Crystallographic Characterization of the Conformation of the 1-Aminocyclohexane-1-carboxylic Acid Residue in Simple Derivatives and Peptides

Giovanni Valle, Marco Crisma, and Claudio Toniolo *
Biopolymer Research Centre, C.N.R., Department of Organic Chemistry, University of Padova, 35131 Padova, Italy
Nirupa Sen, Muppalla Sukumar, and Padmanabhan Balaram *
Molecular Biophysics Unit, Indian Institute of Science, Bangalore-560 012, India

The crystal structures of 1-aminocyclohexane-1-carboxylic acid (H-Acc^6-OH) and six derivatives (including dipeptides) have been determined. The derivatives are Boc-Acc^6-OH, Boc-(Acc^6)$_2$-OH, Boc-L-Met-Acc^6-OMe, ClCH$_2$CO-Acc^6-OH, *p*-BrC$_6$H$_4$CO-Acc^6-OH oxazolone, and the symmetrical anhydride from Z-Acc^6-OH, [(Z-Acc^6)$_2$O]. The cyclohexane rings in all the structures adopt an almost perfect chair conformation. The amino group occupies the axial position in six structures; the free amino acid is the only example where the carbonyl group occupies an axial position. The values determined for the torsion angles about the N–C$^\alpha$ (φ) and C$^\alpha$–CO (ψ) bonds correspond to folded, potentially helical conformations for the Acc^6 residue.

The use of uncommon amino acid residues in the synthesis of peptides with restricted conformational flexibility has acquired increasing importance in the design of specifically folded analogues of biologically active peptides.[1] α,α-Dialkylated residues (H_2N–CR^1R^2–CO_2H) have proved valuable in the construction of conformationally constrained peptide backbones.[2–4]

While considerable attention has been paid to the conformational properties of α,α-dialkylated residues with methyl or linear alkyl substituents, like α,α-dimethylglycine (α-aminoisobutyric acid; H_2N–CMe_2–CO_2H, Aib),[2–9] α,α-diethylglycine (H_2N–CEt_2–CO_2H, Deg),[4,10] and α,α-di-n-propylglycine (H_2N–CPr_2–CO_2H, Dpg),[4,11,12] relatively few stereochemical studies have been reported on peptides containing 1-aminocycloalkane-1-carboxylic acids (Acc^n, where *n* is the number of carbon atoms in the cycloalkane ring).[13–16] Recent studies in our laboratories suggest that both 1-aminocyclohexane-1-carboxylic acid (Acc^6)[14,15] and 1-aminocyclopentane-1-carboxylic acid (Acc^5)[16] residues necessarily adopt folded backbone conformations, in the $3_{10}/\alpha$-helical regions of the conformational space (φ *ca.* $\pm$ 60 $\pm$ 20°, ψ *ca.* $\pm$30 $\pm$ 20°).[17,18] A chemotactic peptide analogue (HCO-L-Met-Acc^6-L-Phe-OMe) has been shown to possess high biological activity,[19] and aspartame analogues incorporating Acc^n (*n* = 3—8) residues have been prepared with sweetness of taste maintained for the analogues having *n* = 3—5(6).[20–22]

As part of a programme to investigate the conformational properties of Acc^6 residues,[14,15] we describe here the crystal structure of the free amino acid, H-Acc^6-OH (**1**), and six derivatives Boc-Acc^6-OH (**2**) (Boc = t-butoxycarbonyl), Boc-(Acc^6)$_2$-OH (**3**), Boc-L-Met-Acc^6-OMe (**4**), ClCH$_2$CO-Acc^6-OH (**5**), *p*-BrC$_6$H$_4$CO-Acc^6-OH oxazolone (**6**), and (Z-Acc^6)$_2$O (**7**) (Z = benzyloxycarbonyl). In particular, the results permit a definition of the conformational features of the cyclohexyl side chain.

Experimental

Materials.—H-Acc^6-OH (**1**),[23,24] ClCH$_2$CO-Acc^6-OH (**5**),[24] and (Z-Acc^6)$_2$O (**7**)[23] were prepared by published procedures. *p*-BrC$_6$H$_4$CO-Acc^6-OH oxazolone (**6**) was obtained by treating the *N*-protected amino acid with acetic anhydride at 120 °C for 20 min. Boc-Acc^6-OH (**2**) was obtained by treatment of the free amino acid with 2-t-butoxycarbonyloxyimino-2-phenylacetonitrile, using a procedure similar to that described earlier.[25] Boc-(Acc^6)$_2$-OH (**3**) and Boc-L-Met-Acc^6-OMe (**4**) were prepared by conventional peptide synthesis procedures as described elsewhere for related compounds.[14]

Crystal Structures.—*X*-Ray diffraction data for compounds (**1**)—(**7**) were collected with a Philips PW 1100 four-circle diffractometer using graphite-monochromatized Mo-K_α radiation (λ = 0.7107 Å). The θ–2θ scan mode up to θ = 25° was used. Intensities were corrected for Lorentz and polarization effects and put on an absolute scale. No absorption corrections were applied. The crystallographic data are summarized in Table 1.[26]

The final positional parameters of the non-hydrogen atoms along with equivalent isotropic temperature factors, anisotropic temperature factors, hydrogen atom positional parameters, and bond lengths and bond angles for structures (**1**)—(**7**) have been deposited at the Cambridge Crystallographic Data Centre.†

Results and Discussion

Perspective views of molecules (**1**)—(**7**) are shown in Figures 1—7 with the atom numbering schemes.

Cyclohexyl Ring Conformation.—The endocyclic cyclohexane ring torsion angles of the structures (**1**)—(**7**) are listed in Table 2. The mean value is $\pm$54.6°. This is close to an almost perfect chair conformation for the cyclohexyl ring. In particular, the total puckering amplitudes *Q* (Table 3) are only slightly lower than the *Q* value for an ideal cyclohexane chair (0.63 Å).[27] The magnitudes of distortion, given by tan θ, are very small ($0.93 < \theta < 7.60$).[27] These results are similar to those already described for the structures of the additional five Acc^6-containing compounds studied previously.[14,15,28]

As expected,[15,23] in the Acc^6 residues of the six *N*-blocked amino acids and dipeptides discussed here the amino function is always found in the axial position (the dihedral angle τ has values close to 90°) (Table 3). This feature has also been observed in the structures of the additional four Acc^6-containing peptides studied previously.[14,15] The axial orientation of the amino group was indeed anticipated in the early

† See section 5.6.3 of Instructions for Authors, in the January issue.

Table 1. Crystal data for H-Acc^6-OH (**1**), Boc-Acc^6-OH (**2**), Boc-(Acc^6)$_2$-OH (**3**), Boc-L-Met-Acc^6-OMe (**4**), ClCH$_2$CO-Acc^6-OH (**5**), *p*-BrC$_6$H$_4$CO-Acc^6-OH oxazolone (**6**), and (Z-Acc^6)$_2$O (**7**)

Compd.	Molecular formula	M (a.m.u.)	$D_{calc.}$/g cm^{-3}	$D_{exp.}$/g cm^{-3}	Space group	Z	a/Å	b/Å
(1)	$C_7H_{13}NO_2$	143.2	1.229	1.23	$P2_1/a$	4	11.047(3)	6.494(3)
(2)	$C_{12}H_{21}NO_4$	243.3	1.206	1.21	$Pbca$	8	12.239(4)	18.980(5)
(3)	$C_{19}H_{32}N_2O_5$	368.5	1.190	1.19	$P\bar{1}$	2	16.513(5)	10.871(4)
(4)	$C_{17}H_{30}N_2O_5S$	374.5	1.178	1.18	$P2_1$	2	12.138(4)	10.569(4)
(5)	$C_9H_{14}ClNO_3$	219.7	1.412	1.41	$P2_1/a$	4	12.552(4)	9.776(3)
(6)	$C_{14}H_{14}BrNO_2$	308.2	1.507	1.51	$P2_1/c$	4	12.232(3)	10.577(3)
(7)	$C_{30}H_{36}N_2O_7$	536.6	1.296	1.30	$C2/c$ (Sp. position 2)	4	19.794(5)	9.031(3)

Compd.	c/Å	α/°	β/°	γ/°	V/Å^3	μ(Mo-K_α)/cm^{-1}	Cryst. from
(1)	10.831(3)		95.9(3)		772.9	0.54	H_2O
(2)	11.522(4)				2 676.5	0.55	MeOH–H_2O
(3)	6.198(2)	99.1(3)	90.6(3)	110.4(3)	1 027.1	0.48	MeOH–H_2O
(4)	8.719(3)		109.5(3)		1 054.4	1.43	MeOH–H_2O
(5)	8.820(3)		107.5(3)		1 032.5	3.01	EtOAc
(6)	11.783(3)		117.8(3)		1 348.5	29.6	PhMe–LP[a]
(7)	15.432(5)		94.4(3)		2 750.5	0.55	PhMe–LP[a]

Compd.	Solved by	No. of unique reflections	Reflections	R	Hydrogen atoms
(1)	MULTAN[26]	1 359	973	0.037	Refined
(2)	MULTAN	2 358	1 057	0.088	Not refined
(3)	MULTAN	3 603	1 614	0.067	Refined
(4)	MULTAN	1 970	1 756	0.051	Not refined
(5)	MULTAN	1 812	1 518	0.035	Refined
(6)	Patterson and Fourier	2 371	1 620	0.046	Not refined
(7)	MULTAN	2 183	1 088	0.043	Refined

[a] LP = light petroleum.

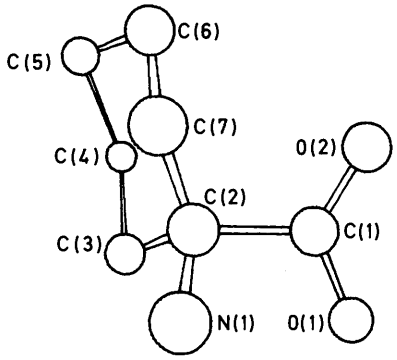

Figure 1. Molecular structure of $^+H_2$-Acc^6-O$^-$ with numbering of the atoms

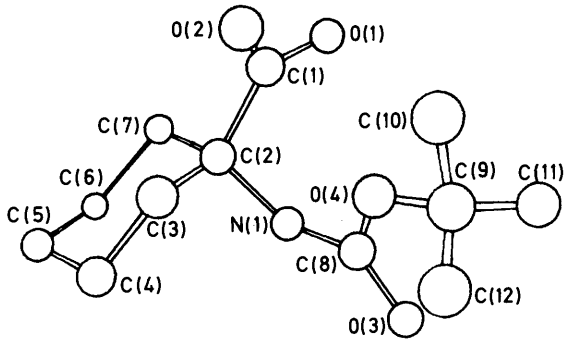

Figure 2. Molecular structure of Boc-Acc^6-OH with numbering of the atoms

work of Kenner and his co-workers.[23] The zwitterionic amino acid (**1**) is the only case where the amino function is equatorial. In contrast, the structure of 1-aminocyclohexane-1-carboxylic acid hydrochloride indicates that the cyclohexane ring has a slightly distorted chair conformation with the carboxy group equatorial and the $^+NH_3$ group axial.[28]

The zwitterionic nature of H-Acc^6-OH (**1**) in crystals (Figure 1) is confirmed by the lengths of the O(1)–C(1) and O(2)–C(1) bonds, 1.241(3) and 1.243(3) Å, respectively, for the –COO$^-$ group. The corresponding values in the structure of the amino acid hydrochloride are 1.317(14) and 1.219(14) Å.[28]

N-*Terminal Groups*.—Bond lengths and bond angles of the *p*-BrC$_6$H$_4$CO moiety of the oxazolone (**6**) (Figure 6) compare well with those found for other *p*-BrC$_6$H$_4$CONH derivatives.[29,30] The phenyl and oxazolone groups are nearly coplanar, the angle between normals to the average planes of these two groups being 7.5°. The angle between normals to the average planes of the phenyl and cyclohexyl groups is 91.5°, *i.e.* the two groups are nearly perpendicular to each other.

The torsion angle δ between the average planes of the amide and carboxylic acid groups in ClCH$_2$CO-Acc^6-OH (**5**) (Figure 5) is 102.9°, an unusual observation for *N*-acylated α-amino acids.[31] The alignment of the C(1)–Cl and amide N(1)–H bonds is suggested by the value of the Cl–C(1)–C(2)–N(1) torsion angle (–17.5°).

The electrostatic repulsion between the two large dipoles of the C(1)–Cl and C(2)–O(3) bonds coupled with the formation of

Table 2. Torsion angles (°) in the cyclohexane ring of compounds (**1**)—(**7**) (e.s.d.s in parentheses)[a]

Compound	C_L^{β}–C^{α}–C_D^{β}–C_D^{γ}	C^{α}–C_D^{β}–C_D^{γ}–C^{δ}	C_D^{β}–C_D^{γ}–C^{δ}–C_L^{γ}	C_D^{γ}–C^{δ}–C_L^{γ}–C_L^{β}	C^{δ}–C_L^{γ}–C_L^{β}–C^{α}	C_L^{γ}–C_L^{β}–C^{α}–C_D^{β}
H-Acc^6-OH (**1**)	52.7(0.2)	−56.2(0.2)	57.4(0.2)	−55.1(0.2)	52.7(0.2)	−51.5(0.2)
Boc-Acc^6-OH (**2**)	−50.8(9.0)	51.9(0.9)	−54.0(0.9)	55.6(0.9)	−55.7(0.9)	53.1(0.9)
Boc-(Acc^6)$_2$-OH (**3**) (i)	−50.8(0.7)	54.8(0.7)	−55.9(0.7)	54.4(0.7)	−51.9(0.7)	49.7(0.7)
Boc-(Acc^6)$_2$-OH (**3**) (ii)	−55.0(0.7)	54.3(0.7)	−53.7(0.7)	54.9(0.7)	−55.7(0.7)	54.9(0.7)
Boc-L-Met-Acc^6-OMe (**4**)	−51.9(0.9)	54.1(0.9)	−55.4(0.9)	55.5(0.9)	−55.4(0.9)	52.9(0.9)
ClCH$_2$CO-Acc^6-OH (**5**)	−52.5(0.2)	53.3(0.2)	−54.3(0.2)	55.5(0.2)	−56.4(0.2)	54.3(0.2)
p-BrC$_6$H$_4$CO-Acc^6-OH oxazolone (**6**)	−55.7(0.5)	57.4(0.5)	−57.0(0.5)	55.2(0.5)	−54.9(0.5)	54.4(0.5)
(Z-Acc^6)$_2$O (**7**)	−49.3(0.6)	55.2(0.6)	−59.8(0.6)	60.7(0.6)	−56.8(0.6)	49.8(0.6)

[a] C_{β} in the Acc^6 residue which occupies the same position as C_{β} in an L-amino acid, is designated C_L^{β}; the other atom is C_D^{β}. The carbon atoms bonded to C_L^{β} and C_D^{β} are designated C_L^{γ} and C_D^{γ}, respectively.

Table 3. Parameters characterizing the Acc^6 residues

Compound	q_2/°[a]	q_3/Å[a]	φ_2/°[a]	Q/Å[a]	θ/°[a]	τ/°[b]
H-Acc^6-OH (**1**)	0.0380	0.5515	−42.3	0.5528	3.94	29.0
Boc-Acc^6-OH (**2**)	0.0318	0.5448	−68.3	0.5457	3.35	82.9
Boc-(Acc^6)$_2$-OH (**3**)	0.0253	0.5498	−143.5	0.5503	2.63	83.4
Boc-L-Met-Acc^6-OMe (**4**)	[c]0.0558	0.5916	−168.9	0.5946	5.77	70.9
	[d]0.0331	0.5359	146.7	0.5369	3.54	84.7
ClCH$_2$CO-Acc^6-OH (**5**)	0.0186	0.5540	−82.2	0.5543	1.93	85.4
p-BrC$_6$H$_4$CO-Acc^6-OH oxazolone (**6**)	0.0091	0.5658	87.8	0.5659	0.93	83.3
(Z-Acc^6)$_2$O (**7**)	0.0748	0.5625	−175.4	0.5675	7.60	72.9

[a] For a definition of these parameters, see ref. 27. [b] Complementary angle between the line connecting N and C_{α} and the normal to the average plane of the cyclohexyl ring. [c] *N*-Terminal Acc^6 residue. [d] *C*-Terminal Acc^6 residue.

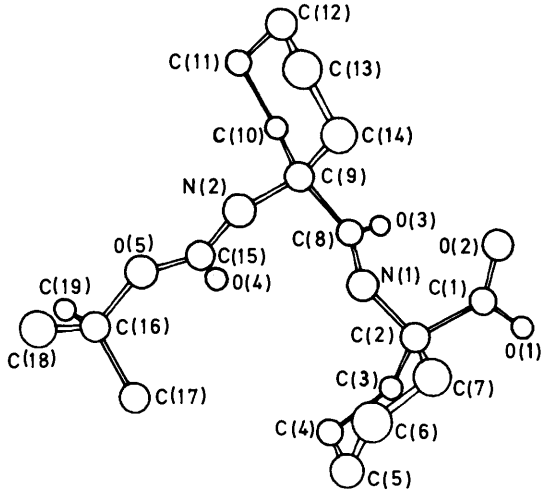

Figure 3. Molecular structure of Boc-(Acc^6)$_2$-OH with numbering of the atoms

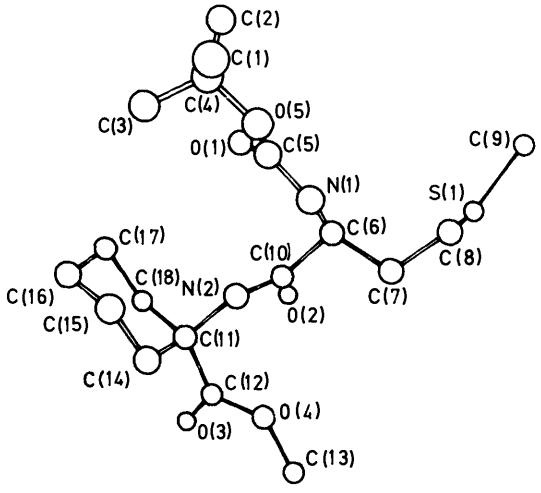

Figure 4. Molecular structure of Boc-L-Met-Acc^6-OMe with numbering of the atoms

the intramolecular N(1)H···Cl H-bond would bring the molecules into the *cis*-conformation for this torsion angle, but the repulsion between Cl and N(1) would prevent them from assuming the exact *cis*-conformation. The net result is expected to produce an angle of twist [Cl–C(1)–C(2)–N(1)] between 0 and 35° (an intermediate position between *cis*- and *gauche*-conformations). The presence of the intramolecularly H-bonded C_5 conformation[32] is corroborated by the following additional observations: (i) the secondary amide torsion angle [C(1)–C(2)–N(1)–C(3)] is 180.0° (the usual *trans*-conformation)[33,34] and (ii) the intramolecular Cl···N(1) and Cl···HN(1) distances are 2.965(3) and 2.553(3) Å. To summarize, among the *N*-monochloroacetylated glycines dialkylated at the α-carbon atom the (*R*)-Iva (isovaline),[35] Deg,[36] and Dpg[36] derivatives adopt the C_5C_5 conformation [with the NH group forming a three-centre, intramolecular H-bond with the adjacent Cl and O(2)], while the Aib[37] and (*R*)-β,β,β-trifluoro-Aib[38] derivatives do not show any intramolecular H-bond. As a third possibility, (*R,R*)-3-methyl-Acc^3 (1-aminocyclopropane-1-carboxylic acid)[39] and the Acc^6 (discussed here) derivatives exhibit a C_5 conformation, where only the ClCH$_2$CONH–moiety is involved in the intramolecular H-bond.

The values of bond lengths and bond angles for the benzyloxycarbonylamino group in (Z-Acc^6)$_2$O (**7**) (Figure 7) are in agreement with the literature data.[40] In particular, the decrease in the bond angle at C(8) by about 7°, as compared with the

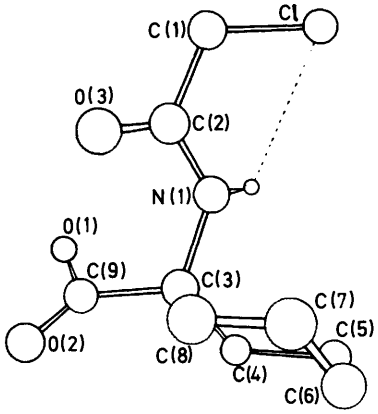

Figure 5. Molecular structure of $ClCH_2CO$-Acc^6-OH with numbering of the atoms; the intramolecular H-bond is shown as a dashed line

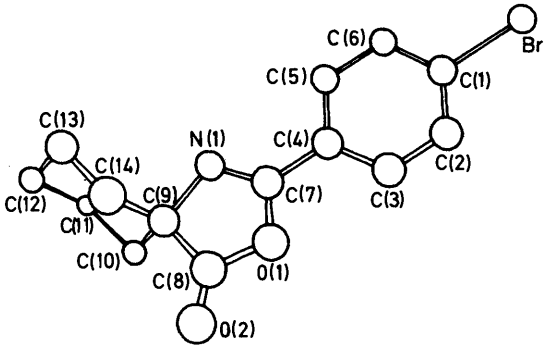

Figure 6. Molecular structure of the oxazolone from BrC_6H_4CO-Acc^6-OH with numbering of the atoms

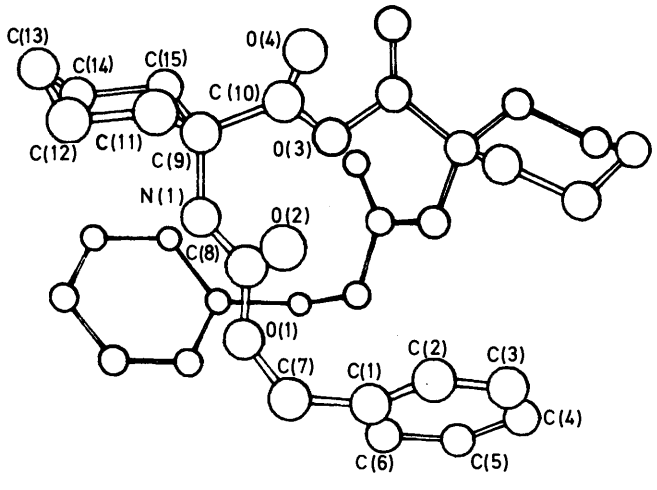

Figure 7. Molecular structure of (Z-Acc^6)$_2$O; only the atoms of one-half of the centrosymmetric molecule are numbered

corresponding bond angle at C′ in the peptide group,[33] must be ascribed to the reduced repulsion between O(1) and the nearest substituent on the N atom in the urethane group, as compared with a corresponding repulsion involving C_α of the peptide group. The angles θ_2 and θ_3, giving the orientation of the phenyl ring relative to the urethane moiety,[40] C(8)–O(1)–C(7)–C(1) and C(6)–C(1)–C(7)–O(1), have values of −90.2 and −70.9°, respectively. Interestingly, in the observed distribution of θ_2 in crystalline Z-derivatives, the values are concentrated in three regions, close to 90, −90, and 180°, respectively; conversely, the distribution of θ_3 values is broad, extending over its entire range.[40] The angle between normals to the average planes of the phenyl and urethane groups is 111.5°. The secondary urethane linkage is found in the usual *trans*-conformation[40–42] [the value of the torsion angle ω_0, C(9)–N(1)–C(8)–O(1) is −173.9°]. This structural property, along with the *trans*-arrangement of the C(7)–O(1) bond relative to the C(8)–N(1) bond [the C(7)–O(1)–C(8)–N(1) torsion angle θ_1 has a value of 180.0°], allows us to classify the urethane moieties of (Z-Acc^6)$_2$O as type *b*.[40–42]

Observed bond lengths and bond angles for the t-butoxycarbonyl groups of Boc-Acc^6-OH (**2**) (Figure 2), Boc-(Acc^6)$_2$OH (**3**) (Figure 3), and Boc-L-Met-Acc^6-OMe (**4**) (Figure 4) are in agreement with previously published results for the geometry of the BocNH group.[41] In particular, unfavourable interactions between the bulky t-butyl group and spatially proximate atoms, especially the carbonyl oxygen, result in alteration of several bond angles, relative to values observed in unhindered esters.[43] The urethane moieties of both Boc-(Acc^6)$_2$-OH and Boc-L-Met-Acc^6-OMe are in the usual type *b* (*trans,trans*) disposition,[41,42] the ω_0, θ_1 set of torsion angles being −170.0, −172.1° for the former and −173.6, −173.1° for the latter. Conversely, the urethane moiety of Boc-Acc^6-OH is found in the uncommon type *a* (*cis,trans*) disposition[41,42] (ω_0 = −17.3°, θ_1 = −175.8°). The angle between normals to the average planes of urethane and carboxylic acid groups in this *N*-protected amino acid is 82.9°.

C-*Terminal Groups*.—In Boc-Acc^6-OH (**2**), Boc-(Acc^6)$_2$-OH (**3**), $ClCH_2CO$-Acc^6-OH (**5**), and Boc-L-Met-Acc^6-OMe (**4**) the carboxylic acid or ester group adopts a conformation with respect to the C–N bond intermediate between anticlinal and antiperiplanar,[44] the N–C_α–C′–O (carbonyl oxygen) torsion angles being −137.2, −147.2, −142.1, and −148.1°, respectively. In addition, the methyl ester group of Boc-L-Met-Acc^6-OMe has the C(13)–O(4)–C(12)–C(11) sequence in the *trans*-disposition (−179.0°).[43]

The N(1)–C(7) bond length, 1.267(6) Å, of the heterocyclic moiety of the oxazolone (**6**) is appropriate for a C–N double bond. This finding confirms the results obtained in the analysis of amino acid and peptide oxazolones the structures of which have been studied previously,[29,45,46] namely that this bond is not conjugated with the lactone moiety C(7)O(1)C(8)O(2)C(9). The O(1)–C(7) and O(1)–C(8) bond lengths are 1.388(6) and 1.385(6) Å, respectively, characteristic of an O–C(sp^2) bond.[47] The exocyclic bond angles about the carbonyl group C(8)–O(2) of the lactone moiety differ by 10.2°, with a larger value for the O(2)–C(8)–C(9) bond angle, 131.3(5)°. This latter value is probably the result of intramolecular interactions between the two C(sp^3) substituents on C(9) and O(2). Again, this finding is in agreement with published data on other oxazolones.[29,45,46] An additional result, common to all oxazolones, is the widening of the N(1)–C(7)–C(4) exocyclic bond angle to >126°. The oxazolone ring is nearly planar. The displacement of the atoms in the five-membered ring from its mean plane varies from −0.008 0(8) to 0.006 7(9) Å [σ(m) = 0.006 Å]. The C(10) and C(14) atoms are displaced by nearly equal amounts on the opposite sides of the average plane of the ring (1.297 and −1.240 Å, respectively).[29,45,46]

The values of bond lengths and bond angles for the anhydride moiety of (Z-Acc^6)$_2$O (**7**) are in agreement with literature data for carboxylic anhydrides.[48–51] In particular, the C(10)–O(3)–C(10′) bond angle [119.1(6)°] deviates markedly from the expected tetrahedral value in ethers (110°). The anhydride

moiety is significant non-planar, the angle between normals to the planes O(3)–C(10)–O(4) and O(3)–C(10′)–O(4′) being 48.7°.[48–52] The conformation of the anhydride is a distorted type-*1* (*trans,trans*),[50,53] the value of the torsion angle C(9)–C(10)–O(3)–C(10′) being 148.2°. The intramolecular distance O(4)···O(4′) would be 2.28 Å for a completely planar type-*1* anhydride with a bond angle C(10)–O(3)–C(10′) amounting to 110°.[49] The observed torsion angle of 48.7° between the two parts of the anhydride moiety and the opening of the C(10)–O(3)–C(10′) bond angle to the experimentally found value of 119.1(6)° increase the intramolecular separation O(4)···O(4′) to the observed value of 2.776(7) Å, this distance being close to the van del Waals distance between non-bonded oxygen atoms. It seems, therefore, that the observed conformation of this type-*1* anhydride is governed mainly by the steric interaction of O(4) and O(4′).[48–52] The angle between normals to the average planes of the urethane and anhydride groups is 109.5°.

Peptide Backbone.—The peptide ω_1 torsion angles[17] of both dipeptides Boc-(Acc^6)$_2$-OH (**3**) and Boc-L-Met-Acc^6-OMe (**4**) are in the usual *trans*-conformation,[33,34] the values being −172.8° and 178.6°, respectively.

The Met residue of Boc-L-Met-Acc^6-OMe and the Acc^6 residues in the five amino acid derivatives and peptides discussed here are always folded, the sets of φ, ψ (or φ, ψ_T)[17] torsion angles falling in the region of the Ramachandran map where both α- and 3_{10}-helices are found. The pertinent values are: $\varphi_1 = 54.4°$, $\psi_{1T} = 47.4°$ for Boc-Acc^6-OH; $\varphi_1 = -57.6°$, $\psi_1 = -46.1°$, $\varphi_2 = 49.3°$, $\psi_{2T} = 38.1°$ for Boc-(Acc^6)$_2$-OH; $\varphi_1 = -71.3°$, $\psi_1 = -21.3°$, $\varphi_2 = 51.2°$, $\psi_{2T} = 38.5°$ for Boc-L-Met-Acc^6-OMe; $\varphi_1 = 54.1°$, $\psi_{1T} = 41.7°$ for ClCH$_2$CO-Acc^6-OH; and $\varphi_1 = 48.0°$, $\psi_{1T} = 38.9°$ for (Z-Acc^6)$_2$O. Two points of interest emerge: (i) in the two *N*-protected dipeptides the signs of the torsion angles φ_1, ψ_1 are opposite to those of the corresponding torsion angles φ_2, ψ_{2T}, as typically found in folded peptides containing α,α-dialkylated glycine residues,[3,6] and (ii) in the compounds discussed here and in those already described[14,15] the Acc^6 residues are always folded.

Crystal Packing.—In the crystals of ClCH$_2$CO-Acc^6-OH (**5**) rows of molecules are held together along the *y* direction through (acid)O–H···O=C(amide) intermolecular H-bonds.[54] The O(1)···O(3) $(1/2 - x, 1/2 + y, -z)$ distance is 2.646(3) Å, falling close to the most probable range for a length of an O–H···O H-bond.[55,56] While the N(1)H group is involved in the intramolecularly H-bonded C_5 structure with the Cl atom,[32] O(2) does not participate in a H-bond. This finding is not in keeping with the principle that the maximum number of proton donors and acceptors will participate in H-bonds, recently put forward in a study on amides and carboxylic acids.[57]

The are no intermolecular H-bonds in the molecules of either (Z-Acc^6)$_2$O[57] (**7**) or the oxazolone (**6**) (however, in the latter compound there are no potential H-bonding donors).

The Boc-Acc^6-OH (**2**) molecules form rows along the *x* direction, characterized by two different intermolecular H-bonds, an (acid)O–H···O=C(urethane) and an (acid)C=O···H–N(urethane) H-bond.[54]

The O(1)···O(3) $(-1/2 + x, y, 1/2 - z)$ separation is 2.637(12) Å,[55,56] and the O(2)···N(1) $(-1/2 + x, y, 1/2 - z)$ separation is 2.984(12) Å, the latter falling within the most probable range for an N–H···O H-bond with an uncharged donor group.[58,59]

The molecules of Boc-L-Met-Acc^6-OMe (**4**) form chains of intermolecular H-bonds of the (peptide)C=O···H–N-(urethane) type in the *y* direction. The O(2)···N(1) $(1 - x, 1/2 + y, 1 - z)$ distance is 2.947(14) Å.[58,59] Neither the peptide N–H nor the urethane and ester C=O groups are involved in the intermolecular H-bonding scheme.[57]

The molecules of Boc-(Acc^6)$_2$-OH (**3**) are held together by the formation of two intermolecular H-bonds of the (acid)O–H···O=C(acid) type across a crystallographic centre of symmetry, giving rise to an eight-membered cyclic dimer, the most commonly observed interlinking motif in carboxylic acids.[60] The O(1)···O(2) $(1 - x, 2 - y, 1 - z)$ distance is 2.622(10) Å.[55,56] In the crystal packing of this *N*-protected dipeptide an additional intermolecular H-bond of the (peptide)C=O···H–N(urethane) type is observed, ultimately producing chains of dimers in the *z*-direction. The O(3)···N(2) $(x, y, -1 + z)$ separation is 2.987(10) Å.[58,59] The peptide N–H and urethane C=O groups do not participate in H-bonds.[57]

In the zwitterionic $^+$H$_2$-Acc^6-O$^-$ molecules the intermolecular H-bonding scheme is developed (i) along the *y* direction between molecules connected by a centre of symmetry, alternately with O(1) and O(2) as acceptors, and (ii) along the *x* direction between molecules connected by a glide plane, exclusively with O(2) as acceptors.[61] The O(1)···N(1) $(1 - x, 1 - y, 2 - z)$, O(2)···N(1) $(1 - x, -y, 2 - z)$, and O(2)···N(1) $(1/2 + x, 1/2 - y, z)$ separations are 2.773(3), 2.808(3), and 2.888(3) Å, respectively. The most probable range for an N–H···O H-bond with a charged donor group is 2.8—2.9 Å.[58]

Acknowledgements

This research was partially supported by a grant from the Department of Atomic Energy, Government of India.

References

1 A. F. Spatola, in 'Chemistry and Biochemistry of Amino Acids, Peptides and Proteins,' ed. B. Weinstein, Dekker, New York, vol. VII, 1983, p. 267.
2 G. R. Marshall, H. E. Bosshard, N. C. E. Kendrick, J. Turk, T. M. Balasubramanian, S. M. H. Cobb, M. Moore, L. Leduc, and P. Needleman, in 'Peptides 1976,' ed. A. Loffet, Editions de l'Université de Bruxelles, Bruxelles, 1976, p. 361.
3 B. V. V. Prasad and P. Balaram, *CRC Crit. Rev. Biochem.*, 1984, **16**, 307.
4 E. Benedetti, B. Di Blasio, V. Pavone, C. Pedone, A. Bavoso, C. Toniolo, G. M. Bonora, M. T. Leplawy, and P. M. Hardy, *J. Biosci.*, 1985, **8**, 253.
5 R. Nagaraj and P. Balaram, *Acc. Chem. Res.*, 1981, **14**, 356.
6 C. Toniolo, G. M. Bonora, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, and C. Pedone, *Biopolymers*, 1983, **22**, 205.
7 C. Toniolo, G. M. Bonora, V. Barone, A. Bavoso, E. Benedetti, B. Di Blasio, P. Grimaldi, F. Lelj, V. Pavone, and C. Pedone, *Macromolecules*, 1985, **18**, 895.
8 R. Bosch, G. Jung, H. Schmitt, and W. Winter, *Biopolymers*, 1985, **24**, 979.
9 R. Bosch, G. Jung, H. Schmitt, and W. Winter, *Biopolymers*, 1985, **24**, 961.
10 C. Toniolo, G. M. Bonora, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, C. Pedone, M. T. Leplawy, K. Kaczmarek, and A. Redlinski, *Biopolymers*, in the press.
11 E. Benedetti, C. Toniolo, P. Hardy, V. Barone, A. Bavoso, B. Di Blasio, P. Grimaldi, F. Lelj, V. Pavone, C. Pedone, G. M. Bonora, and I. Lingham, *J. Am. Chem. Soc.*, 1984, **106**, 8146.
12 G. M. Bonora, C. Toniolo, B. Di Blasio, V. Pavone, C. Pedone, E. Benedetti, I. Lingham, and P. M. Hardy, *J. Am. Chem. Soc.*, 1984, **106**, 8152.
13 R. Kishore and P. Balaram, in 'The Medicinal Chemistry and Molecular Pharmacology of Opioid Peptides and the Opiates,' eds. R. S. Rapaka, G. Barret, and R. L. Hawks, National Institute of Drug Abuse, U.S.A. Research Monograph 69, 1986, p. 312.
14 R. Bardi, A. M. Piazzesi, C. Toniolo, M. Sukumar, P. A. Raj, and P. Balaram, *Int. J. Pept. Protein Res.*, 1985, **25**, 628.
15 P. K. C. Paul, M. Sukumar, R. Bardi, A. M. Piazzesi, G. Valle, C. Toniolo, and P. Balaram, *J. Am. Chem. Soc.*, 1986, **108**, 6363.

16 R. Bardi, A. M. Piazzesi, C. Toniolo, M. Sukumar, and P. Balaram, *Biopolymers*, 1986, **25**, 1635.
17 Backbone torsion angles are defined according to the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature: *Biochemistry*, 1970, **9**, 3471.
18 G. N. Ramachandran and V. Sasisekharan, *Adv. Protein Chem.*, 1968, **23**, 283.
19 M. Sukumar, P. A. Raj, P. Balaram, and E. L. Becker, *Biochem. Biophys. Res. Commun.*, 1985, **128**, 339.
20 J. W. Tsang, B. Schmied, R. Nyfeler, and M. Goodman, *J. Med. Chem.*, 1984, **27**, 1663.
21 M. Rodriguez, J. M. Bland, J. W. Tsang, and M. Goodman, *J. Med. Chem.*, 1985, **28**, 1527.
22 M. Goodman, *Biopolymers*, 1985, **24**, 137.
23 G. W. Kenner, J. Preston, and R. C. Sheppard, *J. Chem. Soc.*, 1965, 6239.
24 P. Tailleur and L. Berlinguet, *Can. J. Chem.*, 1961, **39**, 1309.
25 M. Itoh, D. Hagiwara, and T. Kamiya, *Tetrahedron Lett.*, 1975, 4393.
26 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, 'MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data,' Universities of York and Louvain, 1980.
27 D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, 1975, **97**, 1354.
28 K. K. Chacko, R. Srinivasan, and R. Zand, *J. Cryst. Mol. Struct.*, 1971, **1**, 261.
29 G. Valle, M. Crisma, and C. Toniolo, *Z. Kristallogr.*, 1986, **175**, 73.
30 C. Toniolo, G. M. Bonora, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, and C. Pedone, *Macromolecules*, 1986, **19**, 472.
31 C. S. Chen and R. Parthasarathy, *Int. J. Pept. Protein Res.*, 1978, **11**, 9.
32 C. Toniolo, *CRC Crit. Rev. Biochem.*, 1980, **9**, 1.
33 E. Benedetti, in 'Chemistry and Biochemistry of Amino Acids, Peptides and Proteins,' ed. B. Weinstein, Dekker, New York, vol. 6, p. 105.
34 I. L. Karle, in 'The Peptides,' eds. E. Gross and J. Meienhofer, Academic Press, New York, 1981, vol. 4, p. 1.
35 R. Bosch, H. Brückner, G. Jung, and W. Winter, *Tetrahedron*, 1982, **38**, 3579.
36 G. Valle, G. M. Bonora, C. Toniolo, P. M. Hardy, M. T. Leplawy, and A. Redlinski, *J. Chem. Soc., Perkin Trans. 2*, 1986, 885.
37 G. Valle, G. M. Bonora, and C. Toniolo, *Gazz. Chim. Ital.*, 1984, **114**, 481.
38 J. W. Keller and C. S. Day, *Acta Crystallogr., Sect. C*, 1984, **40**, 1224.
39 J. E. Baldwin, R. M. Adlington, B. J. Rawlings, and R. H. Jones, *Tetrahedron Lett.*, 1985, **26**, 485.
40 E. Benedetti, C. Pedone, C. Toniolo, M. Dudek, G. Neméthy, and H. A. Scheraga, *Int. J. Pept. Protein Res.*, 1983, **21**, 163.
41 E. Benedetti, C. Pedone, C. Toniolo, G. Neméthy, M. S. Pottle, and H. A. Scheraga, *Int. J. Pept. Protein Res.*, 1980, **16**, 156.
42 E. Benedetti, A. Ciajolo, B. Di Blasio, V. Pavone, C. Pedone, C. Toniolo, and G. M. Bonora, *Int. J. Pept. Protein Res.*, 1979, **14**, 130.
43 W. B. Schweizer and J. D. Dunitz, *Helv. Chim. Acta*, 1982, **65**, 1547.
44 J. D. Dunitz and P. Strickler, in 'Structural Chemistry and Molecular Biology,' eds. A. Rich and N. Davidson, Freeman, San Francisco, 1968, p. 595.
45 C. M. K. Nair and M. Vijayan, *Acta Crystallogr., Sect. B*, 1980, **36**, 1498.
46 C. Toniolo, G. M. Bonora, M. Crisma, E. Benedetti, A. Bavoso, B. Di Blasio, V. Pavone, and C. Pedone, *Int. J. Pept. Protein Res.*, 1983, **22**, 603.
47 L. Norskov-Lauritsen, H. B. Bürgi, P. Hofmann, and H. R. Schmidt, *Helv. Chim. Acta*, 1985, **68**, 76.
48 G. Valle, C. Toniolo, and G. Jung, *Liebigs Ann. Chem.*, 1986, 1809.
49 A. J. De Kok and C. Romers, *Recl. Trav. Chim. Pays-Bas*, 1969, **88**, 625.
50 G. Valle, F. Formaggio, M. Crisma, G. M. Bonora, C. Toniolo, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, and C. Pedone, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1371.
51 I. Goldberg, L. T. W. Lin, and H. Hart, *Acta Crystallogr., Sect. C*, 1985, **41**, 1535.
52 C. S. McCammon and J. Trotter, *Acta Crystallogr.*, 1964, **17**, 1333.
53 O. Exner, in 'The Chemistry of Functional Groups: Supplement A, The Chemistry of Double-Bonded Functional Groups,' ed. S. Patai, Wiley, New York, 1977, p. 1.
54 I. Berkovitch-Yellin, S. Ariel, and L. Leiserowitz, *J. Am. Chem. Soc.*, 1983, **105**, 765.
55 J. Mitra and C. Ramakrishnan, *Int. J. Pept. Protein Res.*, 1977, **9**, 27.
56 I. D. Brown, *Acta Crystallogr., Sect. A*, 1976, **32**, 24.
57 M. Etter, *J. Am. Chem. Soc.*, 1982, **104**, 1095.
58 C. Ramakrishnan and N. Prasad, *Int. J. Protein Res.*, 1971, **3**, 209.
59 R. Taylor, O. Kennard, and W. Versichel, *Acta Crystallogr., Sect. B*, 1984, **40**, 280.
60 L. Leiserowitz, *Acta Crystallogr., Sect. B*, 1976, **32**, 775.
61 C. G. Suresh and M. Vijayan, *Int. J. Pept. Protein Res.*, 1983, **22**, 129.

Received 4*th March* 1987; *Paper* 7/398