SYMMETRIES IN SCIENCE IV

Biological and Biophysical Systems

Edited by
Bruno Gruber
and John H. Yopp

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SYMMETRIES IN SCIENCE IV

Biological and Biophysical Systems

FOREWORD

The symposium, "Symmetries in Science IV: Biological and Biophysical Systems," was held at Schloss Hofen, Vorarlberg, during the period July 24-27, 1989. Its purpose was to promote interaction between scientists working in the area of biological-biophysical research with scientists working in physics, mathematical physics, and mathematics.

Reviews in the field of biological-biophysical research were presented by the participants, and subsequently these presentations were analyzed by the interdisciplinary group in a workshop and by means of round table discussions. This volume contains the review presentations as a means of making this subject available to the general scientific community.

The symposium was co-sponsored by:

Southern Illinois University at Carbondale
Land Vorarlberg
U.S. Office of Naval Research, London

We wish to thank these institutions for their support. Moreover, we wish to thank the following individuals:

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Southern Illinois University at Carbondale

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Vice President for Academic Affairs and Research
Southern Illinois University at Carbondale

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Their generous support and steady encouragement has made Symposium IV possible.

Bruno Gruber
John H. Yopp

CONTENTS

SYMMETRY IN SYNTHETIC AND NATURAL PEPTIDES

E. BENEDETTI, B. DI BLASIO, A. LOMBARDI, V. PAVONE and C. PEDONE

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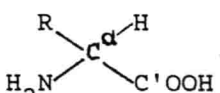
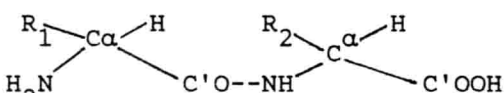
Peptides of synthetic or natural origin are compounds able to exert a variety of biological function: they are hormones, protein substrates and inhibitors, sweeteners, opioides, antibiotics, releasing factors, regulators of biological functions, citoprotectors and so on.

From the chemical point of view peptides are formed when two or more amino acid residues of the type shown above are condensed together, leading to a peptide unit (a secondary amide bond) and the formation of a dipeptide:



amino acid



dipeptide

Peptides are, then, chains of a certain number of covalently linked amino acid residues each of which is intrinsically asymmetric, because of the optically active α-carbon atoms. The amino acid sequence along the chain, the spatial configuration of the asymmetric C^{α} atoms of each residue, the local conformation of part of the molecule or the overall conformation of the entire peptide, together with the intramolecular and intermolecular interactions of various types, are all important factors in determining the biological activity and the mechanism of its action.

The structural characteristic of the peptide unit formed through the linkage of residues i and i+1 are fully described in terms of geometry of bonds, conformation and non-planarity of chemical bonds. According to the IUPAC-IUB Commission on Biochemical Nomenclature (1), the complete description of the conformations of the backbone and of the side chains in peptide and proteins is that given in Figure 1.

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Accurate values for the geometry of the peptide unit as well as for that of most side chains of the twenty naturally occurring amino acid residues have been obtained by the analysis of literature data, using accurately determined crystal structures of small and medium size peptides (2). The magnitudes of bond lengths and valence angles are generally very constant and impervious to intermolecular interactions.

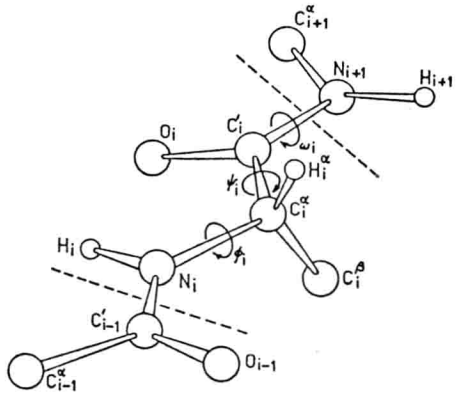
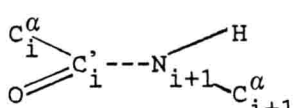


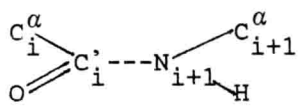
FIG. 1. Two peptide units in a polypeptide chain in a fully extended conformation ($\varphi_i = \psi_i = \omega_i = 180°$) for L-residues. The limits of a residue are indicated as dashed lines and the reccomended notation for atoms and conformational angles are shown.

Molecular conformations is most conveniently and precisely characterized by torsion angles. The shape and consequently the symmetry or the asymmetry of a particular peptide molecule is the consequence of a certain succession of torsion angles $\varphi_i, \psi_i, \omega_i$, for each amino acid residue, while the torsion angles χ_i fully describe the side chain conformation. The ω_i angles in linear peptides usually present values close to 180° corresponding to a <u>trans</u> arrangement of the type:



$\omega_i \approx 180°$

<u>trans</u>



$\omega_i \approx 0°$

<u>cis</u>

which is energetically more stable than the <u>cis</u> arrangement ($\omega_i \approx 0°$) by about 2 Kcal/mol (3). Of course a <u>cis</u> conformation is a necessity in small cyclic peptides (di- and tripeptides) but in higher cyclic peptides this arrangement may or may not occur; in any case the occurrence of a <u>cis</u> peptide unit in a linear chain is to be considered a very rare event. Consequently the molecular conformation of a peptide can be visualized in the (φ, ψ) space by the energy of the molecule as function of these torsion angles. The maps obtained show that all best known secondary structures assumed

by a peptide chain, such as the β-structure, the α-helix, the 3_{10}-helix, occur within energy minima. Conformational energy contour maps have been accurately calculated by Zimmerman et al. (4) and Figure 2 shows the maps obtained for glycine and alanine.

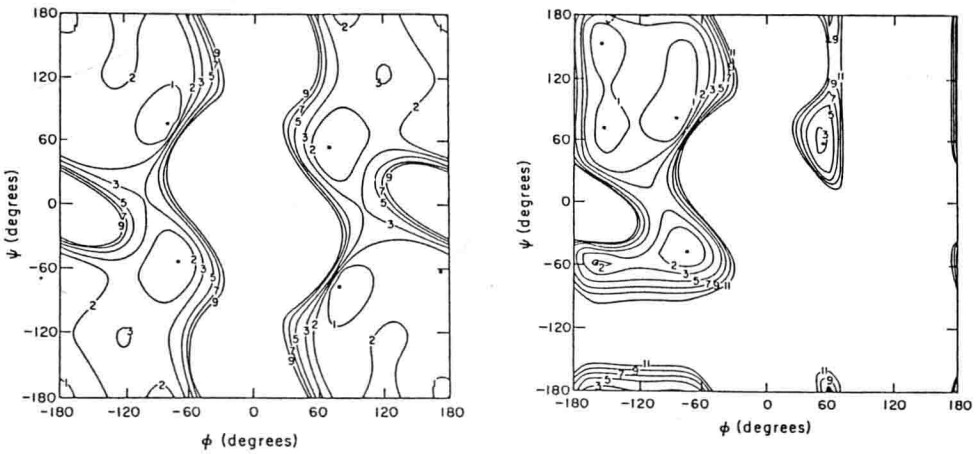


FIG. 2. Conformational energy contour maps of N-acetyl-N'-methyl-glycineamide (on the left) and of N-acetyl-N'-methyl-alanineamide (on the right).

The symmetry shown in the Gly map disappears for the optically active Ala residue and the conformational space available to a Gly residue (54 % of total area) is greatly reduced by the substitution of the hydrogen atom by a methyl group in the Ala residue (18 % of total area).

Thus, very often peptides do not show any symmetry and the only cases for which certain elements of symmetry are maintained are those concerning cyclic peptides or linear peptides in helical arrangement. In the following some examples of symmetry in cyclic and linear peptides will be presented, keeping in mind that any element of symmetry, such as mirror planes or center of inversion, which invert the configuration of the optically active α-carbon atom, should be banned, since it would change the chemical nature of the peptide (unless such inversion of configuration is constitutionally present in the peptide as in regularly alternating L,D peptides). Furthermore, rather often, in the literature the symmetry reported for a peptide refers only to the backbone atoms of the molecule, while side chain atoms are not considered.

CYCLIC PEPTIDES

The structure of cyclic peptides is simplified because the allowed conformations are reduced by the cyclic character of the molecules, which are constrained to contain bends in the backbone.

The simplest cyclic system is represented by cyclic dipeptides. Many natural products contain elements of this structural system, in which the backbone atoms forms a six membered ring. Because of the presence in the backbone of different atomic species having different hybridization, only the center of inversion and symmetry axis perpedicular to the dominant plane of the ring need to be considered in order to define ring conformation in cyclic dipeptides. The conformation experimentally observed for cyclic dipeptides can be grouped in quasi-planar conformation, boat conformation with C^{β} atoms in axial or in equatorial position and chair conformation, as shown in Figure 3.

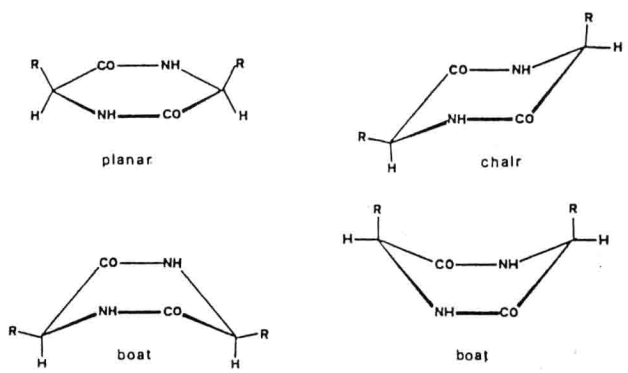


FIG. 3. The four possible conformations for cyclic dipeptides

Quasi-planar and boat conformation have a two-fold symmetry element perpendicular to the average plane of the ring, while chair conformations have no symmetry element. The center of inversion is shown in the cyclic dipeptide of glycine and possibly in cyclic dipeptides of residues with opposite configurations.

The four conformations are characterized by a different sequence of the conformational angles φ_1, ψ_1, ω_1, φ_2, ψ_2, ω_2. Because of the steric requirements, the two dipeptide units are forced to be cis ($\omega \approx 0°$) with only small deviations from planarity. Quasi-planar conformations present values for φ_1, ψ_1, φ_2, ψ_2 close to zero; boat conformations with axial substituents on the C^{α} atom are characterized by positive φ values and negative ψ values, while boat conformations with equatorial substituents on the C^{α} atom have negative φ values and positive ψ values. The chair conformation, finally, is characterized by an alternating sequence of positive and negative values of the six conformational angles.

For cyclic tripeptides, if one does not take into account side-chain atoms, the solid state conformation (5-7), confirmed by solution results also, shows an approximate three-fold symmetry axis perpendicular to the mean plane of the backbone ring atoms. The peptide units are all cis ($\omega \approx 0°$) and the φ and ψ conformational angles present values

ranging from -90° to -110° for φ and 80° to 105° for ψ, for peptides constituted only by L residues.

Several evidences have been gathered on the remarkable similarity shown by cyclic tetrapeptides (2,8-10): their conformational features are strikingly similar in spite of the difference in the chemical structure and confirm solution NMR spectroscopy data on the existence of a predominant conformation. The similarity of the ring symmetry should lie in the intrinsic conformation of the peptide chain itself, which shows for the atoms of the ring an approximate center of inversion (i symmetry).

The flexibility of the ring and consequently the possibility of observing multiple conformations increases with increasing number of residues in the ring system. Then, intraring or transannular interactions, such as hydrogen bonds between N-H and C=O groups, play an important role in stabilizing preferentially one conformation.

Among cyclic peptides, hexapeptides with their 18-membered rings are of special interest, since they are found quite frequently in many biologically important molecules. Literature data show that several significantly different conformations have been experimentally observed; accordingly hexapeptides can be broadly divided in two groups: 1) structures in which the backbone of the peptide chain nearly retains a symmetry element, like a center of symmetry or a two-fold axis (resulting in opposite or equal values, within about 25° to 30°, for the φ and ψ angles of residues i and i+3, respectively). Special cases are represented by cyclic hexapeptides with L,D residues, for which an higher symmetry has been experimentally seen in the solid state as well as in solution.

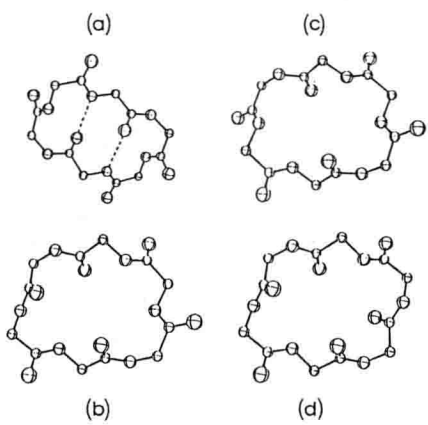


FIG. 4. Four different conformers of cyclo-$(Gly)_6$.

2) asymmetric backbone structure.

The best example which illustrate the above classification is represented by the solid state structure of cyclo-$(Gly)_6$ (11). For this peptide four different conformers, crystallized side by side in the same cell (Figure 4) are

seen, demonstrating in general the flexibility of the ring system for hexapeptides, and furthermore, the existence of multiple conformers is indicative of a very little difference in the energy of such structures.

The most and the least populated conformers of cyclo-$(Gly)_6$ retain in the solid state a center of symmetry as a crystallographic element of symmetry.

The structures of cyclo-$(L\text{-}Ala\text{-}L\text{-}Pro\text{-}D\text{-}Phe)_2$ (12), cyclo-$(Gly\text{-}L\text{-}Pro\text{-}D\text{-}Phe)_2$ (13), cyclo-$(Gly\text{-}L\text{-}Tyr\text{-}Gly)_2$ (14) and cyclo-$(L\text{-}Pro\text{-}L\text{-}Val\text{-}D\text{-}Phe)_2$ (15) exhibit in the solid state either a crystallographic or an approximate C_2 symmetry, as shown in Figure 5).

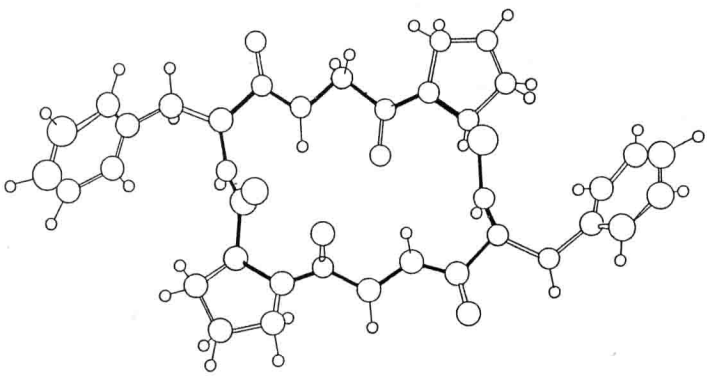


FIG. 5. Molecular structure of cyclo-$(Gly\text{-}Pro\text{-}Phe)_2$.

Finally the structures (16) of cyclo-$(L\text{-}Phe\text{-}D\text{-}Phe)_3$ and cyclo-$(L\text{-}Val\text{-}D\text{-}Val)_3$, are examples of cyclic hexapeptides retaining a center of symmetry or presenting an higher symmetry (S_6 symmetry), respectively.

LINEAR PEPTIDES

A. Relevant Determinants of Secondary Structure

The secondary structure of linear peptides is commonly stabilized by short range atomic interactions in the molecule.

The most important stabilizing factors are the intramolecular hydrogen bonds of the N-H···O=C type. An H-bond between the donor group N-H of residue m and the acceptor group of the residue n is designated as an m--n H-bond. Thus in a system of four linked peptide units, shown in Figure 6, the possibilities of intramolecular H-bond are the 2→2 (or 3→3 or 4→4), the 2→3 (or 3→4), the 2→4, the 3→1 (or 4→2 or 5→3), the 4→1 (or 5→2) and the 5→1. The resulting intramolecular hydrogen-bonded conformations can be also characterized by the number of atoms in the ring obtained by the H-bond formation. Then the above mentioned conformations are called C_5, C_8, C_{11}, C_7, C_{10} and C_{13} conformations, respectively. Among these the more commonly found

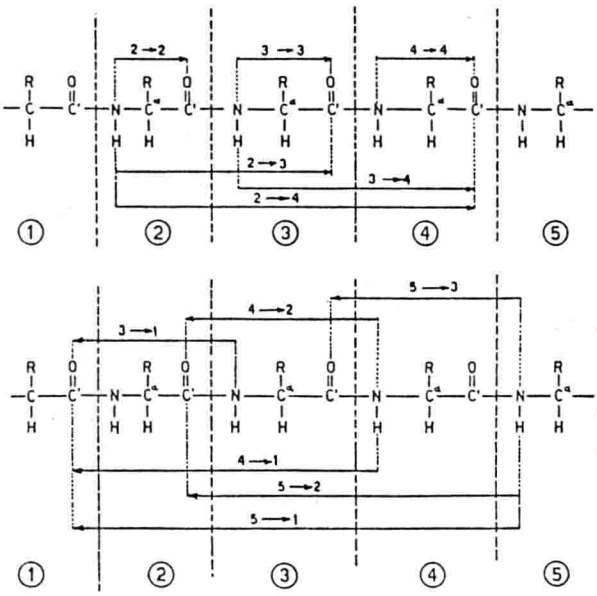


FIG. 6. Possible intramolecular hydrogen bonds occurring in a sistem of four linked peptide residues.

types are the C_{10} and C_{13} conformations. Fewer examples of C_5 and C_7 conformations have also been reported in the literature. With the exception of the 2→2, or C_5 conformation which consists of an intraresidue H-bond, giving rise to an extended conformation, the other types of bonded conformations imply a reversal in the polypeptide chain direction. Consequently an isolated C_7, C_{10} or C_{13} conformation along the peptide chain is also called chain reversal or γ-, β- or α-turn (17) respectively.

The C_5 conformation has been proposed and experimentally seen in a number of peptides (18,19). Most of them are, however, homopeptides derived from α,α-dialkylated glycine residues such as shown in Figure 7.

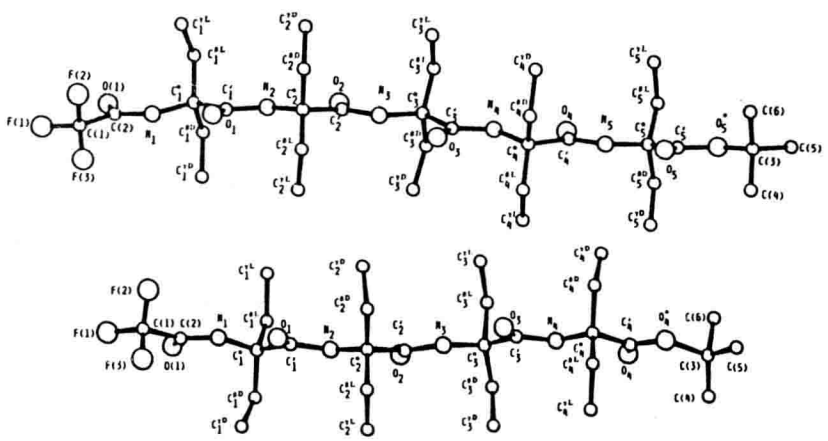


FIG. 7. Structure of TFA-(Deg)$_n$-O<u>t</u>Bu with n = 4, 5.

Glycine or dialkylated glycine residues show the C_5 conformation more than other residues, while the dissymmetry introduced by the side chain consistently increases the warping of these residue.

For a 3→1 C_7 conformation or γ-turn, the planes of the peptide units, preceding and following the central residue, make an angle of about 125°. If the central residue has a chiral C^α atom then two different structures with equatorial and axial side-chains exist depending on the position of the C^α-C^β bond with respect to the intersection line of the two amide planes. For an L-residue at position 2 in an equatorial 3→1 intramolecularly hydrogen-bonded conformation, the torsion angles assume values φ_2=-75, ψ_2=+50 , while they assume opposite values for an axial position of the side chain. Both conformation have been experimentally observed in peptides (20-22).

Among the various intramolecularly hydrogen bonded conformations, the C_{10} forms are the most frequently found in either the solid state or in solution (2,17,23). This bond is characterized by the values of the φ and ψ conformational angles of the central residues at position i+1 and i+2. The formation of the H-bond between the N-H of residue 4 and C=O of residue 1 depends on the relative orientation of three peptides units. Consequently various types of orientations produce different β-bends or C_{10} conformations. Four "standard" β-bends, called type I, II_1, II_3 or III, have been characterized and their φ_{i+1}, ψ_{i+1}, φ_{i+2}, ψ_{i+2} are given in Table I.

Table I. **Dihedral Angles for the "Standard" β-bend of various type.**

β-bend type	φ_{i+1}	ψ_{i+1}	φ_{i+2}	ψ_{i+2}
I	-70	- 35	-70	+35
II_1	-60	+130	+85	+35
II_3	-60	+130	+85	-35
III	-70	- 35	-70	-35

Types I and III have similar φ and ψ values for the i+1 residue, while the values for the i+2 residue are more broadly distributed (they differ mainly by the changed orientation of the third peptide unit). Analogously two forms of type II β-bends can be distinguished, differing by the orientation of the third peptide group. They are labelled II_1 and II_3 according to the structural relations to type I and type III β-bends, respectively. β-Bends are then classified in eight groups (I, II_1, II_3, III and their mirror images).

The intramolecular hydrogen-bonded C_{13} conformation (5→1) occurring between the N-H of the 1+4 residue and the

C=O of the i residue is similar to that occurring in α-helices. In helical structures, however, there is a regular succession of the φ and ψ conformational angles, while in an isolated C_{13} ring structure (or α-bend) a larger flexibility can be observed with a larger variability for the three pairs of the φ, ψ conformational angles of the central residues (i+1, i+2, i+3). Most of the time the trans conformation of the two internal peptide units has been observed. Examples are found in the structures of biologically active peptides and depsipeptides such as β-amanitin (24), valinomycin (25-27), isoleucinomycin (28).

B Helical Structures

If the conformational angles φ, ψ assume the same values for all residues along a peptide chain, then an helical conformation is generated. In the following we will consider only helical structures stabilized by intramolecular H-bonds of the type discussed above.

Thus, we will consider helices in which 3→1, 4→1 and 5→1 H-bonds are the factor stabilizing the conformation, so that they can be visualized as an infinite succession of ring structures (C_7, C_{10}, C_{13}) of the type already discussed. A list of properties and parameters for these helices is given in Table II.

Table II. **Characteristic Parameters of Polypeptide Helical Structures.**

Parameters		2_1-helix	3_{10}-helix	α-helix
Symmetry		2_1	3_1	18_5
Residue Repeat (length per residue in A)		2.75	2.0	1.50
Type of Intramolecular H-bond		3→1	4→1	5→1
Number of Atom in Ring		7	10	13
Conformational Angles for Right-Handed Helices of L-Residues (in degrees)	φ	-80	-60	-55
	ψ	70	-30	-45
	ω	160	180	180
Designation according to Bragg		2_7	3_{10}	3.16_{13}

The 2_1-helices, obtained by a consecutive succession of seven-membered hydrogen-bonded ring structures of the 3--1 type can also be described in terms of symmetry through the operation of a two-fold axis followed by a translation along this axis. This helix, in the Bragg et al. notation (29) is designated as a 2_7 helix, where 2 indicates the symmetry of the helix and 7 is the number of atoms in the H-bonded ring. In the current nomenclature for helices (2_1-helix) 2 stands for the number of units to form a perfect repeat after 1 turn. In principle two helices of this type (left and right-handed)

are possible for a polypeptide chain consisting of all L-residues. For them the position of the C^{β} side chain atom (at position 2 in each successive C_7-ring structure) is equatorial or axial for right- and left-handed helices, respectively. This structure, proposed long time ago, has never been observed in peptides or polypeptides and one of the reason could be the necessity for this helix of substantial systematic deviation from planarity of peptide units.

The 3_{10}-helix can be visualized as a structure consisting of a succession of ten-membered intramolecularly hydrogen-bonded type III β-bend for left-handed and III' β-bend for right-handed helices. Each residue in the peptide chain present values for φ and ψ conformational angles of (-60°, -30°) or (60°, 30°) for right- and left-handed helices, respectively. No substantial distortion from planarity for peptide units seems to be required. In the 3_{10}-helix, 3 residues per turn give rise to an exact three fold symmetry with hydrogen bonds oriented nearly parallel to the triad axis. Peptides containing high percentage of the α,α-dialkylated α-amino isobutyric acid (Aib) (or dimethylglycine), a residue occurring in many microbial peptides, show a structure consisting of successive multiple type III β-bends resulting in incipient 3_{10}-helix (30). Peptides, containing Aib residues, show a very high propensity to fold into 3_{10}- or α-helices with both right- and left-handed twists of the chain.

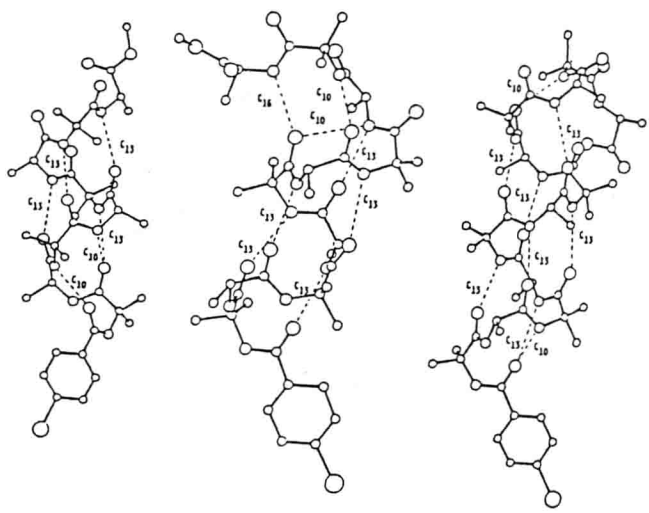


FIG. 8. Structures of Z-(L-Ala-Aib)$_n$-OMe with n = 4, 5, 6.

Among the possible helical structures that peptides and polypeptides can assume, the α-helix is by far the best know. The structure consists of eighteen peptide residues in five turns with all donors (N-H) and acceptors (C'=O) of hydrogen bonds nearly parallel to the helix axis. Successive 5→1 (C_{13}) intramolecularly H-bonds stabilize the structure. According to Bragg et al. (29) the correct nomenclature of the α-helix