INTRAMOLECULARLY HYDROGEN-BONDED PEPTIDE CONFORMATIONS

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I. INTRODUCTION

The object of this article is to review the developments in the field of intramolecularly H-bonded extended and folded conformations in linear and cyclic peptide molecules. The discussion is focused both on model and biologically active peptides. Emphasis is given to solid-state studies, particularly by X-ray diffraction; possible ambiguities in structure assignment as arising from IR absorption spectra are underlined. Conformational energy calculations are also briefly outlined, although most of them have not taken into account fundamental parameters such as presence of solvent. A relatively scarce amount of evidence is given to conformational investigations in solution. In fact, the experimental results obtained using IR absorption, PMR, CMR, and CD spectroscopies, which by far represent the techniques more largely employed in those studies, may give rise to misinterpretations due to intermolecular associations and the simultaneous presence of a variety of species in the conformational equilibrium mixtures. Inherent limitations in the aforementioned techniques often accompanied by an as yet poor knowledge of their theoretical aspects are responsible for the present state of the field. Therefore, it is the opinion of the author that the conclusions derived from those studies should not be accepted uncritically; in this context, conformational investigations using simultaneously all the above techniques should be encouraged. For recent articles complementary to this work which authoritatively review selected topics (i.e., conformational energy calculations, statistical conformational analyses, solid-state or solution conformational preferences of peptide molecules) the reader is referred to References 1 to 26.

A polar hydrogen atom N–H and an oxygen are considered H bonded if the H . . . N distance is less than or equal to 2.3 Å and the N. . .O distance less than or equal to 3.2 Å.

An H bond between N–H of an amino acid sequence number m and C=O of a residue of the sequence number n is designated as $m \rightarrow n$. Therefore, the possible structures in the systems of four linked peptide units taken into account throughout this article are the $2 \rightarrow 2$ (or $3 \rightarrow 3$, or $4 \rightarrow 4$), the $2 \rightarrow 3$ (or $3 \rightarrow 4$), the $2 \rightarrow 4$, the $3 \rightarrow 1$ (or $4 \rightarrow 2$, or $5 \rightarrow 3$), the $4 \rightarrow 1$ (or $5 \rightarrow 2$), and the $5 \rightarrow 1$ intramolecularly H-bonded conformations (Figure 1). On the basis of the number of atoms in the ring formed by closing the H-bond, the aforementioned conformations are also called the C_5, C_8, C_{11}, C_7, C_{10}, and C_{13} conformations. Whereas the C_5 conformation is extended, the others are of the folded type. An alternative nomenclature of common use for the C_7 and

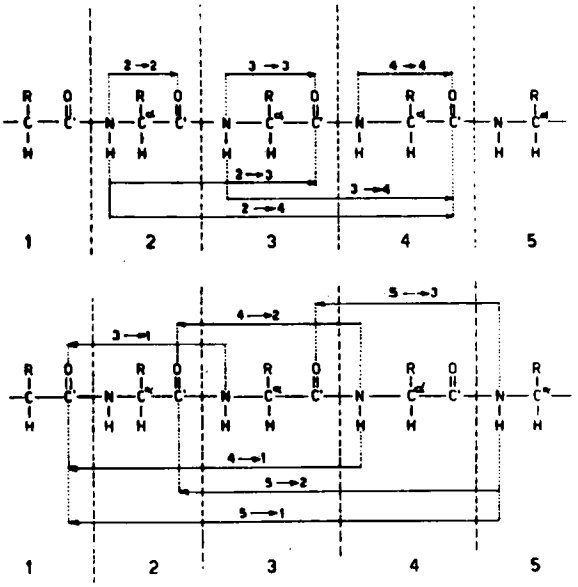

FIGURE 1. The possible intramolecularly H-bonded structures in a system of four linked peptide units.

C_{10} conformations is γ- and β-turn, respectively (the latter has been also referred to as reverse turn, chain reversal, hairpin bend, β-bend, β-twist, β-loop, U-fold). To complete this nomenclature it is proposed here to refer the C_8, C_{11}, and C_{13} folded conformations as to the δ-, ε-, and α-turn, respectively. The C_8, C_{10}, C_{11}, and C_{13} forms should or may include *cis* peptide configurations. Helical conformations (e.g., 2.2, helix, 3_{10} helix, 3.6_{13} helix, or α-helix) and annular structures formed by more than one intramolecular H bond are not considered.

Structures containing bifurcated H bonds and the oxy analogs of the various intramolecularly H-bonded peptide conformations are also discussed. The last section describes intramolecularly H-bonded peptide structures involving a side-chain group, the N-protecting group (in synthetic, linear model compounds), β-amino acids, and N−H. . .π H bonds. For the description of the conformation of polypeptide chains the convention proposed by the IUPAC-IUB Commission on Biochemical Nomenclature in 1969 is followed (Figure 2).

II. THE 2→2 INTRAMOLECULARLY H-BONDED PEPTIDE CONFORMATION

The 2→2 intramolecularly H-bonded peptide conformation is quite similar to the fully extended form ($\phi = \psi = 180°$) (Figure 2). The relative disposition of the two dipoles, N(2)−H(2) and C′(2)=O(2), is such that there is obviously some interaction between them (Figure 3). These four atoms together with the Cᵅ(2) atom are involved in a pentagonal ring, and it is for this reason that this conformation is also called the C_5 structure[11].

The occurrence of this conformation has been proposed in model peptides using mainly IR absorption (the stretching frequency of the corresponding bonded N−H is located near 3420 cm^{-1}) and PMR and an apolar noninteracting solvent such as carbon tetrachloride (at a very low concentration, in order to avoid any self-association of the

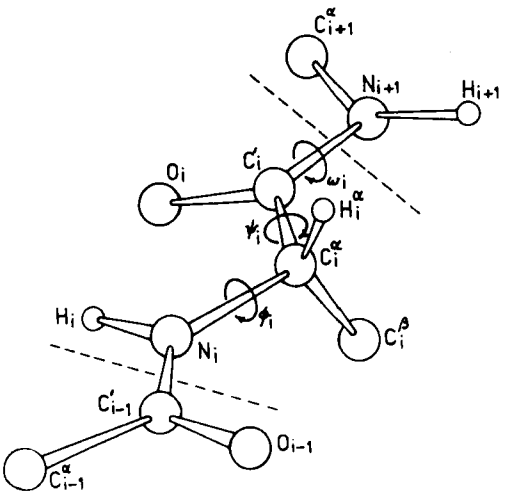

FIGURE 2. Perspective drawing of a section of polypeptide chain representing two peptide units. The limits of a residue are indicated by dashed lines, and recommended notations for atoms and torsion angles are shown. The chain is represented in a fully extended conformation ($\phi_i = \psi_i = \omega_i = +180°$), and the residue illustrated is in the L configuration. (From Toniolo, C., in *Bioorganic Chemistry*, Vol. 3, van Tamelen, E. E., Ed., Academic Press, New York, 1977, 265. With permission.)

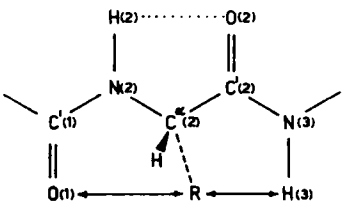

FIGURE 3. Internal steric repulsions that induce the warping of the 2→2 intramolecularly H-bonded (C_5) peptide conformation. (From Toniolo, C., in *Bioorganic Chemistry*, Vol. 3, van Tamelen, E. E., Ed., Academic Press, New York, 1977, 265. With permission.)

solute)[11,12,27-46]. Glycyl derivatives show the highest population of C_5 structure in the conformational equilibrium mixtures if compared to the derivatives of the amino acid residues containing a side chain. The influence of the bulkiness of the side substituent can easily be explained by considering the intramolecular nonbonded interactions between the group R and the atoms H(3) and O(1) as shown in Figure 3. Due to its peculiar geometry, the C_5 conformation of the glycyl derivative is very near to the fully stretched structure; on the contrary, the dissymmetry introduced by increasing the size of the substituent in the derivatives of the amino acid residues containing a side chain induces a consistently increasing warping of these molecules. In addition, when the side chain is not completely "inactive", e.g., in the phenylalanyl, cysteinyl, methionyl, seryl, and homoseryl derivatives, anomalies are observed in the relative stabilization or destabilization of the C_5 conformation (see below the section dealing with intramolecularly H-bonded conformations involving a side-chain group).

It was also shown that in a system of enantiomeric molecules consisting of two linked peptide units (e.g., *N*-acyl aminoacyl *N'*-alkylamides) stereoselective aggregation takes place at higher concentration of the solute in carbon tetrachloride.[43,47-52] The IR absorption and PMR spectroscopic features indicate the occurrence of two kinds of C_5 cyclic dimers associated by two symmetrical and intermolecular H(3) . . . O(1) H bonds. The first one, built around a twofold axis, associates two configurationally identical C_5 conformers, and is called isotactic dimer (Figure 4); the second one associates two enantiomeric C_5 conformers, i.e., it is a syndiotactic and centrosymmetrical dimer (Figure 5), and is more stable in cases involving bulky side chains. The higher stability of the syndiotactic dimer results from the release of the steric hindrance between side chains R as occurring in the isotactic dimer.

An unequivocal verification of the occurrence of this intramolecularly H-bonded

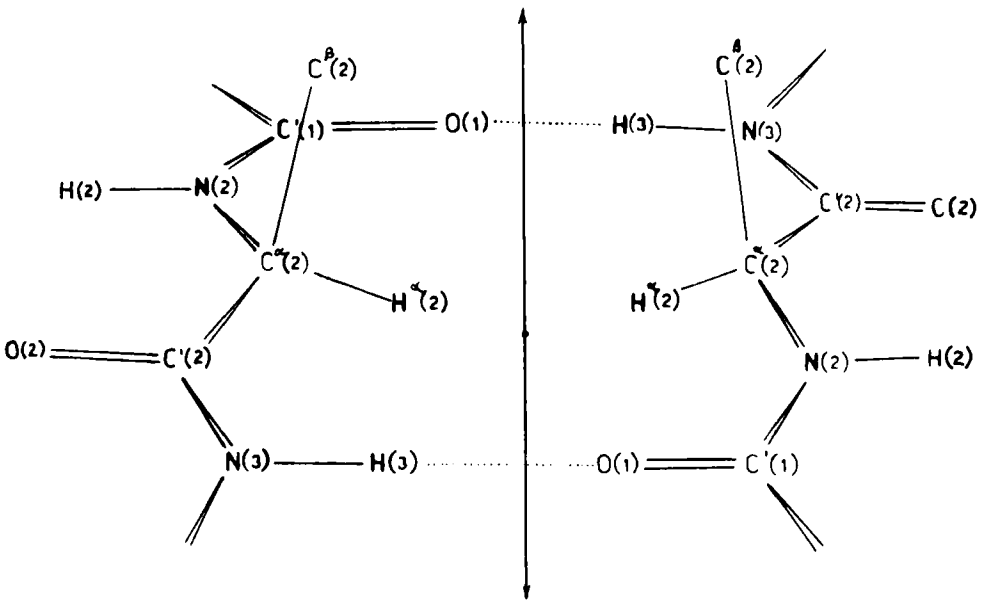

FIGURE 4. Representation of the isotactic cyclic dimer formed by two configurationally identical C_5 peptide conformers.

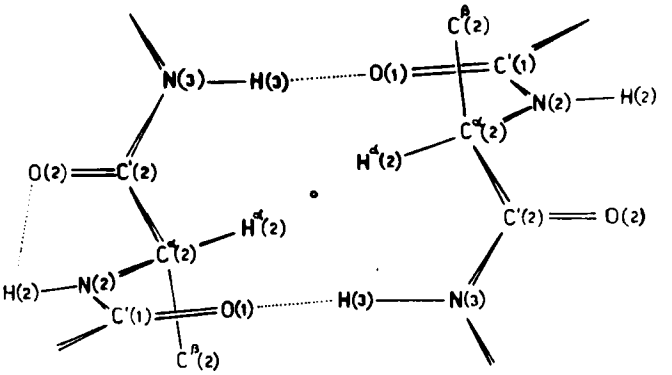

FIGURE 5. Representation of the syndiotactic, centrosymmetrical, cyclic dimer formed by two enantiomeric C_5 peptide conformers.

peptide conformation in the solid state has been obtained in our laboratory in the case of *t*-Boc-Gly-L-Pro-OH (*t*-Boc stands for *tert*-butyloxycarbonyl) using IR absorption and X-ray diffraction.[53] The positions of the urethane N–H stretching and amide I C=O bands have been found at 3417 and 1644 cm^{-1}, respectively, indicating that both groups are H bonded, although not strongly. The X-ray diffraction analysis definitely demonstrated the presence of an intramolecular H bond between the urethane N(2)–H(2) and the amide carbonyl C'(2)=O(2) groups (Figure 6). It is clear that the C_5 H bond is relatively weak: the O(2) . . . H(2) distance (2.13 Å) is near the cutoff for being considered an H bond, and the O(2) . . . H(2)–N(2) angle deviates substantially from linearity; the N(2) . . . O(2) distance is 2.59 Å. The torsional angles observed for the glycyl residue are $\phi_2 = +172°$ and $\psi_2 = +1770°$, very near to the optimal values for a C_5 conformation. The pyramidal character of the nitrogen atoms seems to be very small, if any, since the two ω values are $-179°(\omega_1)$ and $-178°(\omega_2)$, respectively, (*trans* configuration, as it should be for the occurrence of a C_5 structure).

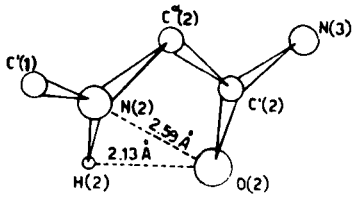

FIGURE 6. The C_5 conformation of the gycyl residue in *t*-Boc-Gly-L-Pro-OH.

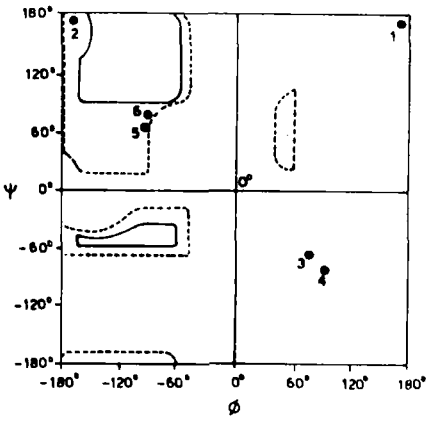

FIGURE 7. Ramachandran conformational map showing the ϕ, ψ torsional angles of the known C_5 and C_7 peptide conformations (1, C_5Gly; 2, C_5Gly; 3, C_7Aib; 4, C_7D-Pro; 5, C_7L-Ala; 6, C_7L-Pro).

Two other examples of C_5 structure in the solid state have been reported. The compounds examined are Pe-3-CO-Gly-NH*i*Pr (Pe-3 stands for *n*-pentyl-3, and *i*Pr for *iso*-propyl)[54] and *t*-Boc-Gly-L-Ala-OH[55]: in the latter case the alanyl residue, not the glycyl one, is involved in the intramolecular chelate.

The Pe-3-CO-Gly-NH*i*Pr molecule is quasi-extended ($\phi = -169°$ $\psi = +175°$) with almost planar *trans* amide groups ($\omega_1 = +176°$, $\omega_2 = +179°$). The two peptide bonds are almost coplanar, the corresponding dihedral angle being 9°. The N(2) . . . O(2) distance is 2.72 Å. The H(2) atom is also involved in an intermolecular H bond.

The form of *t*-Boc-Gly-L-Ala-OH is of the V type, unusual for a dipeptide molecule. The H(2) . . . . O(2) and N(2) . . . . O(2) distances are 2.09 and 2.61 Å, respectively. The O(2) . . . . H(2)–N(2) angle is 113.4°. The Ramachandran map[1] showing the ϕ,ψ torsional angles of the known C_5 structures is illustrated in Figure 7.

Not surprisingly, these three examples of C_5 structure have been found in the most favorable cases, i.e., in glycyl and alanyl derivatives. In this context, an X-ray diffraction investigation of the existence of the C_5 structure stabilized by a further intramolecular interaction involving a side-chain group would be of special interest. Also, the application of other techniques, e.g., Raman spectroscopy,[56] to the characterization of the C_5 structure, should be encouraged. Finally, it should be mentioned that the presence of the five-membered-ring structure has been considered in conformational energy calculations[5,57-70] and proposed as an important feature of more complex conformations in solution involving intramolecularly bifurcated H bonds (see section below).

III. THE 3→1 INTRAMOLECULARLY H-BONDED PEPTIDE CONFORMATIONS

The 3→1 intramolecularly H-bonded peptide conformations (also called C_7 forms, γ-turns) are ring structures that are folded by an H bond between the H(3) and O(1) atoms, as shown in Figure 8. The *trans* amide groups lie in two planes, which make an angle of about 115°. When R in –NH–CHR–CO– is not an H atom, two different conformers (equatorial and axial) can exist which are represented on the usual conformational map[1] by two centrosymmetric points, the coordinates of which (for an L-

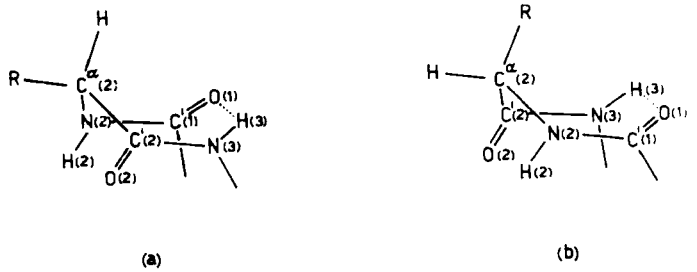

FIGURE 8. The equatorial (a) and axial (b) 3→1 intramolecularly H-bonded (C_7) peptide conformations (γ-turns). (From Toniolo, C., in *Bioorganic Chemistry*, Vol. 3, van Tamelen, E. E., Ed., Academic Press, New York, 1977, 265. With permission.)

residue) are $\phi = -75°$, $\psi = +50°$ (for the equatorial form) and $\phi = +75°$, $\psi = -50°$ (for the axial form).[11] While the H bond is strongly bent it has a normal H···O distance, and it still makes a sizable contribution to the stabilization of the folded structures. Actually, some variation of the values ($|\Delta\omega| \simeq 10°$) is necessary for the stabilization of the 3→1 intramolecularly H-bonded peptide conformations. However, as already noted, the small energy of torsional rotation is more than compensated for by the energy of the H bond.[71]

The 3→1 H bond has been demonstrated in the crystal state in the natural cyclotetrapeptide dihydrochlamydocin, which contains peptide units that are considerably less planar than have been observed in other peptides.[72] In particular, the ω angles for the Aib and D-Pro residues involved in the two 3→1 intramolecularly H-bonded forms are +162° and −156°, respectively (the torsional angles for the Aib residue are $\phi = +72°$, $\psi = -65°$, respectively, and those for the D-Pro residue are $\phi = +82°$, $\psi = -73°$, respectively). The N . . . O distances are 2.82 and 2.92 Å, respectively (Figure 9).

A further example of a 3→1 intramolecular H bond in a crystal has been shown in the case of the cyclic undecapeptide cyclosporin A.[73] The amino acid residue involved is L-Ala[7] ($\phi = -92°$, $\psi = +64°$, $\omega = -166°$). Interestingly, cyclosporin A contain a *cis*-amide bond linking the MeLeu[9]-MeLeu[10] residues.

An L-Pro residue is involved in the C_7 conformation present in *c*-(Gly-L-Pro-Gly-D-Ala-L-Pro)- in the crystal state ($\phi = -86°$, $\psi = +70°$, $\omega = -160°$)[74,75]. The H . . . O separation is 2.25 A and the N−H . . . O angle is near 121°. Figure 7 shows the ϕ,ψ angles of the known C_7 peptide conformations in the Ramachandran map.

In proteins in the solid state the C_7 conformation has been found only in thermolysin, involving an L-Thr residue,[76] and in horse heart ferricytochrome C,[77] involving the sequence -L-Pro[44]-Gly.[45] In this context, it is of interest that it has been demonstrated by X-ray diffraction that Ac-L-Pro-NHMe,[78] Ac-Aib-NHMe,[28] Ac-L-Ala-NHMe,[79] and Ac-Gly-NHMe[80] do not adopt the C_7 form in the solid state. An X-ray diffraction investigation of the model compound Ac-L-Thr-NHMe should be rewarding.

The occurrence of the 3→1 intramolecularly H-bonded forms in solution has been proposed by several groups using mainly IR absorption, NMR, and CD measurements. (See References 11-13, 17, 26-31, 35-39, 43-45, 47-52, 54, 56, 70, and 81-146.) In the case of derivatives of trifunctional amino acid residues these folded conformations can be relatively stabilized or destabilized by additional intramolecular side-chain/main-chain interactions (see section below).

The 3→1 intramolecularly H-bonded peptide forms have been considered in conformational energy calculations of model and naturally occurring peptides, such as luli-

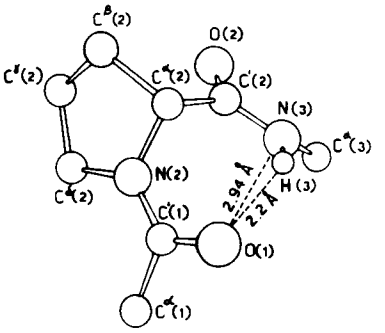

FIGURE 9. The C_7 conformation of the D-Pro residue in dihydrochlamydocin.[8,72]

berin, thyroliberin, melanostatin, angiotensin II, malformin A, and valinomycin. (see References 1, 3, 5, 17, 34, 57-69, 139, 140, 143, 144, and 147-193. Other examples of these folded structures are discussed below in the sections dealing with intramolecularly bifurcated H-bonded peptide conformations and intramolecularly H-bonded forms involving a side-chain group.

IV. THE 2→3 INTRAMOLECULARLY H-BONDED PEPTIDE CONFORMATION

No detailed studies on the 2→3 intramolecularly H-bonded peptide conformation have yet appeared in the literature.[10] This type of folded form (δ-turn, C_8 form) has been considered not possible for allowed conformations by Venkatachalam[194] and Ramachandran and Sasisekharan[1]; the possibility of occurrence of this conformation has also been discarded by Urry et al.[195] for the pentapeptide model of elastin having the sequence L-Val-L-Pro-Gly-L-Val-Gly.

However, from examination of molecular models and an analysis of data from *N*-acetyl-*N'*-methyl dipeptides,[196] it appears that the existence of an eight-membered-ring peptide form, although unlikely, is not impossible. In fact, if the configuration of the central amide group in Figure 10 is taken as *cis* and those of the first and third amide groups as *trans*, it is possible to build this H-bond with the N . . . . O distance within the ideal values (≃ 3.0 Å). In the case of the sequence -Gly-L-Pro- the most favorable dihedral angles are $\phi_2 = +173°$, $\psi_2 = +85°$, $\phi_3 = -75°$, $\psi_2 = +167°$. In addition, if the value of the central amide group is allowed to vary, a consistent stabilization of the structure is achieved when $\Delta\omega$ is in the range of 10 to 15°. Nonplanar deformation of the amide unit (in the *trans* configuration) with $|\Delta\omega|$ up to 15° has been recently shown to be quite probable, since the energy increase for such deviations from planarity are only of the order of 0.5 kcal/mol;[71] also, nonplanar distortions at the nitrogen atom of the peptide unit have been observed in the solid state in cyclic peptides having *cis*-amide bonds.[8] Permitting some bending of bond angles would distribute the energy of distortion value over several smaller values. Crystallograpic studies on medium-ring lactams carried out by Dunitz and co-workers showed that in the case of enantholactam the eight-membered ring is not large enough to accommodate the torsion angle of approximately 180° of the *trans*-amide configuration. The constraints of the geometry of the eight-membered ring force the amide in the *cis*-configuration with both N–H and C=O groups pointing outward[197].

In principle, a relatively high probability of occurrence of this new type of reverse

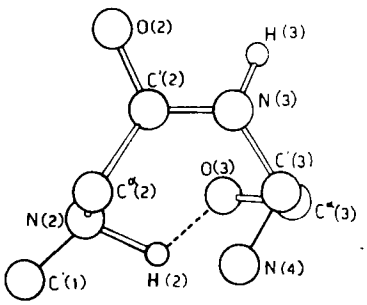

FIGURE 10. The 2→3 intramolecularly H-bonded (C_8) peptide conformation (ά-turn). The central amide group is in the *cis* configuration.

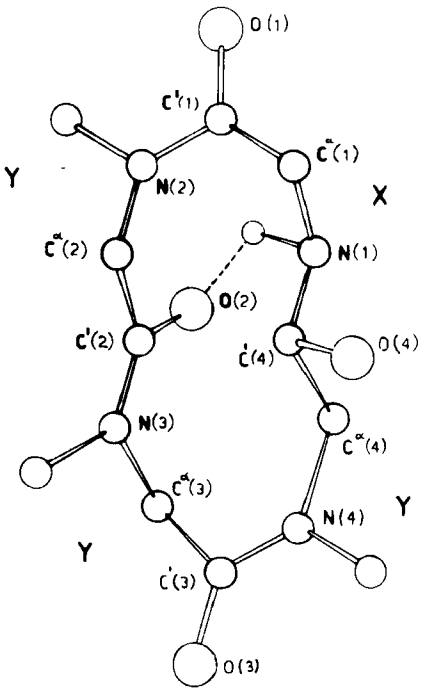

FIGURE 11. Model of a cyclopeptide of the type *c*-(X-Y_3)- with the amide configuration sequence *cis-trans-cis-trans* containing a C_8 conformation (ά-turn).

turn exists in the case of cyclotetrapeptides of the sequence *c*-(X-Y_3)- (where X = α-amino acid residue, and y = *N*-alkyl-α-amino acid residue) (Figure 11). From the low-temperature PMR spectrum of cyclotetrasarcosyl it was concluded that there is only one conformer in solution and that by symmetric arguments the amide configuration sequence had to be *cis, trans, cis, trans.*[198] This was subsequently confirmed for the crystal.[199] Thus if an intramolecular H-bond is present in the *c*-(X-Y_3)- molecule (with the aforementioned amide configuration sequence, the −NH−CO− group being in the *trans* configuration and the −NR−CO− group of the central *N*-alkyl-α-amino acid residue also in the *trans* configuration), it can give rise only to a conformer containing an eight-membered ring, in addition to a *cis* ten-membered ring (see below). A recent X-ray diffraction study revealed that in the solid state the *c*-(Gly-Sar_3)- and *c*-(DL-Ala-Sar_3)- molecules indeed adopt the *trans-, cis-, trans-, cis*-amide configuration sequence.[200] However, the single N−H group of each molecule is not involved in intramolecular H bonding, but is bonded to a neighbor molecule. The occurrence of intramolecular H bonding has been excluded for these molecules also in chloroform solution.[201,202] It should be mentioned, however, that only slight rotations of the ring torsional angles are required for turning from the observed conformation to that involving the eight-membered-ring intramolecularly H-bonded peptide structure. It is possible that such a conformation would exist in solvents of lower polarity at higher dilutions. Two intramolecular H bonds have been found in the solid state in the naturally occurring cyclotetrapeptide dihydrochlamydocin (this peptide is of the type *c*-(X_3-Y)-,[8,72] giving rise to two 3→1 intramolecularly H-bonded peptide structures (see above). But in this compound the amide configuration sequence is *all-trans*, a new observation for a cyclic tetrapeptide.

It is also possible that the 2→3 intramolecularly H-bonded peptide conformation would exist in linear peptides in a solvent such as carbon tetrachloride at a very low concentration. Fully protected dipeptides of the type -X-Y-appear to be the major candidates. Experimental investigation on such compounds are continuing in our laboratory, even though a preliminary IR absorption study in carbon tetrachloride at high dilution of *N*-acyl-L-valylsarcosine methyl esters have indicated the absence of this folded form.[203]

Recently, Urry[144] has carried out energy calculations of the various intramolecularly H-bonded forms of *N*-acetyl-L-valyl-glycine methyl ester incorporating the effect of solvent. It was found that in carbon tetrachloride solution various conformers, including the C_8 one, may co-exist. In addition, according to Urry, ^1H, ^{13}C, and ^{15}N NMR studies of the protected dipeptide in deuterochloroform have argued for the occurrence of the C_8 form.

Several groups of workers, independently, have suggested the occurrence of the C_8 form in aqueous solution (pH > 6) to explain their ^1H and ^{13}C NMR, and IR absorption data on small linear peptides.[204-209] In these cases a charged species (the carboxylate ion) is often involved as the H-acceptor; the H-donor is either an ammonium or an amide N−H group.

Finally, it should be mentioned that the molecular conformation in the solid state of an eight-membered ring in peptide molecules (but without intramolecularly H-bonds) has been obtained by X-ray diffraction analysis of the cyclic sulfide from the dipeptide L-cysteinyl-L-cisteine.[210,211] The amide group is in the *cis*-configuration ($\omega \simeq 10°$) with both N−H and C=O groups pointing outward. It is evident that further theoretical and experimental work is required before a detailed picture of the δ-turn can be established.

V. THE 4→1 INTRAMOLECULARLY H-BONDED PEPTIDE CONFORMATIONS

Venkatachalam[194] was the first to characterize three types (*trans* I—III) of the 4→1 intramolecularly H-bonded folded peptide conformation (also called C_{10} form, β-turn, etc.) where there is an H-bond between the C=O group of residue 1 and the N−H group of residue 4 (Figure 12). The type-I bend has $\phi_2 = -60°$, $\psi_2 = -30°$ and $\phi_3 = -90°$, and $\psi_3 = 0°$, while the type-II bend has $\phi_2 = -60°$, $\psi_2 = 120°$ and $\phi_3 = 80°$, and $\psi_3 = 0°$. They are interrelated by rotation of 180° in the second peptide group, so the oxygen atom is directed into the plane for type I and out of the plane for type II. The type-III bend has $\phi_{2,3} = -60°$ and $\psi_{2,3} = -30°$, thus being part of one turn of the 3_{10} helix. Obviously, bends type I′, II′, and III′ also exist, where the prime superscript indicates that the given bend is the mirror image of the corresponding unprimed one except, of course, for the positions of the C^β and other atoms of the side chains. For the H-bond to remain intact only certain side-chain groups may be accommodated at $C^\alpha(2)$ and $C^\alpha(3)$.

All three types of the *trans* C_{10} folded conformation have been found in crystals of synthetic and naturally occurring linear and cyclic oligo- and depsipeptides according to X-ray diffraction analyses (Table 1). Curiously, only if an α,α-dialkyl amino acid residue (Aib) is present will the type-III bend occur. Globally, about 40 different compounds have been found to contain about 80 C_{10} folded forms.[8,9,14,54,73-75,212-248] The shortest linear compounds containing the C_{10} form are N- and C-protected di-[54,213] and monodepsipeptides;[54,213] the smallest cyclic compounds containing the C_{10} form are cyclopentapeptides.[227]

Recently, Chou and Fasman[6,249] utilized X-ray atomic coordinates from 29 proteins of known sequence, the structures of which were published during the period of 1968

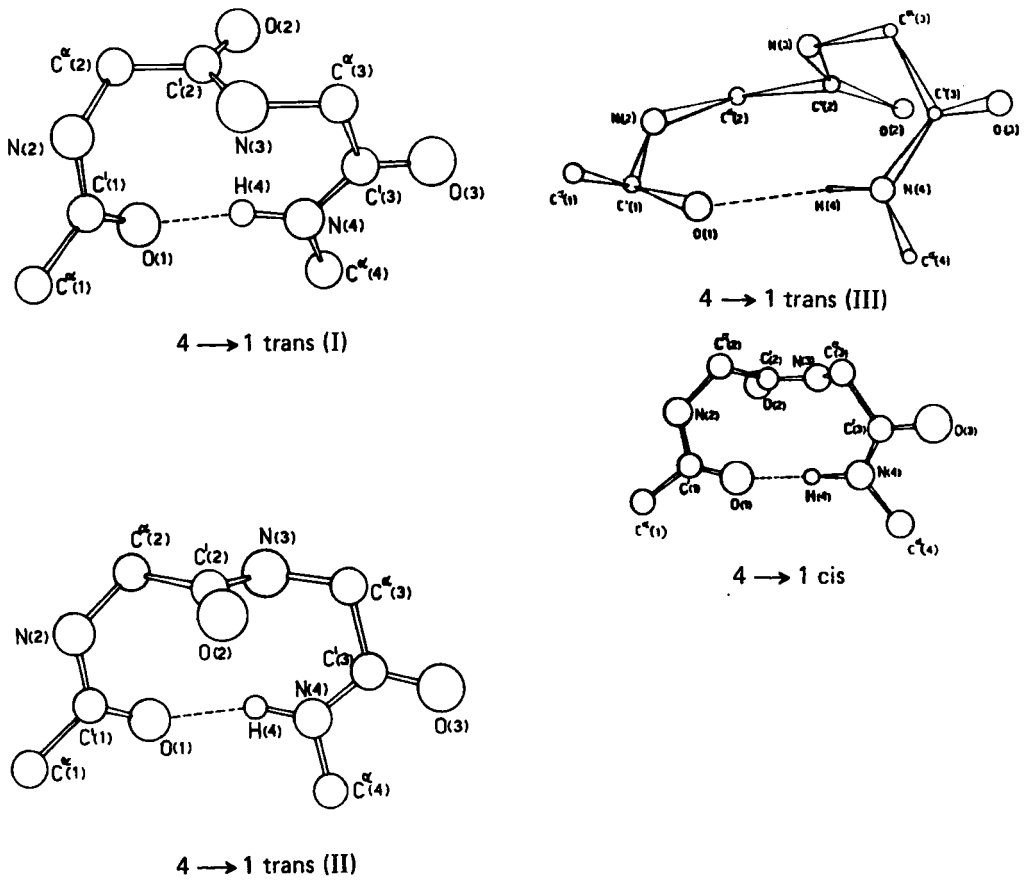

FIGURE 12. The four types of the 4→1 intramolecularly H-bonded (C_{10}) peptide conformation (β-turn).

to 1975, to elucidate 220 *trans* 4→1 intramolecularly H-bonded peptide conformations in regions of chain reversal. In the proteins examined the average frequency of *trans* β-turns is about 30%, as compared to the 38% helices and 20% β-sheets. The most frequently occurring bend residues are Asn, Cys, and Asp in the first position; Pro, Ser, and Lys in the second position; Asn, Asp, and Gly in the third position; and Trp, Gly, and Tyr in the fourth position. Residues with the highest β-turn potential in all four positions are Pro, Gly, Asn, Asp, and Ser, with the hydrophobic residues (i.e., Val, Ile, and Leu) showing the lowest bend potential. The C_{10} folded forms in proteins are stabilized by antiparallel β-sheets as well as α-β interactions. A survey of residues occupying bend types I′, II′, and III′ showed that Gly appeared most frequently in the third position in bend types I′ and III′, as well as in the second position in bend types II′ and III′. Contrary to Venkatachalam's calculations[194] 14 type-II bends were found without a Gly at the third position. (Analogous cases elucidated in oligopeptides are listed in Table 1). References 250 to 275 contain specific comments on the C_{10} folded conformations found in proteins, the three-dimensional structures of which have been reported in the literature from 1975 to 1978 (i.e., those published too recently to be considered by Chou and Fasman[6,249] in their statistical calculations).

It is evident that among the various intermolecularly H-bonded folded conformations the *trans* C_{10} ones have been by far the most frequently found in peptides and proteins in the solid state. The exploding interest for these fundamental bend confor-

Table 1
TRANS β-BENDS FOUND IN SYNTHETIC AND NATURALLY OCCURRING LINEAR AND CYCLIC OLIGOPEPTIDES

Compound	Residues in position 2 and 3	Type	N . . . O (Å)	Ref.
Ac-L-Pro-L-Ala-NHMe	L-Pro-L-Ala	II	3.05	54
Ac-L-Pro-D-Ala-NHMe	L-Pro-D-Ala	II	3.10	54
*i*BuCO-L-Pro-L-Ala-NH*i*Pr	L-Pro-L-Ala	II	3.05	212
*i*BuCO-L-Pro-D-Ala-NH*i*Pr	L-Pro-D-Ala	II	3.10	212
Ac-L-Pro-L-Lac-NHMe	L-Pro-L-Lac	I	2.89	54, 213
Ac-L-Pro-D-Lac-NHMe	L-Pro-D-Lac	II	2.97	54, 214
t-Boc-L-Pro-L-Leu-Gly-OH	L-Pro-L-Leu	I	2.95	215[a]
t-Boc-L-Pro-L-Pro-Gly-NH_2	L-Pro-L-Pro	I		215
H-L-Pro-L-Leu-Gly-NH_2	L-Leu-Gly	II	3.04	216
t-Boc-L-Pro-Aib	L-Pro-Aib	III	2.97	217
L-Ala-Aib-OH	Aib-L-Ala	I	3.09	
H-L-Cys(Bzl)-L-Pro-L-Leu	L-Pro-L-Leu	I	3.02	218, 219
-Gly-NH_2	L-Pro-L-Leu	I	3.08	
	L-Leu-Gly		3.13	
H-L-SeCys(Bzl)-L-Pro-LL-Pro-L-Leu	L-Pro-L-Leu	I	3.00	218, 219
-Gly-NH_2	L-Pro-L-Leu	I	2.97	
	L-Leu-Gly		3.20	
(*p*-Br)Z-Gly-L-Pro-L-Leu-Gly-OH	L-Pro-L-Leu	I	2.97	220
Z-Aib-L-Pro-Aib-L-Ala-OMe	Aib-L-Pro	III	3.16	221
	L-Pro-Aib	I, III	3.06	
H-L-Tyr-Gly-Gly-L-Phe-OH	Gly-Gly	I		222
Z-Gly-L-Pro-L-Leu-Gly-L-Pro-OH	L-Pro-L-Leu	I		215[a]
(*o*-Br)Z-Gly-L-Pro-L-Leu-Gly-L-Pro-OH	L-Pro-L-Leu	I	3.00	223
c(Gly-L-Pro-Gly-D-Ala-L-Pro)	L-Pro-Gly	II	2.87	74,75
c(Gly_6)	Gly-Gly	I	2.96	224
	Gly-Gly	I′	2.96	
c(Gly_4-D-Ala_2)	Gly-Gly	I	3.04	225
	D-Ala-D-Ala	I′	3.16	
c(L-Ala-L-Pro-D-Phe)$_3$	L-Pro-D-Phe	II	3.20	226
	L-Pro-D-Phe	II	3.20	
c(L-Ala-L-Ala-Gly-Gly-L-Ala-Gly)	L-Ala-L-Ala	I	2.92	227
c(L-Ala-L-Ala-Gly-	L-Ala-Gly	I′	3.10	227
L-Ala-Gly-Gly)	L-Ala-L-Ala	I	2.99	
[Leu^5]Enkephalin	Gly-Gly	I′		228
Tuberactinomycin O	L-Ser-U Δ Ala	I	2.95	229
Tuberactinomycin N		I		215
Viomycin	L-Ser-U Δ Ala	I		230
Ferrichrome A	L-Ser-Gly	II	2.98	231
Ferrichrisin	L-Ser-Gly	II	3.15	232
Li$^+$-Antamanide	L-Ala-L-Phe	I	3.05	233, 234
	L-Phe-L-Phe	I	3.00	
Na$^+$[Phe^4,Val^6]Antamanide	L-Phe-L-Phe	I	3.18	233, 235
	L-Phe-L-Phe	I	3.29	
β-Amanitin	L-Ile-Gly	II	2.85	236, 237
Sporidesmolide	L-MeIle-D-Hyv	I′	3.03	238, 239
	L-MeIle-D-Hyv	I′	2.98	
c(D-Val-L-Hyv-	L-Val-D-Hyv	II		240
L-Val-D-Hyv)$_3$	L-Val-D-Hyv	II		
	L-Val-D-Hyv	II		
	D-Val-L-Hyv	II′		
	D-Val-L-Hyv	II′		
	D-Val-L-Hyv	II′		

Table 1 (continued)
TRANS β-BENDS FOUND IN SYNTHETIC AND NATURALLY OCCURRING LINEAR AND CYCLIC OLIGOPEPTIDES

Compound	Residues in position 2 and 3	Type	N . . . O (A)	Ref.
Valinomycin	L-Val-D-Hyv	II	2.88	241, 242
	L-Val-D-Hyv	II	3.10	
	D-Val-L-Lac	II′	2.81	
	D-Val-L-Lac	II′	2.96	
	L-Val-D-Hyv	II	2.87	
	L-Val-D-Hyv	II	3.06	
	D-Val-L-Lac	II′	2.82	
	D-Val-L-Lac	II′	2.98	
	L-Val-D-Hyv	II	2.85	
	L-Val-D-Hyv	II	3.06	
	D-Val-L-Lac	II′	2.83	
	D-Val-L-Lac	II′	2.98	
	L-Val-D-Hyv	II	3.07	244
	L-Val-D-Hyv	II	2.90	
	D-Val-L-Lac	II′	2.86	
	D-Val-D-Hyv	II′	2.99	
	L-Val-D-Hyv	II	3.06	
	L-Val-D-Hyv	II	2.90	
	D-Val-L-Lac	II′	2.81	
	D-Val-L-Lac	II′	2.99	
K^+-Valinomycin	D-Val-L-Lac	II′		243
	L-Val-D-Hyv	II		
	D-Val-L-Lac	II′		
	L-Val-D-Hyv	II		
	D-Val-L-Lac	II′		
	L-Val-D-Hyv	II		
	D-Val-L-Lac	II′		245
	L-Val-D-Hyv	II		
	D-Val-L-Lac	II′		
	L-Val-D-Hyv	II		
	D-Val-L-Lac	II′		
	L-Val-D-Hyv	II		
Cyclochlorotine	L-diCl Pro-L-Abu	I		246
Iodo-cycloclosporin A	Sar-L- MeLeu			73

Note: (Ac), acetyl; (-NHMe), methylamide; (*i* BuCO), *iso* butyrylcarbonyl; (-NH*i* Pr), *iso* propylamide; (Lac), lactic acid; (*t*- Boc), *tert* -butyloxycarbonyl; [Cys(Bzl)], S-benzyl cysteine; [SeCys(Bzl)], selenium analog of S-benzyl cysteine; [(*p* -Br)Z], *para* -bromo-benzyloxycarbonyl; (Z), benzyloxycarbonyl; (OMe), methoxy; [*o* -Br)Z], *ortho* -bromo-benzyloxycarbonyl; (UΔAla), 3-ureido-dehydroalanine; (MeIle), N-methyl isoleucine; (Hyv), α-hydroxy-valeric acid; (diCl-Pro), 3,4-dichloroproline; (MeLeu), N-methyl leucine.

• Locally cited.

mations is also testified by the extremely large body of papers dealing with statistical analysis, conformational energy calculations, and model building of peptides and proteins. (See References 1-4, 6, 17, 18, 24, 34, 57, 58, 61, 62, 65, 68, 107, 137, 139, 140, 148, 149, 154, 160-162, 165-167, 171, 179, 180, 190, 192-194, 249 and 276-368.)

As far as the former compounds are concerned, investigations have suggested the possible occurrence of the *trans* C_{10} forms in α-amanitin, gramicidin *S*, tuftsin analogs, valinomycin, enkephalin, luliberin, thyroliberin, somatostatin, melanostatin, angiotensin II, oxytocin, glucagon, biologically active fragments of growth hormone, relaxin, insulin, proinsulin, proinsulin C-peptide, prohormones → hormones conversion, fibrinogen-like peptides, repeat peptides as models of tropoelastin, N- and C-protected model di- and tripeptides, sequential polydepsipeptides, and model cyclopenta-, cyclohexa-, and cylodecapeptides.

In proteins the *trans* C_{10} forms have been shown to represent an important factor in the mechanism of folding, e.g., in the formation of the antiparallel β-structure, in controlling glycosylation, phosphorylation and hydroxylation reactions, aggregation tendency, neurotoxicity, immunogenicity, thermophilic properties, and repressor-operator complexation.

Due to space limitations the immense literature of conformational investigations of the *trans* C_{10} forms in solution is not examined here. The author's opinion reported in the Introduction to this article seems to be particularly pertinent to the present case. The *trans* C_{10} forms are also discussed below in the sections dealing with intramolecularly bifurcated H-bonded peptide conformations and intramolecularly H-bonded forms involving a side-chain group.

The most unusual type of 4→1 intramolecularly H-bonded peptide form is that having the central amide group in the *cis*-configuration (Figure 12). It is obvious that in this structure, as in the *trans*-structures, the terminal amide groups are in the *trans* configuration. Model building indicates that because of the dimensions of the ring generated by the 4→1 intramolecular H bond, only one type of *cis*-peptide ring structure exists, i.e., that with both C=O and N−H bonds of the central amide group pointing outward.

Studies in which the 4→1 intramolecularly H-bonded *cis*-peptide conformation is discussed are rare.[6,161,369-373] No conformational energy calculations have been carried out for bends of this type. Chain reversals with bonds in the *cis* configuration have been found in proteins:[6,161,253,369] in six of them (all of the X-Pro type) an intramolecular H-bond is present.[6] It would be worthwhile for the crystallographers to reexamine the bend regions in proteins for possible elucidation of additional *cis* C_{10} forms. The only two cases where *cis* 4→1 intramolecularly H-bonded structures have been definitely demonstrated to occur in the solid state in oligopeptides are represented by the cyclic heptapeptide ilamycin B_1[370] and the cyclic hexapeptide bouvardin,[371] as shown by recent X-ray diffraction studies.

In ilamycin B_1 the amide bonds connecting residues 2 and 3, and 6 and 7 are both *cis*, as seen from the values of ω angles ($\omega_2 = -11°$ and $\omega_6 = +1°$, respectively) and serve to fold the peptide chain to form a cyclic structure.[370] It should be noted that both residues 3 and 7 are *N*-methyl-L-leucine, an N-substituted amino acid. Two intramolecular H bonds [N(4) . . . . O(1) of 2.98 Å and N(1) . . . . O(5) of 2.80 Å] stabilize the conformation. The torsional angles are $\phi_2 = -61°$, $\psi_2 = +126°$; $\phi_3 = -121°$, $\psi_3 = +38°$; $\phi_6 = -86°$, $\psi_6 = +117°$; and $\phi_7 = -128°$, $\psi_7 = +99°$.

A 300-MHz PMR study of this molecule, on the basis of the H⇌D exchange rate of amide hydrogen atoms at room temperature, indicated that the exchanges of H(1), H(4), and H(5) took several days, whereas those at H(2) and H(6) took only a few hours.[370] As is clear from the solid-state structure,[370] only H(1), H(4), and H(5) turn to inside of the molecule, which causes a strong interaction with the carbonyl oxygen

atoms, and the change rate of these hydrogen atoms should consequently be reduced. It appears that this conformation is only slightly solvent dependent.

In bouvardin the single *cis* peptide bond involves the two modified *N*-methyl-L-tyrosines in position 5 and 6 ($\omega = -8°$).[371] Even with a *cis* amide bond, molecular models indicate that the 14-membered nonpeptide ring, which also contains a *para*- and a *meta*cyclophane annular system, possesses some angle strain and very little flexibility; e.g., this strain is exemplified by the expanded angles $C^{\alpha}(6)-N(6)-C'(5)$ and $N(6)-C'(5)-C^{\alpha}(5)$ which are 124.8 and 123.5°, respectively. On the other hand, models suggest considerable flexibility in the 18-membered ring of the cyclic hexapeptide part of the molecule. The weak intramolecular H-bonding connects the amide carbonyl oxygen O(4) to the amide N–H hydrogen of residue 1 [N(1) . . . . O(4): 3.2 Å]. An additional stabilizing force is provided by a further intramolecular H-bond involving the β-hydroxyl group of residue 5 with the amide carbonyl oxygen O(5) (for this side-chain/main-chain H-bond see the pertinent section below). The torsional angles are $\phi_5 = -121°$, $\psi_5 = +101°$ and $\phi_6 = -84°$, $\psi_6 = +165°$. It should be mentioned that a previous NMR investigation[143] has demonstrated that cyclohexapeptides of the types c-(Gly-L-Pro-L-X)$_2$ display in solution the above nonsymmetric conformation containing a single *cis* Gly-L-Pro bond. When valine is the X residue, the results indicate that in dimethylsulfoxide solution this conformer is largely favored. However, no intramolecular H bond is present, since the solvent employed is a strong H-bond acceptor.

A further example of a 4→1 intramolecularly H-bonded *cis*-peptide form has been recently proposed as occurring in solution in the cyclic nonapeptide cyclolinopeptide A.[372,373] An NMR investigation has indicated the occurrence of (1) an intramolecular H-bond between the N–H hydrogen of the Phe[3] residue and the amide carbonyl oxygen of the Val[9] residue, and (2) a *cis*-peptide bond between Pro[2] and Pro[3] residues. Interestingly, formation of the K^+ complex does not appear to change the conformation of the peptide chain. The single-crystal X-ray investigation of this peptide[374] will show whether this conformer is that present in the solid state.

Thus, the observation of the *cis* 4→1 intramolecularly H-bonded form in three cyclic compounds (in one of them so far only in solution) and in six bend regions in proteins indicates that this also could be an important structural element in peptide molecules (see also the above discussion of the possible occurrence in c-(X-Y$_3$)- of the 2→3 intramolecularly H-bonded peptide conformation, which is automatically accompanied by a *cis* C_{10} conformation if the amide configuration sequence is *cis, trans, cis, trans*). Studies aiming to reveal this folded form in linear peptides should also be strongly encouraged.

VI. THE 2→4 INTRAMOLECULARLY H-BONDED PEPTIDE CONFORMATIONS

The C_{11} conformations (ε-turns) are found in reversals of the polypeptide chain where an intramolecular H-bond between the amide proton of the i unit and the carbonyl oxygen of the $i + 2$ unit is formed. Several types of ε-turns can exist, depending upon the configuration of the two peptide groups (ω angles) internal of the annular structure and φ, ψ torsional angles (Figure 13).

Interestingly, these ring forms are the smallest ones which could contain a further intramolecular H-bond (the most common conformation which could be enclosed into an eleven-membered-ring form is the C_7 conformation.) (See References 8, 26, 72, 74-76, 88, 89, 101-104, 108-112, 137, 140, 170, 193, and 287.) However, in the nomenclature proposed in this article an intramolecularly H-bonded folded peptide form is characterized by the smallest ring structure; in other words, the ε-turn does not have any internal H-bond. There are no examples of ε-turns in the solid state.

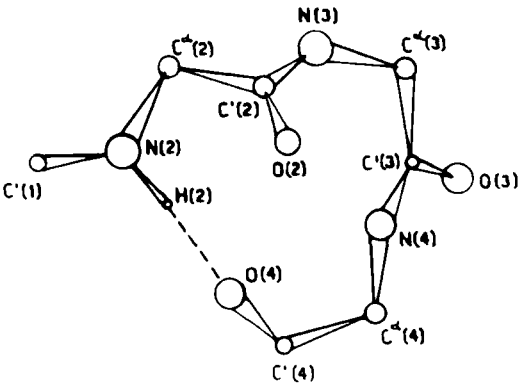

FIGURE 13. A 2→4 *trans, trans* intramolecularly H-bonded (C_{11}) peptide conformation (ε-turn).

De Santis and co-workers were the first to propose the occurrence of a folded form of this type (with a *cis, cis* peptide configuration sequence involving D-Val-L-Pro and L-Pro-Sar tertiary amide bonds) in the cyclopeptide lactone fragment of actinomycin D.[375,376] In the conformational energy calculations the refinement led to the following torsional angles: $\phi = -50°$ and $\psi = -92°$ (D-Val), $\phi = -68°$ and $\psi = +157°$ (L-Pro), $\phi = -86°$ and $\psi = -164°$ (Sar). As may be noted, the L-Pro-Sar sequence closely resembles a fragment of the poly-L-proline I structure. This conformation is in line with the results of the PMR experiments. It would be interesting to compare the crystal structure of this heterodetic cyclic pentapeptide to that of actinomycin itself which contains two such peptide ring structures connected to a phenoxazone group.[377]

In the actinomycin molecule a strong H-bond exists between the two neighboring cyclic pentapeptide chains connecting the N−H of the D-valyl residue with the carbonyl oxygen of the other D-valyl residue, i.e, the H bonds are of the intercycle type.

In homodetic cyclic tetra- and pentapeptides containing a single intramolecular H-bond the C_{11} conformation is accompanied by a C_7 and a C_{10} conformation, respectively. An example of the second case is known.[378] In *c*-(-Gly-L-Ala-Gly-Gly-L-Pro-)- on the basis of a PMR study it has been suggested that the conformation occurring in a minor amount in DMSO solution would contain a C_{11} form in the Gly^3-Gly^4-L-Pro^5 sequence with $\phi = -160°$ and $\psi = +30°$ (first glycyl residue), $\phi = +60°$ and $\psi = +100°$ (second glycyl residue), and $\phi = -60°$ and $\psi = +160°$ (L-prolyl residue); in addition, the Gly-L-Pro bond would take the *cis*-configuration. In the proposed more abundant all-*trans* conformer two intramolecular H-bonds are simultaneously present, giving rise to two different C_{11} forms involving the Gly^3-Gly^4-L-Pro^5 and Gly^4-L-Pro^5-Gly^1 sequences, respectively; the torsional angles are $\phi_1 = 0°$ and $\psi_1 = -90°$, $\phi_3 = -160°$ and $\psi_3 = +40°$, $\phi_4 = +150°$ and $\psi_4 = -130°$, $\phi_5 = -60°$ and $\psi_5 = +150°$.

In linear oligopeptides, spectroscopic investigations and analyses of structure ≒ activity relationships of the peptide hormone eledoisin and various C-terminal fragments have suggested that the peptide chain would have a turning point at the -L-Ile-Gly-L-Leu- sequence, the amide proton of the isoleucyl residue making an intramolecular H-bond with the carbonyl oxygen of the leucyl residue (ε-turn).[379] In this all-*trans* conformation the side chains of the hydrophobic amino acids are oriented to the same direction of the molecule, i.e., they are the site with which the interaction of the receptor takes place to exhibit the biological activity. Clearly, too little progress is being made in this interesting area, which could possibly lead to elucidation of a new important type of chain reversal in peptides and proteins.

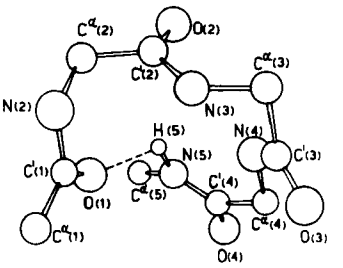

FIGURE 14. A 5→1 *trans,trans* intramolecularly H-bonded (C_{13}) peptide conformation (α-turn).

VII. THE 5→1 INTRAMOLECULARLY H-BONDED PEPTIDE CONFORMATIONS

The most classical intramolecularly H-bonded peptide conformation is the α-helix where the chain folds forming H-bonds between the amide proton of the $i + 4$ unit and the carbonyl oxygen of the i unit (C_{13} ring structure).[380,381] In the right- and left-handed α-helices the ϕ angles of all residues are -57 and $+57°$, respectively, the ψ angles -47 and $+47°$, respectively, and the peptide groups in the *trans* configuration.[382] The ω-helix, like the α-helix, is formed of 13-membered H-bonded rings, and indeed it is simply a distorted α-helix[383] ($\phi = \pm 64.4°$, $\psi = \pm 55.4°$). The distortion can be achieved only by relaxing the conditions of linear N–H . . . . O=C bonds, though if the peptide groups are allowed to be nonplanar this nonlinearity of H bonds may be reduced. The situation is, however, energetically less favorable than that of the α-helix. These two structures, in particular the α-helix, are common features of synthetic polypeptides and proteins. Herewith the discussion will be focused on other types of the 5→1 intramolecularly H-bonded peptide conformation (C_{13} ring structure, α-turn) (Figure 14) but, as stated in the preceding section, only those not containing additional intramolecular H-bonds, e.g., a C_{10} form as found for example in ilamycin B_1[370] and β-amanitin.[236,237]

Three cases of α-turns have been elucidated in the solid state (by X-ray diffraction analysis), in the three biologically active cyclic peptides valinomycin,[241,242,244] [Phe^4, Val^6] antamanide,[384-386] and β-amanitin.[236,237]

Uncomplexed valinomycin, a cyclododecadepsipeptide antibiotic, grown from nonpolar solvents crystallizes in a triclinic form with two crystallographically unrelated molecules in the cell.[244] The two independent molecules have the same conformation with four C_{10} forms (see the pertinent section above) and two intramolecular H-bonds of the 5→1 type involving amide carbonyl oxygens. Formation of the α-turns is associated with a flattened oval shape of the molecule. These folded forms involve the L-Lac^4-L-Val^5-D-Hyv^6 and D-Hyv^{10}-D-Val^{11}-L-Lac^{12} sequences. In the two molecules the torsional angles are: L-Lac^4, $\phi = -74°$ ($-75°$) and $\psi = -6°$ ($-11°$); L-Val^5, $\phi = -108°$ ($-110°$) and $\psi = +78°$ ($+78°$); D-Hyv^6, $\phi = +146°$ ($+150°$) and $\psi = -11°$ ($-12°$); D-Hyv^{10}, $\phi = +82°$ ($+77°$) and $\psi = +3°$ ($+8°$); D-Val^{11}, $\phi = +108°$ ($+104°$) and $\psi = -69°$ ($-71°$); and L-Lac^{12}, $\phi = -164°$ ($-162°$) and $\psi = +23°$ ($+27°$). The ω angles are in the range ± 170 to 179°. These 5→1 H-bonds are relatively weak. Not only the N . . . . O distances are rather large (in the range 2.99 to 3.13 Å), but also the N–H . . . . O angles deviate greatly from 180° (120 to 125°) and the H . . . . O distances are near 2.32 Å (the sum of the van der Waal's radii for H and O is generally assumed to be 2.6 Å).

Two forms of uncomplexed valinomycin have been crystallized and examined by X-ray diffraction by Duax and co-workers[241,242] (a monoclinic form from *n*-octane and triclinic form from ethanol-water solutions). An analysis of the conformations of the three independent molecules, one from the monoclinic form and two from the triclinic form, indicates that the gross features are the same, e.g., all three molecules have two α-turns. Similar to the above, the H bonds have N . . . . O distances in the range 2.98 to 3.18 Å, H . . . . O distances in the range 2.15 to 2.41 Å and N–H . . . . O angles in the range 120 to 138°. Moreover, the same α-amino and α-hydroxy acid residues are involved, and only minor differences in the ϕ, ψ and ω angles have been observed.

The occurrence of one of the rapidly equilibrating conformers of uncomplexed valinomycin in $CDCl_3$ solution, containing two α-turns, as found in the solid state, has been recently proposed by Davies and Khaled[387] on the basis of a detailed PMR investigation. A new type of α-turn has been detected in [Phe^4, Val^6] antamanide, a synthetic, biologically active analog of the cyclic decapeptide antitoxin isolated from *Amanita phalloides*.[384-386] Both in the uncomplexed tri- and dodecahydrate forms one pair of α-turns exist (L-Pro-L-Pro-L-Phe sequence) with the L-Pro-L-Pro tertiary amide bonds in the *cis* configuration ($\omega = +5°$). The N . . . . O distances are 2.90 to 2.91 Å. For the trihydrate form the ϕ, ψ angles are: $\phi = -67°$ and $\psi = +153°$ ($Pro_{2,7}$), $\phi = -98°$ and $\psi = +4°$ ($Pro_{3,8}$), and $\phi = -97°$ and $\psi = -35°$ ($Phe_{4,9}$); furthermore, only small differencies in ϕ, ψ and ω torsional angles are observed in the dodecahydrate form.

More recently, an all-*trans* α-turn has been found in the solid state by Lipscomb and co-workers in β-amanitin, a bicyclic octapeptide toxin isolated from the same poisonous mushroom *A. phalloides* which produces the antitoxin peptide antamanide.[236,237] The sequence involved is L-Hyp-L-Hyi-L-Hyt (where Hyp stands for 4-hydroxy-proline, Hyi for γ, δ-dihydroxy-isoleucine, and Hyt for 6-hydroxy-tryptophan), and the N . . . . O distance 2.93 Å. The ϕ, ψ angles are: $\phi = -60°$ and $\psi = -37°$ (L-Hyp), $\phi = -79°$ and $\psi = -23°$ (L-Hyi), $\phi = +109°$ and $\psi = -40°$ (L-Hyt). A combined investigation of PMR and conformational energy calculations has shown that the structure of α-amanitin in solution (Asn^1 in a α-amanitin is replaced by Asp^1 in β-amanitin) is similar to the structure of β-amanitin in the crystalline state; in particular the peptide proton of the glycyl residue following L-Hyt forms an intramolecular H-bond to carbonyl oxygen of the aspartyl residue preceding L-Hyp.[309]

Thus, the α-turn is a well-established feature of cyclic oligo (depsi) peptides in the solid state and in solution. Hopefully, new examples of these chain reversals will be discovered in the future. Investigations on suitably selected linear peptides could be rewarding.

VIII. THE INTRAMOLECULARLY BIFURCATED H-BONDED PEPTIDE CONFORMATIONS

The first example of a bifurcated H-bond, i.e., one hydrogen atom shared by two H-bond acceptors was reported by Albrecht and Corey in crystals of the α-form of glycine.[388] This situation was pointed out by Pauling to represent an exception to the condition that "the coordination of hydrogen does not exceed two."[389] The position of the hydrogen atoms was later verified by Marsh in a detailed X-ray diffraction study.[390] Some structural details of such an unusual H-bond are presented in Figure 15, in which it can be seen that although the nitrogen is closer to one oxygen, the hydrogen is closer to the other because, as suggested by Marsh,[390] of the more favorable angle of attack.

In the last 40 years the structures of a number of molecules containing bifurcated

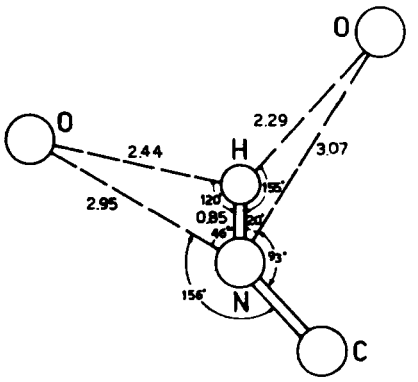

FIGURE 15. The intermolecularly bifurcated H-bond in glycine in the α-form. (From Toniolo, C., in *Bioorganic Chemistry*, Vol. 3, van Tamelen, E. E., Ed., Academic Press, New York, 1977, 265. With permission.)

H bonds have been published.[145,391] However, bifurcated H-bonded conformations formed by two intramolecular H bonds (e.g., of the type C_7C_5, $C_{10}C_5$, etc.) in peptides without artificially introduced N-blocking group (see section below) have never been reported as occurring in the solid state.

Some recent papers by Néel and colleagues suggest the occurrence of these intramolecularly bifurcated H-bonded peptide conformations in diluted carbon tetrachloride solution.[28,145,146,392] IR absorption and PMR were employed for such an investigation.

If the general formula of the N- and C-protected linear dipeptides examined is considered to be R-CO-L-Pro-X-Y, it appears that the stability of the structure containing the intramolecular bifurcated H-bond depends on the nature of R, X, and Y.[28,145,146] The Nancy group found that Ac-L-Pro-D-Ala-OMe showed the highest content of this conformation in the inert solvent. The structure proposed for this peptides is illustrated in Figure 16. The steric repulsion between O(2) and the methyl group in the side chain of the D-alanine residue dictates a minimal distance O(1) . . . . O(3) of 3 Å, thus permitting the formation of a rather strong intramolecular bifurcated H-bond, O(1) . . . . H(3) . . . . O(3). This type of H-bond stabilizes a 3→1,3→3 conformation (also called the C_7C_5 form), where an equatorial 3→1 form involving the L-proline residue ($\phi = -75°$, $\psi = +50°$) is juxtaposed in part to an extended 3→3 form involving the D-alanine residue ($\phi = +158°$, $\psi = +180°$). The two amide bonds are in the *trans* configuration. The perturbation experienced by the H(3) atom results in a large bathochromic frequency shift for the corresponding ν(N−H) absorption maximum, which is observed at 3277 cm^{-1}, and in a relevant frequency shift to lower field for the corresponding proton signal in the PMR spectrum.

In addition, in N- and C-protected tridepsipeptides, e.g., Ac-D-Val-L-Lac-L-Val-OMe, it has been suggested that the NH hydrogen of the third residue would take part in an intramolecularly bifurcated H-bond stabilizing a conformer with two fused ten- and five-membered rings ($C_{10}C_5$).[392] An interesting example of the intramolecularly bifurcated H-bonded peptide conformation C_7C_5 has been proposed in solvents of low polarity by Madison for cyclo(L-Pro-Gly)$_3$ on the basis of a thorough investigation using PMR and CMR, theoretical and experimental CD, and potential-energy calculations.[107,143,152,351] Recently, these peptide forms have been taken into consideration in theoretical papers devoted to the prediction of the most probable conformations in cyclic and linear peptide molecules.[58,62,297]

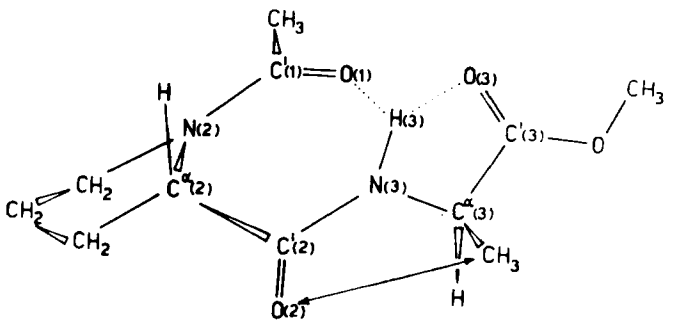

FIGURE 16. The intramolecularly bifurcated H-bonded peptide conformation of Ac-L-Pro-D-Ala-OMe. (From Toniolo, C., in *Bioorganic Chemistry*, Vol. 3, van Tamelen, E. E., Ed., Academic Press, New York, 1977, 265. With permission.)

It can be concluded that intramolecularly bifurcated H-bonded peptide conformations are rare but certainly not extinct. More examples will doubtlessly be discovered in the future.

IX. THE OXY ANALOGS OF THE INTRAMOLECULARLY H-BONDED PEPTIDE CONFORMATIONS

In the oxy analogs of the 3→1 intramolecularly H-bonded peptide conformations, which could represent an essential feature of polypeptide chains near their C-terminal end, the C-terminal −OH group and the carbonyl group nearest the C-terminal are involved in a seven-membered ring containing a somewhat bent H-bond. As in the case of the 3→1 intramolecularly H-bonded peptide forms, (1) such an H-bond is possible only in the *trans*-amide isomer, and (2) when R in −NH−CHR−CO− is not a hydrogen atom, two different conformers (equatorial and axial) can exist. An example of an oxy analog of the 3→1 intramolecularly H-bonded peptide conformation is illustrated in Figure 17.

The IR absorption spectra of the *t*-Boc derivatives of all *N*-alkylamino acids so far examined in the solid state indicate that the urethane (carbamate) C=O is H-bonded (obviously with the −OH group).[393-395] Among the *t*-Boc derivatives of the various aliphatic amino acids, *t*-Boc-D-Val-OH shows strong evidence of an H-bond involving the urethane carbonyl.[393] To ascertain *inter alia* if the urethane carbonyl of these compounds takes part in an intramolecular H-bond (giving rise to the oxy analog of a 3→1 H-bonded peptide conformation) or in an intermolecular one, X-ray diffraction analyses of various *t*-Boc-X-OH (where X = L-Pro; L-Aze, azetidine-2-carboxylic acid; L-Thz, thiazolidine-4-carboxylic acid; D-Val) and also of the analogous compound *t*-Aoc-L-Pro-OH (*t*-Aoc denotes *tert*-amyloxycarbonyl) were carried out by our group and others.[393,395-398] The molecular structure of *t*-Boc-D-Val-OH is shown in Figure 18. The prerequisite for the formation of the oxy analogs of the 3→1 H-bonded peptide forms, i.e., *trans*-amide configuration, is not met by the five N-protected amino acids. An intermolecular H-bond (2.63 to 2.66 Å) linking the −OH and urethane carbonyl is apparent in all cases. In the *t*-Boc-D-Val-OH molecule, which contains a secondary urethane, an additional intermolecular H-bond is present between the N−H and the C=O group of the carboxylic acid moiety (2.92 Å). A preliminary X-ray diffraction investigation indicated the absence of such folded forms also in the case of Z-Gly-OH (Z denotes benzyloxycarbonyl)[399] which also possesses an urethane N-protecting group.

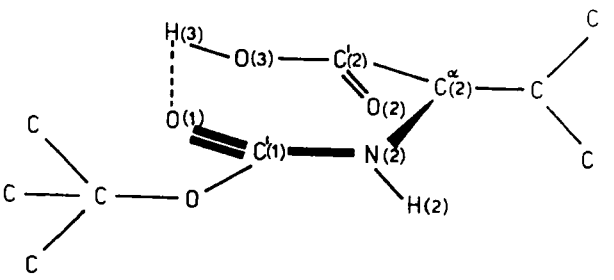

FIGURE 17. The oxy analog of the 3→1 intramolecularly H-bonded (C_7) peptide conformation for *t*-Boc-D-Val-OH.

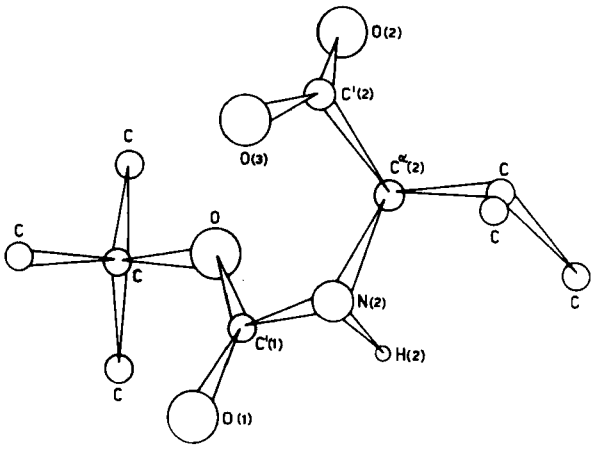

FIGURE 18. The molecular structure of *t*-Boc-D-Val-OH. (From Toniolo, C., in *Bioorganic Chemistry*, Vol. 3, van Tamelen, E. E., Ed., Academic Press, New York, 1977, 265. With permission.)

N-Acetylamino acids as model compounds of the C-terminal regions of polypeptide chains are superior to *N-tert*-butyloxycarbonylamino acids. The higher basicity of the amide carbonyl with respect to that of the urethane carbonyl and the weaker van der Waals interactions of *N*-acetyl derivatives if compared with those of *N-tert*-butyloxycarbonyl derivatives could lead to different types of structures. However, it should be admitted that all the Ac-X-OH (X = Gly, L-Nva, L-Leu, L-Cys, L-His, L-Trp, L-Gln, and L-2-(*p*-tolyl) Thz) so far examined by X-ray diffraction, although having the amide group in the *trans* configuration and the −OH linked to the amide C=O (2.53 to 2.60 Å), do not adopt such a conformation.[400-410] No evidence for the oxy-C_7 form in the solid state was also found in other N-acyl α-amino acids, i.e., HCO-L-Met-OH,[411] BrAc-L-Leu-OH,[412] ClAc-L-Nva-OH,[413] and ClAc-DL-Ala-OH,[414] and *N*-peptidyl α-amino acids.[410]

The presence of oxy analogs of the various types of ten-membered 4→1 intramolecularly H-bonded peptide conformations has been recently proposed by Deber[415] when the sequences Gly-L-Pro, L-Pro-Gly, and L-Pro-D-Pro occur in the two residues at the C-terminus of the polypeptide chain. In *t*-Boc-dipeptides experimental evidence for this folding was obtained from the observation in the IR absorption spectra of a $\simeq$ 30-cm^{-1} shift to lower frequency of the urethane carbonyl band, due to H-bond formation.

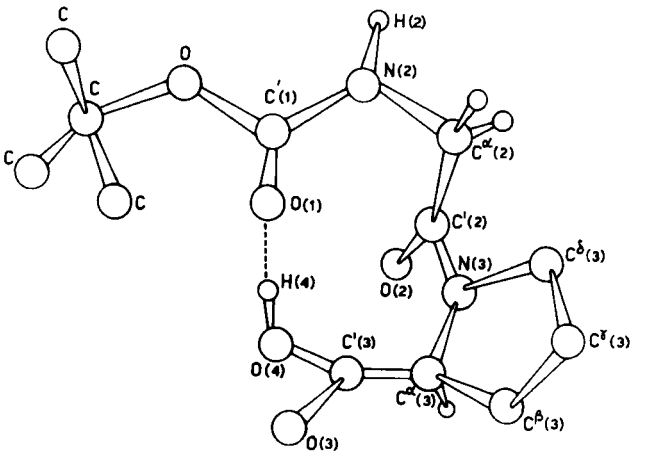

FIGURE 19. The oxy analog of the *trans*-II′ 4→1 intramolecularly H-bonded (C_{10}) peptide conformation proposed by Deber[415] for *t*-Boc-Gly-L-Pro-OH in the solid state. (From Toniolo, C., in *Bioorganic Chemistry*, Vol. 3, van Tamelen, E. E., Ed., Academic Press, New York, 1977, 265. With permission.)

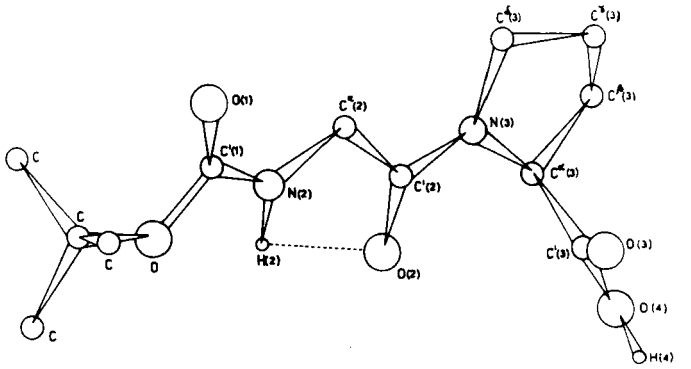

FIGURE 20. The molecular structure of *t*-Boc-Gly-L-Pro-OH. (From Toniolo, C., in *Bioorganic Chemistry*, Vol. 3, van Tamelen, E. E., Ed., Academic Press, New York, 1977, 265. With permission.)

The structure proposed by Deber[415] for *t*-Boc-Gly-L-Pro-OH is illustrated in Figure 19. In the molecular structure of *t*-Boc-Gly-L-Pro-OH (Figure 20), as determined by our group using the X-ray diffraction technique, two different types of H-bond occur.[53] The first is an intramolecular H-bond between the urethane N—H and the amide carbonyl (2.59 Å). As discussed above, this H-bond gives rise to the formation of a five-membered ring in the molecule. The second type of H-bond is intermolecular between the O—H and the urethane C=O (2.64 Å). Thus, the hypothesis of the folding of the *t*-Boc-Gly-L-Pro-OH molecule in the solid state put forward on the basis of the IR absorption results,[415] has to be rejected. An extended conformation is also adopted in the solid state by Z-Gly-L-Pro-OH.[416]

No evidence of an oxy analog of a 4→1 intramolecularly H-bonded peptide conformation (Figure 21) was found in the solid state in the case of *t*-boc-L-Pro-Gly-OH on the basis of our recent X-ray diffraction study (Figure 22).[141] The molecules are held in the crystal state by two intermolecular H-bonds; the former (2.85 Å) is achieved between the N—H group of the glycyl residue and the C=O group of the urethane

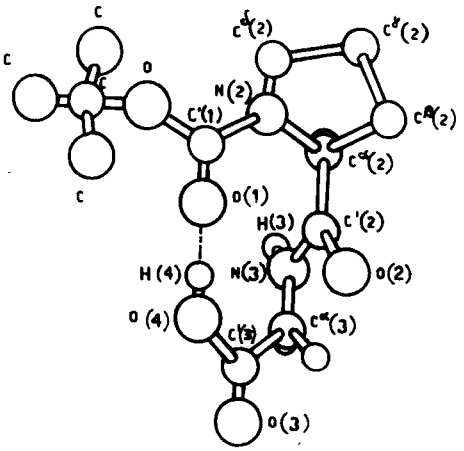

FIGURE 21. The oxy analog of the *trans*-II 4→1 intramolecularly H-bonded (C_{10}) peptide conformation proposed by Deber[415] for *t*-Boc-L-Pro-Gly-OH in the solid state.

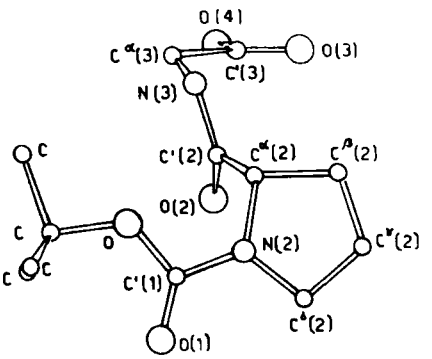

FIGURE 22. The molecular structure of t-Boc-L-Pro-Gly-OH.

moiety, while the latter (2.68 Å) links the O—H group of the carboxylic acid and the amide C=O of the prolyl residue. On the other hand, from Figure 22 it is evident that the prerequisite for the formation of the oxy analogs to the β-turns in *N*-*t*-Boc dipeptides, namely *trans* urethane $-CON\lesssim$ or $-CONH-$ configuration, is not met by *t*-Boc-L-Pro-Gly-OH.

An X-ray diffraction analysis of *t*-Boc-L-Pro-D-Pro-OH, the last of the three N-protected dipeptides existing in the oxy analog of the 4→1 intramolecularly H-bonded peptide conformation according to Deber's IR aborption investigation,[415] is currently in progress in our laboratory. The occurrence of this type of folded form in the solid state could possibly be demonstrated also in the oxy analogs to those peptide segments and N-protected peptide amides, the structure of which has already been determined by X-ray diffraction and found to be of the β-turn type (see the pertinent section above). Studies along this line are also underway in our laboratory, using combined application of the IR absorption and X-ray diffraction analysis.

In summary, the X-ray diffraction studies discussed in this section have demonstrated the absence of the oxy analogs of the 3→1 and 4→1 intramolecularly H-bonded peptide forms (including the possible 4→1 *cis* form) for the various N-protected amino acids and peptides in the solid state. Intermolecular H-bonds due to crystal packing effects prevail. Crystallographic data on other N-protected amino acids and peptides are required before any permanent conclusion can be drawn about the occurrence of the oxy analogs of the 3→1 and 4→1 H-bonded peptide conformations in the solid state. It is possible that specific crystallization solvents may also play a role in favoring these folded forms. In addition, as Deber correctly pointed out, "X-ray crystallography remains the method of choice for substantiation of the postulated intramolecularly H-bonded structure."[415] In fact, merely on the basis of the IR absorption data it is impossible to rule out unequivocally intermolecular H-bonding effects in the crystals of these acids as the source of the shifted carbonyl frequencies.

By means of PMR and CMR, IR absorption, ORD, and CD spectroscopies, indications have been obtained that the oxy analogs of the 3→1 and 4→1 intramolecularly H-bonded peptide conformations could be present in solution. The extent of the population in the conformational equilibrium mixture seems to be dependent on chemical

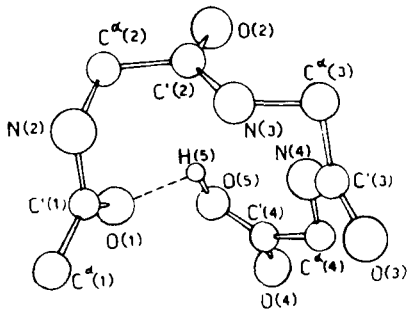

FIGURE 23. The oxy analog of an 5→1 intramolecularly H-bonded (C_{13}) peptide conformation.

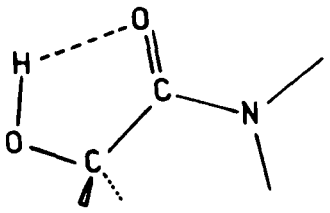

FIGURE 24. The oxy analog of the intramolecularly H-bonded C_5 peptide conformation in the "O terminal" part of a linear depsipeptide chain.

structure, solvent, concentration, and temperature. (See References 53, 141, 142, 147, 205, 206, 208, 393, 395, 415, and 417-421.)

To our knowledge, the oxy analogs of the various types of the thirteen-membered 5→1 intramolecularly H-bonded peptide form (Figure 23) have never been found or considered in conformational analysis. However, it would be easy to predict that the current interest in the area of the oxy analogs of the intramolecularly H-bonded peptide conformations will certainly cause this gap to be filled.

Finally, oxy analogs of the C_5, C_8, and C_{11} intramolecularly H-bonded peptide conformations can possibly exist in the "O-terminal" part of a linear depsipeptide chain (for the C_5 form see Figure 24). Among them only the oxy analog of the C_5 form has been detected (in model compounds of the type HO−CHR−CO−X (X= NR′R″, OR) in diluted carbon tetrachloride solutions by IR absorption and CD in the IR region.[422-424] Large $\Delta\nu$ (O−H) shifts (≃200 cm^{-1}) have been reported as due to the onset of the intramolecular O−H . . . O H−bond forming the pentagonal ring. However, the oxy analogs of both the intramolecularly H-bonded C_5 and C_8 species are absent in the solid state in H-D-Hyv-L-MeVal-O*t* Bu, the only model of linear depsipeptide molecules suitable for the formation of such conformations so far examined by X-ray diffraction.[425] It is hoped that this discussion will encourage more detailed analysis of these conformations in linear depsipeptide molecules containing an α-hydroxy acid as the first residue in the chain.

X. MISCELLANEOUS INTRAMOLECULARLY H-BONDED PEPTIDE CONFORMATIONS

A. Intramolecularly H-Bonded Peptide Conformations Involving a Side-Chain Group

If unionized amino acid residues are considered, the H-bonding donor groups >NH (Lys and lower homologs, His, Trp, Asn, and Gln), −OH (Ser, Thr, Tyr, Asp, and Glu), and −SH (Cys) and the H-bonding acceptor groups tertiary amino (His), thioether sulfur (Cys and its S-derivatives, Met, cystine), carbonyl oxygen (Asn, Gln, Asp, and Glu), and ether oxygen (Ser and Thr and their derivatives) might be involved in side-chain/main-chain intramolecularly H-bonded ring structures (H-bonded forms of the side-chain/side-chain type are not discussed here). In addition, these structures can stabilize or destabilize the various main-chain/main-chain H-bonded peptide conformations examined in the previous sections, since they can be formed with −CO−-NH− groups preceding or following in the sequence.

If the attention is restricted to amino acids, amino acid derivatives, and linear and

cyclic oligopeptides, the following scattered examples have been found in the solid state by X-ray diffraction analysis:

1. (Backbone) NH . . . S (side chain) five-membered-ring structure in *meso*-lanthionine[426] and D-penicillamine disulfide[427]
2. (Backbone) NH . . . . O=C (side chain) seven-membered-ring structure in Piv-L-Gln-NHMe (Piv stands for pivalyl)[54,428]
3. (Backbone) NH . . . OH (side chain) five-membered-ring structure in N-(purin-6-ylcarbamoyl)-L-Thr-OH[429,430]
4. (Hyt[1] backbone) NH . . . . O=C (Asn[6] side chain) twelve-membered-ring structure in β-amanitin[236,237]
5. OH . . . . O=C between the β-OH group of an unusual β-hydroxy α-amino acid and the backbone carbonyl group of the same residue (six-membered-ring structure) in bouvardin[371]
6. NH . . . . O between the backbone −NH of a N^{δ}-hydroxy, N^{δ}-acyl ornithine and the N^{δ}-hydroxy oxygen of the same residue (eight-membered-ring structure) in ferrichrome A[231] and ferrichrysin.[232]

In natural high-molecular-weight polypeptides, perhaps the most interesting type of side-chain/main-chain intramolecular H-bonding has been established in iron-sulfur electron transport proteins, i.e., ferredoxin, rubredoxin, and high-potential iron protein.[431-433] Two nine-membered-ring structures (called *trans*-I and *trans*-II in analogy to the corresponding C_{10} forms) have been shown, involving a NH . . . . S H-bond between the backbone NH of the *n* residue and the thioether sulfur of the *n*-2 Cys residue. These structures seem to be features peculiar to proteins which are coordinating metal atoms with cysteines. It is of interest that synthetic high-molecular-weight homopolypeptides derived from α-amino acids with a heteroatom attached to the β-carbon, i.e., cysteine and its S-derivatives (and their oxygen analogs), have been classified as non-α-helix formers on the basis of solid-state and solution experimental results; the failure of these polypeptides to assume that helical structure has been related in part to side-chain/main-chain intramolecular H-bond formation.[434] Intramolecular (backbone) NH . . . . S (*S*-alkyl cysteine and Met side chains) H-bonds are present also in low-molecular-weight model compounds, particularly in solvents of low polarity.[11,12,27,435-437]

A very large number of conformational energy calculation studies and stereochemical investigations in solution have stressed the importance of intramolecular side-chain main-chain H-bond formation on the structure of biologically active linear and cyclic oligopeptides (e.g., enkephalin, thyroliberin, α-amanitin, contraceptive tetrapeptide, angiotensin II, oxytocin, serratamolide, evolidine, gramicidin S, ferrichrome, and a variety of model compounds with the side chains taking part in such interactions being essentially those of His, Tyr, Ser, Thr, Asp, Glu, Asn, and Gln. Unfortunately, space limitations do not allow a detailed analysis of the various conformations to be performed here; however, many of the already cited review articles and specific papers deal in part with this problem.

B. Intramolecularly H-Bonded Peptide Conformations Involving the N^{α}-Blocking Group (in Synthetic Linear Peptides)

Several previous sections of this article have dealt with the occurrence of intramolecularly H-bonded peptide conformations involving N^{α}-blocking groups of urethane or amide types (e.g., in connection with the discussion on C_7 and C_{10} forms, intramolecularly bifurcated H bonds, oxy analogs to the C_7 and C_{10} forms, and intra-

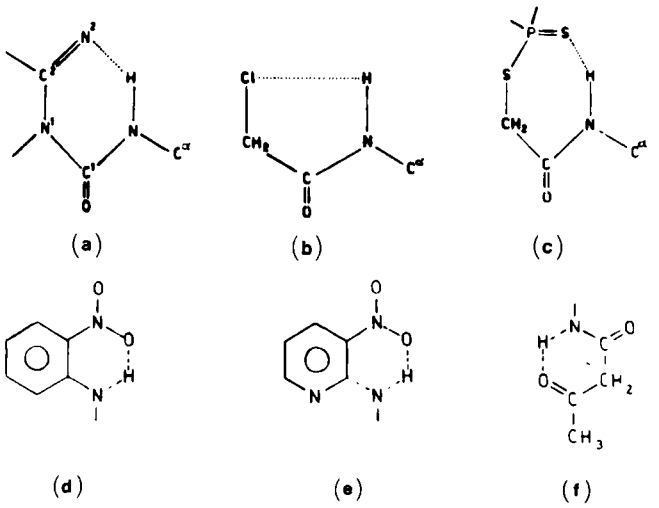

FIGURE 25. Intramolecularly H-bonded peptide conformations involving a heteroatom of the N-blocking group as the H-bonding acceptor and the N-terminal N−H as the H-bonding donor.

molecularly H-bonded forms involving a side-chain group). In particular, as far as the solid state is concerned, various examples are listed in Table 1 (see entries 1 to 8, 10, and 14) where the formation of *trans*-C_{10} structures involves the participation of the C=O group of an urethane (either *t*-Boc or Z) or acyl (either Ac or *i*BuCO) moiety as the H-acceptor.[54,212-215,217,221]

A series of *N*-(purin-6-yl-carbamoyl)-amino acids have been crystallized and their molecular structure determined by X-ray diffraction to investigate the possible role of hypermodified bases adjacent to the anticodon loop of some tRNAs in condon-anticodon interactions.[429,430,438-442] In all the ureidopurines examined, a planar six-membered ring is formed by an intramolecular H-bond from the carbamylated α-amino group of the α-amino acid residue to the N(1) nitrogen of the pyrimidyl ring of the purinyl moiety (Figure 25a). The N . . . . O distances are in the range 2.70 to 2.78 Å.

A number of structurally different N-blocking groups have been shown to form an intramolecular H-bond in solution with the α-amino group of the first linked amino acid residue as the H-bonding donor; for example, the haloacetyl (Figure 25b),[443,444] thiophosphorylacetyl (Figure 25c),[33] 2-nitro-phenyl (Figure 25d),[445] 3-nitro-2-pyridyl (Figure 25e),[445] and acetoacetyl (Figure 25f)[446] groups. However, in none of them has a clear-cut proof of the existence of such H-bonds in the solid state been found.[412-414,447-450] X-ray diffraction studies devoted specifically to fill this gap should represent the next step in this field.

C. Intramolecularly H-Bonded Peptide Conformations Involving N−H . . . . π Bonds

Two types of intramolecularly H-bonded peptide conformations involving N−H · · · π bonds have been discussed in the literature: the former has the amide C=O as the H-bonding acceptor, the latter an aromatic ring present in the amino acid side chain, e.g., that of a Phe residue.

A C_6' form (Figure 26), also called C'$_5$ form[60] or P state,[100] arising out of interaction between the amide proton of the *i* peptide unit and the π-electrons of the *i*-1 peptide unit, has been considered in conformational energy calculations for H-bonded forms of glycyl and alanyl dipeptides[60] (this attractive interaction, but of the intermolecular type, has also been discussed in a theoretical analysis employing *ab initio* molecular orbital methods[451]). Pyroglutamic acid *N'*-monoalkyl amides and *N*-acyl-α-iminoacyl

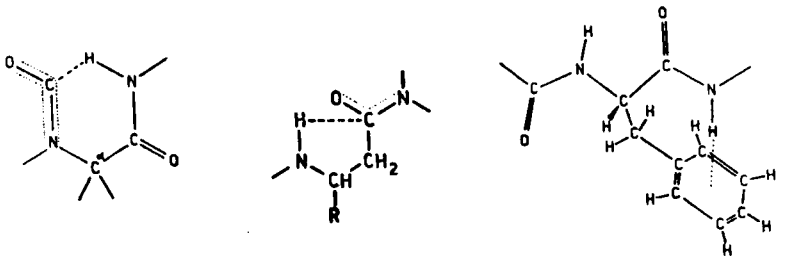

FIGURE 26. Three types of N−H . . . . π intramolecularly H-bonded peptide conformations.

N'-monoalkylamides adopt in part the C'_6 form in diluted CCl_4 solution;[100] however, in the solid state L-pyroglutamic acid *N'*-methylamide[52,452] and Ac-L-Pro-NHMe[78] assume a more extended conformation without the intramolecular H bond. In an L peptide sequence, the C'_6 N−H . . . . π interaction results in a preferential state ($\phi \simeq -90°$, $\psi \simeq 0°$) close to the conformation of the third residue in a *trans*-I C_{10} conformation and can cooperate with the 4→1 intramolecular H bond to stabilize such a chain reversal.[100] It is probable that this N−H . . . . π interaction might contribute to the stabilization of the three-dimensional architecture of proteins.

A C'_5 form (also called C'_6 form) with a N−H . . . . π interaction involving an amide proton and the π-electrons of the following amide unit (Figure 26) has been detected in β-amino acid derivatives of the type Ac-NH-CH(R)-CH_2-CO-NR'R" in diluted apolar solvents.[422,453]

Dipole (N−H)-induced dipole (aromatic ring) interactions in both linear and cyclic oligopeptides containing at least one Phe or other aromatic amino acid residue have been reported. IR and PMR investigations in solvents of low polarity from the Nancy[11,12,27] and Padua[10,46,436,454] groups have shown that in linear Phe derivatives and peptides extended structures are preferentially stabilized over folded structures due to intramolecular N−H . . . phenyl ring interactions (Figure 26). Similar results have been obtained in independent spectroscopic studies and conformational energy calculations.[5,68,455,456] In cyclic dipeptides (diketopiperazines) from an α-amino acid and an aromatic α-amino acid, e.g., *c*(L-Pro-L-Phe), conformational energy calculations and spectroscopic investigations in solution have strongly suggested that a N−H · · · phenyl ring interaction might stabilize the rotamer extended toward nitrogen.[457-460] Hopefully, the crystal structure of that diketopiperazine will be determined soon.

D. Intramolecularly H-Bonded Peptide Conformations Involving β-Amino Acids

Obviously, the intramolecularly H-bonded peptide conformations involving β-amino acid residues exhibit ring structures containing one more atom than the corresponding ones derived from α-amino acid residues (Figure 27). The C_{12} form has been established in the solid state in the case of the toxic cyclopentapeptide cyclochlorotine, the sequence involved being -Ser-β-aminophenylpropionic acid-Ser.[246]

In $CDCl_3$ solution the model compounds for the repeating unit of nylon-3 or substituted poly (β-amino acids) Ac-NH-CH(R)-CH_2-CO-NH-R' show evidence of formation of C_6 and C_8 ring structures, as determined by an IR absorption study.[422,454] Two symmetrical states are possible for the C_6 conformation, depending upon the position of the R side-substituent relative to the six-membered ring. The C_6 structure prevails because the C_8 conformer is sterically strained.

The N−H proton of the methylamide moiety of H-L-Pro-L-Leu-βAla-$NHCH_3$ has been suggested to participate in an intramolecular H-bond in $CDCl_3$ solution, which

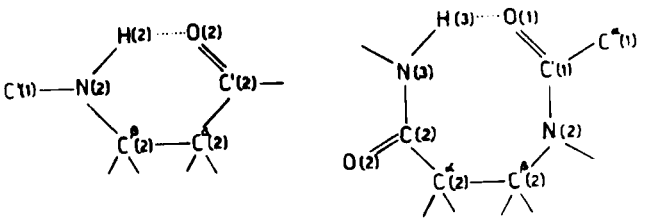

FIGURE 27. Examples of intramolecularly H-bonded forms, corresponding to the C_5 and C_7 conformations of α-amino acid residues, respectively, involving a β-amino acid residue.

involves the C=O of leucine to form an eight-membered-ring structure.[118] An intramolecularly H-bonded peptide conformation of the N−H . . . π type including a β-amino acid has been discussed in the preceding section. Finally, it should be mentioned that in depsipeptide model compounds of the type $HO-CH_2-CH_2-OC-NRR'$ oxy analogs of the C_6 forms occur in diluted carbon tetrachloride solutions.[422]

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