements [3.12 Å for N(9)···O(16), 2.98 Å for N(9)···O(w) and 2.77 Å for



a) b) c)

Fig. 7 Crystal structures of the arginine complexes. (*a*) L-arginine D-glutamic acid, (*b*) L-arginine D-aspartic acid (the gray boxes show the hydrogen-bonded amino acid groupings) and (*c*) DL-arginine DL-glutamic acid (the frames indicate the structural patches, see text)

Table 2 Hydrogen bonds in the structure of L-arginine D-glutamate monohydrate and L-arginine D-aspartate

Interlayer			Intralayer		
Atomic assignment	Monomers involved	Bond length/Å D···A	Atomic assignment	Molecules involved	Bond length/Å D···A
L-arginine D-glutamate monohydrate					
N(1) O(1)	Arg Arg	2.77	N(1) O(12)	Arg Glu	2.83
N(11) O(11)	Glu Glu	2.80	N(1) O(12)	Arg Glu	2.81
			N(11) O(2)	Glu Arg	2.81
			N(11) O(2)	Glu Arg	2.79
L-arginine D-aspartate					
N(1) O(31)	Arg I Asp II	2.809	N(1) O(11)[a]	Arg I Asp I	2.725
N(31) O(1)	Asp II Arg I	2.799	N(1) O(12)[a]	Arg I Asp I	2.752
N(11) O(21)	Asp I Arg II	2.983	N(21) O(32)	Arg II Asp II	2.831
N(21) O(12)	Arg II Asp I	3.132	N(21) O(22)	Arg II Arg II	2.920
			N(11) O(2)	Asp I Arg I	2.789
			N(11) O(12)	Asp I Asp I	2.910
			N(31) O(22)	Asp II Arg II	2.767

[a] Bifurcated hydrogen bridge

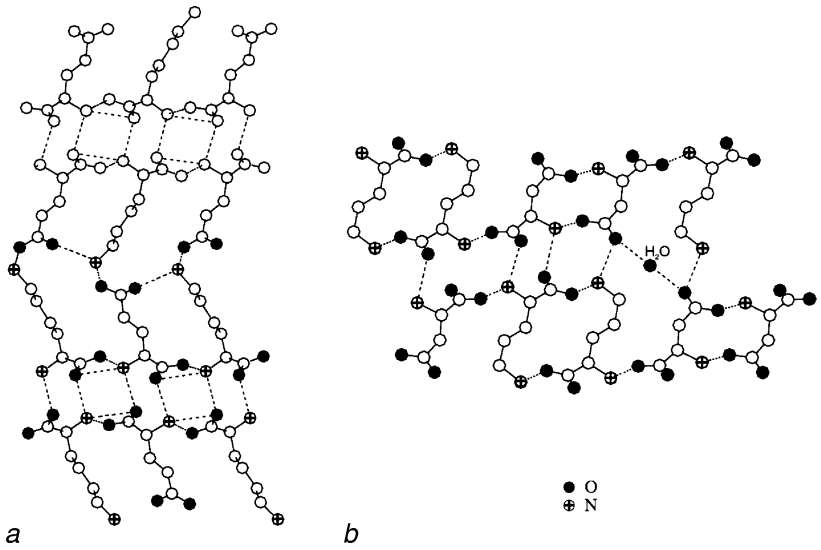


Fig. 8 (*a*) Layer structure of L-lysine D-glutamic acid and (*b*) columns of the like pairs in L-ornithine L-aspartic acid monohydrate

O(w)···O(17)]. A single water molecule seems to conceal a slight imperfection in this arrangement.

In the aspartate complex (Fig. 7*b*) the shortness of its side-chain causes a limited interdigitation of the guanidyl groups and the carboxylate's orientation towards the guanidyl group of the neighbouring arginine leads to another strong hydrogen bond [2.872 and 2.778 Å (Arg I Asp I) and 2.856 and 2.734 Å (Arg II Asp II)]. The arginine side-chain has a *gauche* kink with an angle X^3 ($C^\beta—C^\gamma—C^\delta—N^\varepsilon$) of $-65.0°$ and 63.7°, respectively, in each of its conformers. The perfect linearity of the amino acid group arrangement is lost. The values for the hydrogen bridges, given in Table 2, reflect this imperfection.

An interesting abnormal pattern is found in the crystals of the DL-arginine DL-glutamate complex[32] (Fig. 7*c*): the arginine pairs form loops, as in L-arginine dihydrate (see above), the side-chain arrangement resembles that of the LD complex and both motifs are built of different enantiomers.

More simple arrangements are found with lysine and ornithine as the basic units. The structures of L-ornithine L-aspartate monohydrate,[33] L-ornithine D-aspartate hemihydrate,[34] L-lysine L-aspartate,[35] L-lysine D-aspartate monohydrate[36] and L-lysine D-glutamate[36] are known. Although all five structures are different, some findings point to specific arrangements with regard to odd-even effects. In both the ornithine co-crystals the γ-ammonium group is involved in a loop of two ammonium and two carboxylate groups. No such loops exist in the lysine complexes. Instead, there are infinite hydrogen bond chains of alternating δ-ammonium groups and the α-carboxylate groups of the aspartate. In L-lysine D-glutamate[36] two such hydrogen bond

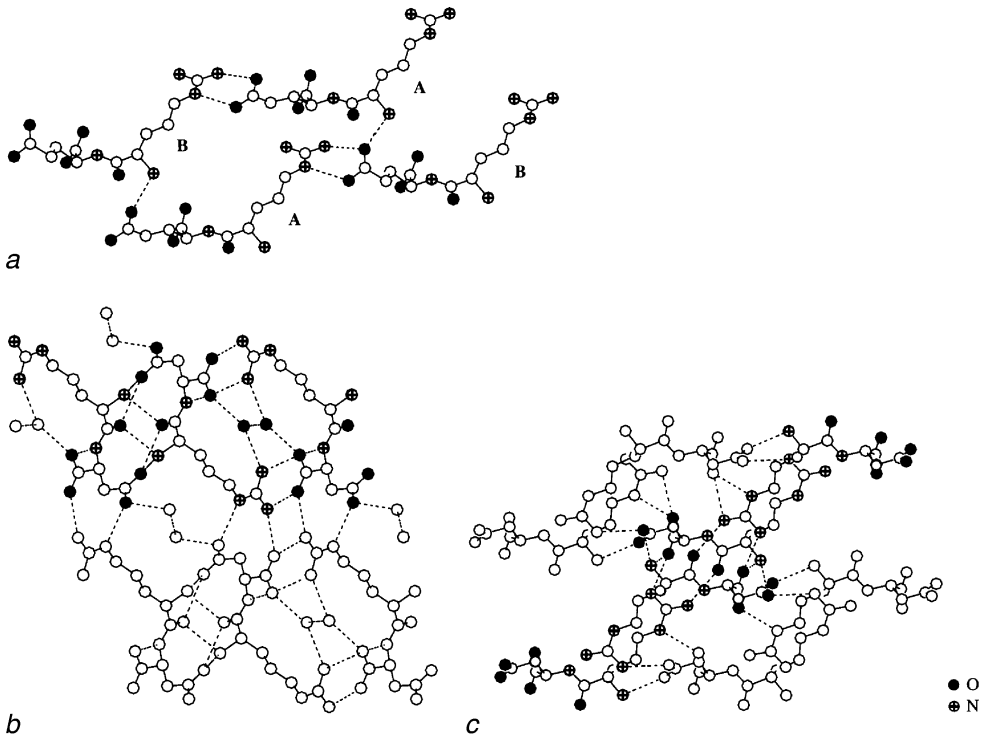


Fig. 9 Arginine-containing dipeptides: (*a*) L-arginyl L-glutamic acid dihydrate, where **AB** successions of head-to-tail-arranged molecules build up an α-network, (*b*) L-arginyl L-aspartic acid dihydrate and (*c*) L-arginyl L-aspartic acid monohydrate

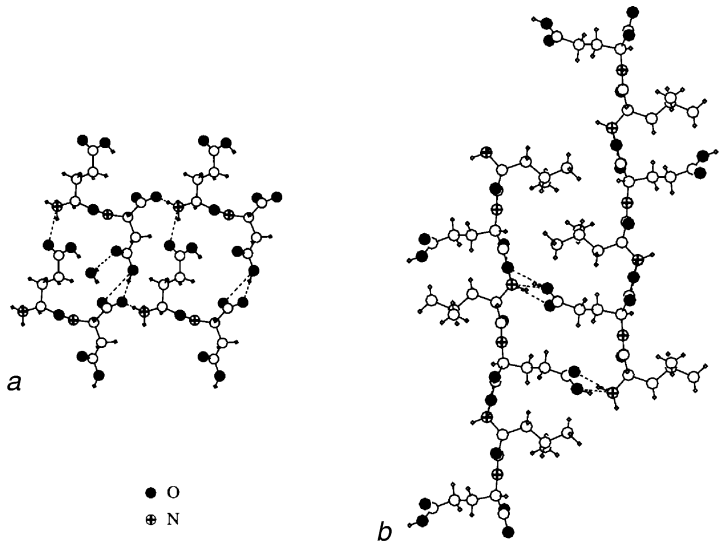


Fig. 10 Typical dipeptide arrangements: (*a*) L-glutamyl L-aspartic acid and (*b*) L-valyl L-glutamic acid

chains exist and both are pure side-chain side-chain interactions (Fig. 8*a*). In addition, this is the only crystal of the five that is built up from alternating double layers. In L-ornithine L-aspartate monohydrate[33] (Fig. 8*b*), we find only columns of pairs of like molecules (this crystal looks very much like the DL-arginine DL-glutamate complex[32]), whereas in the remaining three structures monolayers, separated by pairs of aspartate or glutamate molecules, respectively, are formed.

In dipeptides the amino acids are linked *via* amide bonds reflecting exactly the pattern that has to be assumed for their dipolar interactions in water and which has been found in most amino acid crystals. With the formation of the amide group the charge per unit is, however, reduced, the pK_as are much more moderate, and the number of possible hydrogen bridges (seven with respect to the main chain of the amino acids only) is reduced to two or three with the amide group. So, we can hope to get a more detailed insight into the pure side-chain interactions. As an instructive example we briefly discuss three structures of dipeptides containing L-arginine together with L-aspartic acid or L-glutamic acid (Fig. 9). This corresponds to the molecular complexes, which we discussed above.

The crystal of arginyl glutamic acid dihydrate[37] contains two slightly different conformers of the glutamate's methylene side-chain. The positions and orientations of the functional groups are almost the same. The most interesting feature is the specific interaction of the γ-carboxylate with the guanidyl group of the neighbouring molecule, in which only one of the terminal nitrogen atoms, together with the ε-nitrogen, is involved. Thus, a succession of side-chain-linked molecules in AB order build up the crystal. Sixteen out of twenty-six observed hydrogen bridges are directed to or from water molecules; of the remaining ten, four are involved in the specific side-chain interaction (2.8 ± 0.1 Å). The longer distance of two of these bonds comes from the existence of a second bridge that is donated from a neighbouring molecule's α-ammonium group towards the side-chain's oxygen. No amide hydrogen bond chains, as in the β-pleated sheets of polypeptides, exist in any of the dipeptides. In the two structures made of arginyl aspartic acid[38,39] no specific interaction of the guanidyl side-chain appears, although the arginyl residue of the dihydrate[38] has almost the same conformation as in arginyl glutamate dihydrate. A similar interaction with the guanidyl group could be expected but is not found. The change in the β-carboxylate's orientation leads to structural differences in otherwise closely related compounds. This is the same as we have indicated for the packing differences in the DL complexes of the three amino acids.

Many of the other investigated dipeptides have structures similar to those of the amino acid crystals and the polypeptides, with the main chains aligned in the peptide pattern (Fig. 10).

Fibers in bulk water

In bulk water, one obtains large molecular assemblies of amino acids only, when the charged groups are partly or totally derivatized with long alkyl chains or other hydrophobic skeletons. The best-known examples are Kunitake's glutamic acid amphiphiles, where both carboxylic acids carry a long ester chain and the amino group is amidated with an ω-trimethylammonium-α-amine.[40] These triple-chain amphiphiles with a single headgroup form bilayer vesicles upon sonication and then rearrange to long helical strands of light-microscopic dimensions. On an electron microscopic scale, these fibers consist of wide twisted ribbons made of molecular bilayers.[41] Single-chain amino acid amphiphiles have been investigated by Imae *et al.*[42] They found the same linear and twisted bilayer fibers in water with head groups containing one (Ala) or two (Asp, Glu) carboxylate anions. The diameter of the fibers was, however, in the range between 12 and 20 nm or 4–7 times thicker than a bilayer. One must therefore assume not only a linear α-network-type assembly, but it seems likely that the acid endgroups pair within the fibers *via* strong hydrogen bridges between carboxylate anions and protonated carboxyl groups. A similar arrangement has been held responsible for extended interfiber bindings in μm assemblies of tartaric acid amides.[43]

α-Networks or rods with a diameter of 4 nm occur as the primary product from bolaamphiphiles with an ornithine or lysine endgroup on one end and an amino group on the other[44] (Fig. 11). The same α-amino-ω-ornithine bolaamphiphiles constitute a pure, curved β-network, when they appear as vesicular monolayer tubules in bulk water at pH 9 (Fig. 12). Length growth is only limited by the amount of material that can be dissolved in water. Appropriate feeding techniques can be envisaged that would lead to millimeter-long tubules.

It is thus possible to obtain the amino acid bilayers with an α-amino acid surface and a hydrophobic or hydrophilic surface not only in 3D crystals, but also in bulk water. If the same kind of molecular assemblies are needed in organic solvents, one just applies the hydrophobic COO- and/or N-

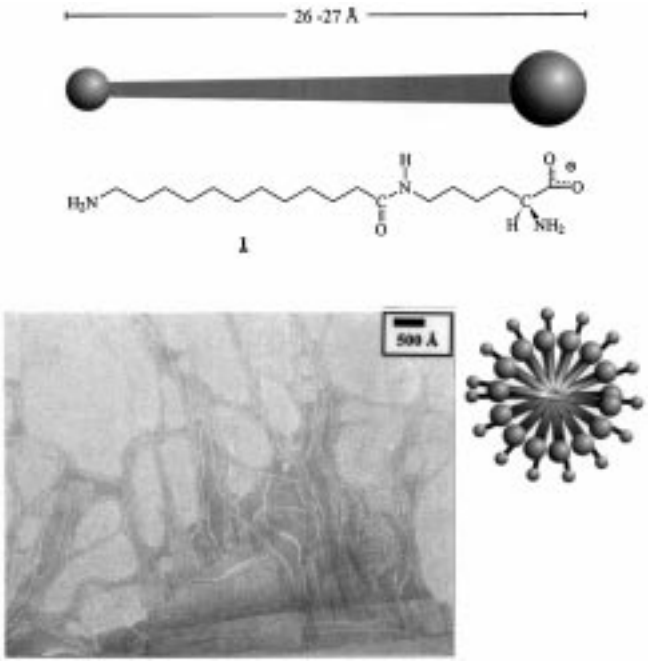


Fig. 11 Electron micrographs of 4 nm monolayers of **1** in water, as an example of a monolayer α-structure

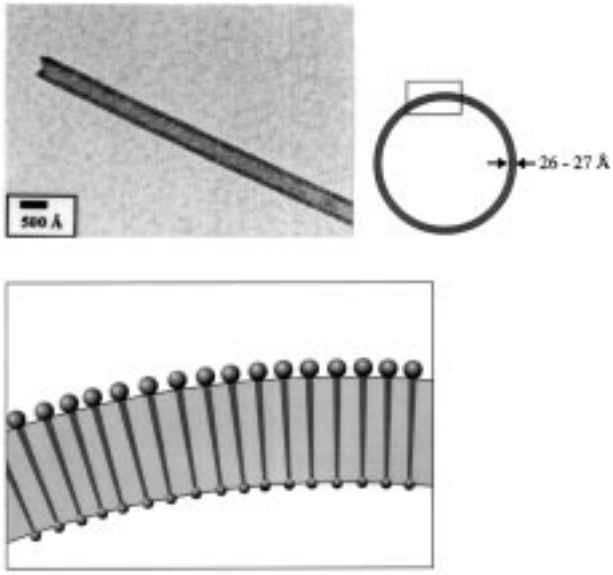


Fig. 12 Monolayer tubules made of the bolaaphiphile **1** in water at pH 9. They constitute the most simple β-network in bulk water

protected derivatives known from peptide synthesis. The same type of assemblies can then be made in toluene or chloroform.

Recently, we found molecular bilayer tubules made of *N*-dodecanoyl-L-serine in toluene as well as in water. The bilayer arrangement in the crystals[45] shows a twofold screw axis. This arrangement is thought to be responsible for the formation of twisted ribbons, which then close to form tubules. The building principle of all these noncovalent molecular assemblies is the same as the one in covalent proteins: the side-on assembly of carboxyl and amino functionalities combined with side- or end-on side-chain hydrophobic effects and chiral bilayer effects. This assembly may then either be solvated or paired face-to-face with the same chain of a neighboring assembly.

Multilayers on solid subphases

In order to build up extensive multilayers on solid surfaces, one may now start with an amino acid covalently linked by its side-chain to the subphase, for example cysteine to gold. This will expose the amino acid zwitterion to water and allow the self-assembly of another amino acid, such as tyrosine or cysteine. The amino acid sheet may then be left as it is and one can build crystals on these bilayers. One may also stabilize the bilayer by a condensation polymerization and then functionalize it, such as by oxidation or coupling of a side-chain to a reactive dye or ascorbate of similar redox-active molecules. Everything that has been learnt from the arrangement of amino acid side-chains in crystals, co-crystals and dipeptides can then be applied directly. Fig. 13 summarizes the possible

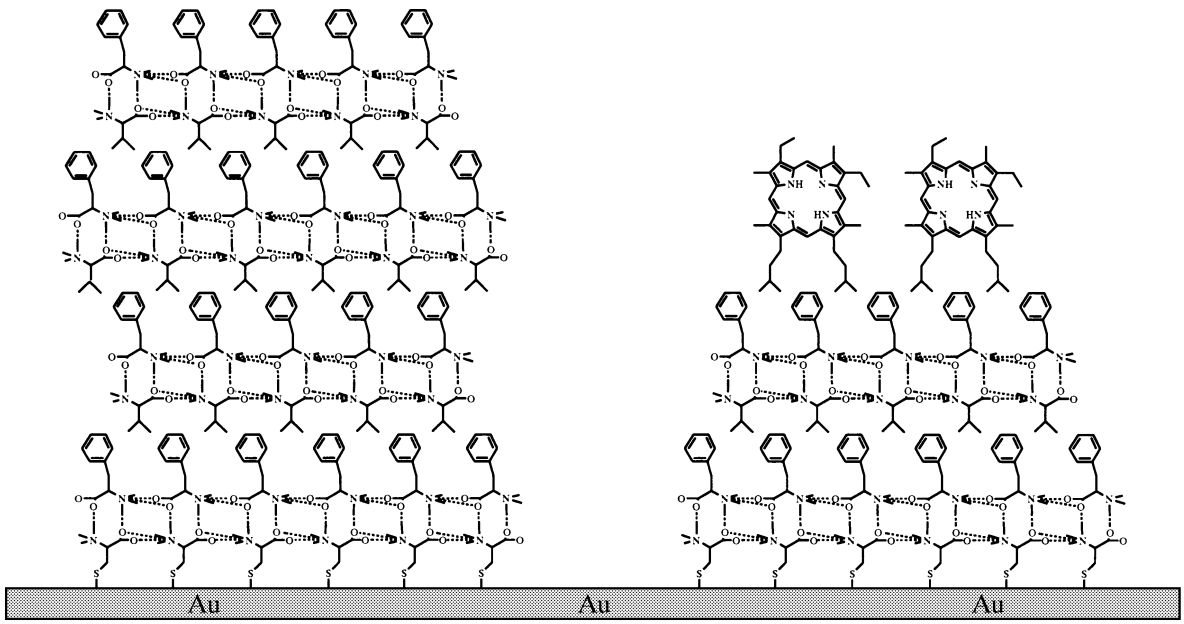


Fig. 13 Possible layer structures based upon the co-crystals of L-phenylalanine D-valine. The layers may be grown on a network of D-cysteine, which has self-assembled on gold

applications of amino acids in the formation of complex multilayers, which might be thought of as an extension of the simple β-networks, where alternation of only two molecular species occurs.

An example of how to use amino acids as building blocks in membranes is given by Whitesell and Chang.[46] They constructed polyalanine helices that grew out of an aminotrithiol-based 'tripod' on gold. In contrast to the considerations given above, these membranes contain α-networks that are pointing perpendicular to the surface.

Conclusion

The main conclusion from the crystal structures is that the protein main chain is preformed in most amino acid crystals, irrespective of hydrophilicity, enantiomeric purity or formation of co-crystals. Whenever one obtains a co-crystal with the head-to-head interaction of the amino acid group, one may form the alternating co-polymer by solid state condensation reactions. To the best of our knowledge, this has so far not been verified experimentally, but alternating Val-Lys and similar polymers show the crystal-like pleated sheet structure.[47,48] Furthermore, basic side-chains, in particular the guanidyl group of arginine, may lead to strong distortions of the linear amino acid layers, sometimes disrupting them. Odd-even effects in side-chain interactions influence a perfect chain-like arrangement.

The construction of β-networks from amphiphilic or bola-amphiphilic compounds with amino acid headgroups on solid subphases should always lead to stiff membranes, because of the stiff linear hydrogen bonds. The advantage of amino acids, in comparision to the popular saccharides, lies in the chemical diversity of the side-chains. All kinds of chiral surfaces become accessible with these synkinons.

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