Intramolecularly Hydrogen-bonded Peptide Conformations. Preferred Crystal-state and Solution Conformations of *N*-Monochloroacetylated Glycines Dialkylated at the α-Carbon Atom

Giovanni Valle, Gian Maria Bonora, and Claudio Toniolo *
Biopolymer Research Centre, C.N.R., Department of Organic Chemistry, University of Padova, 35131 Padova, Italy
Paul M. Hardy *
Department of Chemistry, University of Exeter, Exeter EX4 4QD
Miroslaw T. Leplawy * **and Adam Redlinski**
Institute of Organic Chemistry, Technical University, 90—924 Lodz, Poland

A crystal-state structural analysis of *N*-monochloroacetylated glycines diethylated and di-n-propylated at the α-carbon was performed by *X*-ray diffraction. In both structures the α-amino acid residue shows a φ,ψ_T set of torsion angles in the region of the conformational energy map where fully extended conformations are found. The conformation about the amide bond is *trans*, and the substituted acetamido and carboxylic acid groups are nearly coplanar. The two structures are characterized by a three-centre, doubly intramolecular hydrogen bond (C_5,C_5 conformer) of the Cl···H(N)···O (carboxylic acid) type. For both compounds these interactions survive in deuteriochloroform solution, as shown by ^{1}H n.m.r. and i.r. absorption analysis.

The intramolecularly hydrogen-bonded C_5 peptide conformation (Figure 1c) is similar to the fully extended form ($\varphi = \psi = 180$ °C).[1] The relative disposition of the two dipoles, N–H and C(1)=O, is such that there is obviously some interaction between them. These four atoms, together with the α-carbon atom, are involved in a pentagonal ring, and it is for this reason that this conformation is called C_5.

In recent publications we have been able to show both theoretically and experimentally that the *C*-α,α-diethylated and -di-n-propylated glycine residues (hereafter called Deg and Dpg, respectively) strongly prefer the fully extended C_5 ring conformation.[2–4] This result is in contrast to that found for the glycine residue dimethylated at the α-carbon (α-aminoisobutyric acid, abbreviated as Aib) which exhibits a remarkable tendency to give folded forms.[2–8] Interestingly, the behaviour of the *chiral* residue with one methyl and one ethyl group at the α-carbon (isovaline, abbreviated as Iva) is intermediate,[9] in the sense that the energies of the fully extended and folded forms are comparable.[2]

In our continuing effort to reveal patterns of geometrical and conformational preferences of α-halogenoacetylated α-amino acids (Figures 1a—d),[10,11] in this paper we describe the results of an *X*-ray diffraction analysis of mClAc-Deg-OH (mClAc, monochloroacetyl) and mClAc-Dpg-OH. The results will be discussed in comparison with those of the *N*-monochloroacetylated derivatives of Aib,[10] (*R*)-Iva,[9] (*R*)-β,β,β-trifluoro-Aib,[12] and (*R*,*R*)-3-methylAcc^3 (Acc^3, α-aminocyclopropanecarboxylic acid),[13] all residues dialkylated at the α-carbon. The present investigation was also extended to a solvent of relative low polarity ($CDCl_3$) by using ^{1}H n.m.r. and i.r. absorption, where a comparison has been made with mClAc-Aib-OH and Ac-Aib-OH.

The main questions to be addressed are as follows. (i) Do mClAc-Deg-OH and mClAc-Dpg-OH adopt the C_5,C_5 conformation[1] with the three-centre, doubly intramolecular (bifurcated) hydrogen bond[14,15] (Figure 1a) in the crystal state? (ii) Does this conformation survive in $CDCl_3$ solution?

This investigation is of interest since α-halogenoacetylated α-amino acids are often used as substrates of proteolytic enzymes.[9,12,13] The study, therefore, of their conformational preferences is fundamental for an understanding of the interactions at the active site.

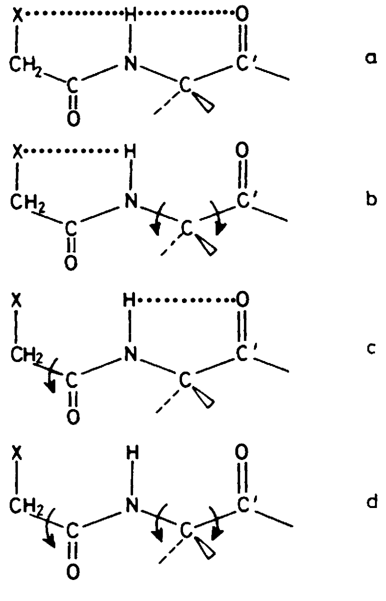

Figure 1. Schematic representation of the C_5,C_5 conformer *a*; the two types of C_5 conformers *b* and *c*; and an open conformer, *d*, of an *N*-halogenoacetylated α-amino acid. Intramolecular hydrogen bonds are indicated as dotted lines

Experimental

Materials.—The synthesis and characterization of Ac-Aib-OH[16–18] and mClAc-Aib-OH[10] have been reported. mClAc-Deg-OH and mClAc-Dpg-OH were prepared under alkaline conditions by using the relevant acid chloride as the monochloroacetylating agent. Their characterization is given below: mClAc-Deg-OH, m.p. 189—191 °C (ethyl acetate–n-hexane 1:2) (Found: C, 46.1; H, 6.6; N, 6.9; Cl, 16.85. $C_8H_{14}ClNO_3$ requires C, 46.3; H, 6.8; N, 6.7; Cl, 17.1%); mClAc-Dpg-OH, m.p. 215—216 °C (ethyl acetate) (Found: C, 51.15; H, 7.95; N, 5.8; Cl, 15.0. $C_{10}H_{18}ClNO_3$ requires C, 51.0; H, 7.7; N, 5.9; Cl, 15.1%).

Crystal Data for mClAc-Deg-OH.—$C_8H_{14}ClNO_3$, M = 207.7. Orthorhombic, a = 7.755(3), b = 12.162(4), c =

Table 1. Bond lengths (Å) for mClAc-Deg-OH and mClAc-Dpg-OH with e.s.d.s in parentheses

mClAc-Deg-OH		mClAc-Dpg-OH	
Cl–C(1)	1.760(4)	Cl–C(1)	1.788(5)
O(3)–C(6)	1.307(3)	O(3)–C(4)	1.329(5)
C(1)–C(2)	1.502(4)	C(1)–C(2)	1.513(6)
C(3)–C(6)	1.535(3)	C(3)–C(8)	1.466(7)
O(2)–C(6)	1.205(3)	C(8)–C(9)	1.525(8)
N(1)–C(3)	1.460(3)	O(2)–C(4)	1.196(5)
C(3)–C(5)	1.531(4)	N(1)–C(3)	1.491(5)
C(5)–C(7)	1.512(6)	C(3)–C(5)	1.542(6)
O(1)–C(2)	1.231(3)	C(6)–C(7)	1.525(8)
N(1)–C(2)	1.332(3)	O(1)–C(2)	1.245(5)
C(3)–C(4)	1.532(4)	N(1)–C(2)	1.360(5)
C(4)–C(8)	1.492(5)	C(3)–C(4)	1.570(6)
		C(5)–C(6)	1.450(8)
		C(9)–C(10)	1.454(9)

Table 2. Bond angles (°) for mClAc-Deg-OH and mClAc-Dpg-OH with e.s.d.s in parentheses

mClAc-Deg-OH		mClAc-Dpg-OH	
C(2)–N(1)–C(3)	127.7(3)	C(2)–N(1)–C(3)	127.1(4)
O(1)–C(2)–N(1)	123.3(3)	O(1)–C(2)–N(1)	124.6(4)
N(1)–C(2)–C(1)	116.9(3)	N(1)–C(2)–C(1)	119.2(4)
N(1)–C(3)–C(5)	110.1(2)	N(1)–C(3)–C(5)	112.1(4)
C(4)–C(3)–C(5)	111.4(2)	C(5)–C(3)–C(8)	110.5(4)
C(5)–C(3)–C(6)	108.7(2)	C(4)–C(3)–C(5)	109.5(3)
C(3)–C(5)–C(7)	114.7(3)	O(3)–C(4)–C(3)	113.4(4)
O(3)–C(6)–C(3)	112.0(2)	C(3)–C(5)–C(6)	115.9(4)
Cl–C(1)–C(2)	114.6(2)	C(3)–C(8)–C(9)	117.4(4)
O(1)–C(2)–C(1)	119.7(2)	Cl–C(1)–C(2)	114.0(3)
N(1)–C(3)–C(4)	112.1(2)	O(1)–C(2)–C(1)	116.2(4)
N(1)–C(3)–C(6)	104.3(2)	N(1)–C(3)–C(4)	105.9(3)
C(4)–C(3)–C(6)	110.0(2)	N(1)–C(3)–C(8)	108.8(4)
C(3)–C(4)–C(8)	115.3(3)	C(4)–C(3)–C(8)	109.8(4)
O(2)–C(6)–C(3)	123.7(2)	O(2)–C(4)–C(3)	124.2(4)
O(2)–C(6)–O(3)	124.3(2)	O(2)–C(4)–O(3)	122.4(4)
		C(5)–C(6)–C(7)	112.2(5)
		C(8)–C(9)–C(10)	112.8(6)

22.567(5) Å, V = 2 128.43 Å^3, space group *Pbca* (no. 61), Z = 8, D_m = 1.285(5) g cm^{-3}, D_c = 1.289 g cm^{-3}, μ = 2.90 cm^{-1} (*Mo*-K_α), final R value 0.044.

Crystal Data for mClAc-Dpg-OH.—$C_{10}H_{18}ClNO_3$, M = 235.7. Monoclinic, a = 7.694(3), b = 7.976(3), c = 20.665(5) Å, β = 94.2(2)°, V = 1 264.67 Å^3, space group $P2_1/c$ [*no. 14*]. Z = 4, D_m = 1.235(5) g cm^3, D_c = 1.237 g cm^{-3}, μ = 2.48 cm^{-1} (Mo-K_α), final R value 0.060.

X-Ray Crystal Structure Determination of mClAc-Deg-OH *and* mClAc-Dpg-OH.—Crystals of both compounds were grown by slow evaporation of acetone solutions. Philips PW1100 diffractometer, θ–2θ scan mode up to θ = 25°; graphite-monochromated Mo-K_α radiation (λ = 0.710 69 Å); 1 878 unique reflections and 1 147 with $I > 3\sigma(I)$ considered observed for mClAc-Deg-OH; 2 221 unique reflections and 1 254 with $I > 3\sigma(I)$ considered observed for mClAc-Dpg-OH. Both structures were solved with MULTAN 80[19] and refined by full-matrix least-squares, $\omega = 1/0.308\ [\sigma^2(F) + 0.000\,24\ F^2]$ for mClAc-Deg-OH and $\omega = 1/0.335\ [\sigma^2(F) + 0.001F^2]$. The thermal parameters were anisotropic for all non-hydrogen atoms. The hydrogen atoms of mClAc-Deg-OH were found on a difference Fourier map and refined isotropically; the hydrogen atoms of mClAc-Dpg-OH were found partly on a difference Fourier map and partly calculated, and were not refined.

Table 3. Torsion angles* ( ) for mClAc-Deg-OH and mClAc-Dpg-OH with e.s.d.s in parentheses

mClAc-Deg-OH		mClAc-Dpg-OH	
C(3)–N(1)–C(2)–O(1)	−3.8	C(3)–N(1)–C(2)–O(1)	−5.0
C(2)–N(1)–C(3)–C(4)	55.4	C(2)–N(1)–C(3)–C(4)	178.3
C(2)–N(1)–C(3)–C(6)	174.4	C(2)–N(1)–C(3)–C(8)	−63.6
Cl–C(1)–C(2)–N(1)	−31.9	Cl–C(1)–C(2)–N(1)	−24.4
C(5)–C(3)–C(4)–C(8)	176.5	N(1)–C(3)–C(4)–O(3)	180.0
N(1)–C(3)–C(5)–C(7)	−60.6	C(5)–C(3)–C(4)–O(3)	−58.3
C(6)–C(3)–C(5)–C(7)	53.2	C(8)–C(3)–C(4)–O(3)	63.2
N(1)–C(3)–C(6)–O(3)	−178.5	C(4)–C(3)–C(5)–C(6)	−59.6
C(4)–C(3)–C(6)–O(3)	−58.1	N(1)–C(3)–C(8)–C(9)	−59.0
C(5)–C(3)–C(6)–O(3)	64.0	C(5)–C(3)–C(8)–C(9)	177.5
C(3)–N(1)–C(2)–C(1)	178.9	C(3)–C(8)–C(9)–C(10)	180.0
C(2)–N(1)–C(3)–C(5)	−69.2	C(3)–N(1)–C(2)–C(1)	176.1
Cl–C(1)–C(2)–O(1)	150.7	C(2)–N(1)–C(3)–C(5)	58.9
N(1)–C(3)–C(4)–C(8)	52.7	Cl–C(1)–C(2)–O(1)	156.6
C(6)–C(3)–C(4)–C(8)	−63.0	N(1)–C(3)–C(4)–O(2)	1.2
C(4)–C(3)–C(5)–C(7)	174.4	C(5)–C(3)–C(4)–O(2)	122.2
N(1)–C(3)–C(6)–O(2)	2.2	C(8)–C(3)–C(4)–O(2)	−116.2
C(4)–C(3)–C(6)–O(2)	122.6	N(1)–C(3)–C(5)–C(6)	57.7
C(5)–C(3)–C(6)–O(2)	−115.3	C(8)–C(3)–C(5)–C(6)	180.0
		C(4)–C(3)–C(8)–C(9)	56.6
		C(3)–C(5)–C(6)–C(7)	173.4

* Ref. 22. Each molecule, having no chiral atoms, crystallizes in a centrosymmetric space group; thus, the signs of the torsion angles reported in this Table are only relative.

^{1}H *N.m.r.*—The ^{1}H n.m.r. spectra were recorded with a Bruker WP 200SY spectrometer. Measurements were carried out in deuteriochloroform (99.96% ^{2}H; Fluka) and in dimethyl sulphoxide (99.96% $^2H_6$; Fluka) with tetramethylsilane as internal standard.

I.r. Absorption.—I.r. absorption spectra were recorded with a Perkin-Elmer model 580B spectrophotometer equipped with a Perkin-Elmer model 3600 data station and a model 660 printer. Cells with path lengths of 10, 1.0, and 0.1 mm and CaF_2 windows were used. Deuteriochloroform (99.8% ^{2}H) was a Fluka product.

Results and Discussion

Crystal-state Conformations.—Bond lengths, bond angles, and torsion angles for mClAc-Deg-OH and mClAc-Dpg-OH are listed in Tables 1—3. Figures 2 and 3 show the molecular structures of the two *N*-monochloracetylated derivatives.

Bond lengths of the two compounds compare well with those found in mClAc-Aib-OH,[10] mClAc-(*R*)-Iva-OH,[9] and mClAc-(*R*)-β,β,β-trifluoro-Aib-OH.[12] As for bond angles, it is worth noting that the values of the N(1)–C(3)–C(6) angle of mClAc-Deg-OH and of the corresponding N(1)–C(3)–C(4) angle of mClAc-Dpg-OH are much smaller than the usual tetrahedral value of 110°[20] (104.3 and 105.9°, respectively). This is a first indication of the presence of an intramolecular interaction between the N–H and (carboxylic acid) C=O groups[9] forming the pentagonal structure illustrated in Figures 1a and c.

The dihedral angles δ between the average planes of the amide and carboxylic acid groups is 7 and 5.2° for mClAc-Deg-OH and mClAc-Dpg-OH, respectively, an unusual observation for *N*-acylated α-amino acids.[21] The torsion angles[22] N(1)–C(3)–C(6)–O(2) and N(1)–C(3)–C(4)–O(2) have values of 2.2 and 1.2°, respectively, thereby indicating a synplanar arrangement[23] for the carboxylic acid and N–H groups. In addition, the alignment of the Cl and O(2) atoms for close approach to the amide HN(1) atom is suggested by the values of the Cl–C(1)–C(2)–N(1) torsion angle, −31.9 and −24.4° for mClAc-Deg-OH and mClAc-Dpg-OH, respectively.[9] The electrostatic repulsion between the two large dipoles of the C(1)–Cl and C(2)=O(1) bonds coupled with the formation of the intramolecular N(1)–H···Cl hydrogen bond would bring the molecules to the *cis* conformation for this torsion angle, but the repulsion between the Cl and N(1) atoms 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).

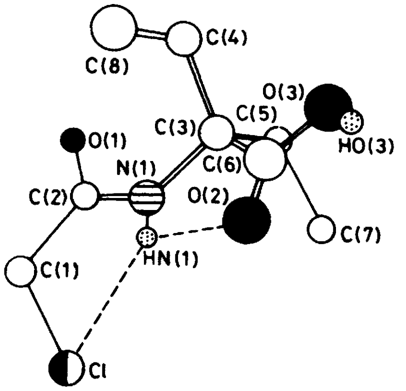

Figure 2. Molecular structure of mClAc-Deg-OH with the numbering of the atoms. Intramolcular hydrogen bonds are indicated as dashed lines

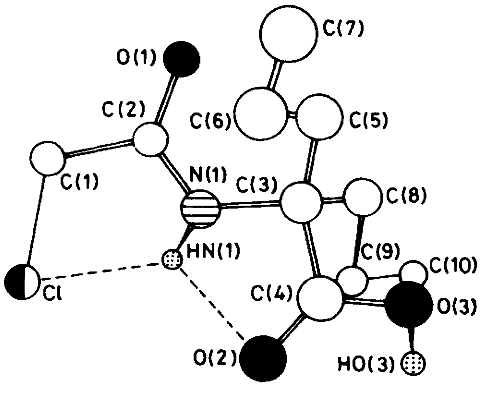

Figure 3. Molecular structure of mClAc-Dpg-OH with the numbering of the atoms. Intramolecular hydrogen bonds are indicated as dashed lines

The presence, in the two compounds, of the three-centre doubly intramolecular (bifurcated)[14,15] hydrogen-bonded C_5,C_5 conformation,[1] schematically shown in Figure 1a and illustrated in detail in Figures 2 and 3, is corroborated by the following additional observations. (i) The secondary amide torsion angle ω [C(1)–C(2)–N(1)–C(3)] is 178.9 and 176.1 for mClAc-Deg-OH and mClAc-Dpg-OH, respectively (the usual *trans* conformation).[24] (ii) The Deg and Dpg residues are fully extended, the sets of φ,ψ_T torsion angles being 174.4 and 178.5 for the former, and 178.3 and 180.0° for the latter.[2,4] (iii) The intramolecular Cl···N(1) and Cl···HN(1) distances are 2.96 and 2.49 Å for mClAc-Deg-OH, and 3.00 and 2.71 Å for mClAc-Dpg-OH.[9] (iv) The O(2)···N(1) and O(2)···NH(1) distances are 2.60 and 2.22 Å for mClAc-Deg-OH, and 2.69 and 2.13 Å for mClAc-Dpg-OH.[9,25]

Each molecule in the crystals of the two compounds participates in one intermolecular hydrogen bond. The carboxylic acid O(3)H links the acceptor amide O(1) atoms of a neighbouring molecule[26] with symmetry translations and O(3)···O(1) distances 1 − *x*, *y*, *z* and 2.612(4) Å[27,28] for mClAc-Deg-OH and *x*, *y* − 1, *z* and 2.676(5) Å[27,28] for mClAc-Dpg-OH.

To summarize, among the *N*-monochloroacetylated glycines dialkylated at the α-carbon the (*R*)-Iva,[9] Deg, and Dpg derivatives adopt the C_5,C_5 conformer (Figure 1a) while the Aib,[10] (*R*)-β,β,β-trifluoroAib,[12] and (*R*,*R*)-3-methylAcc[3,13] derivatives do not show a fully extended conformation in their -NH-CR^{1}R^2-CO-part. Interestingly, only the latter derivative still appears to exhibit the intramolecular N–H···Cl interaction,[13] as illustrated in Figure 1b. The results for the *N*-monochloroacetylated Aib,[10] (*R*)-Iva,[9] Deg, and Dpg derivatives are in excellent agreement with published theoretical and crystal-state experimental data on other derivatives and peptides from these $C^{\alpha,\alpha}$-dialkylated glycines.[2,4–8]

Solution Conformations.—In the 3 550—3 300 cm^{-1} region the i.r. absorption spectrum of mClAc-Deg-OH in CDCl$_3$, a solvent of relatively low polarity, shows three bands at *ca.* 3 512,

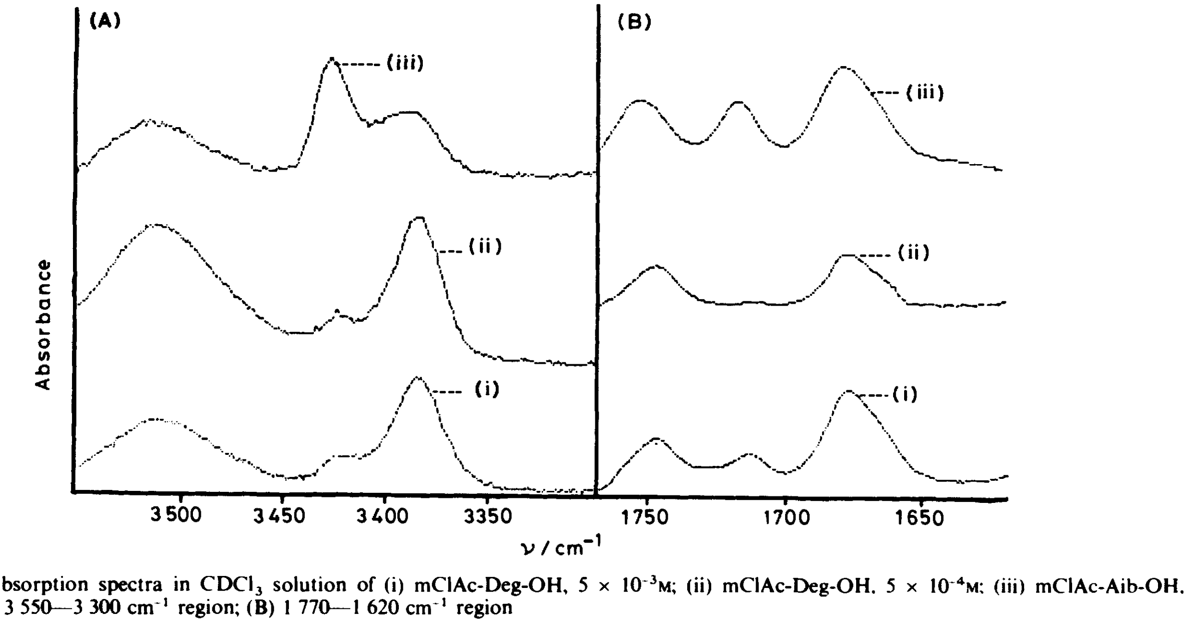

Figure 4. I.r. absorption spectra in CDCl$_3$ solution of (i) mClAc-Deg-OH, 5 × 10^{-3}M; (ii) mClAc-Deg-OH, 5 × 10^{-4}M; (iii) mClAc-Aib-OH, 5 × 10^{-3}M. (A) 3 550—3 300 cm^{-1} region; (B) 1 770—1 620 cm^{-1} region

3 420, and 3 384 cm^{-1} (Figure 4). The strong absorption at 3 512 cm^{-1}, the intensity of which decreases with increasing concentration, is assigned to the stretching mode of free carboxylic acid O–H groups.[29,30] The weak and strong absorptions at 3 420 and 3 384 cm^{-1}, respectively, are assigned to the stretching modes of weakly intramolecularly hydrogen-bonded N–H groups of the Cl$\cdots$HN and Cl$\cdots$H(N)$\cdots$O (carboxylic acid) types, respectively.[31–34] In the 1 770—1 620 cm^{-1} region the spectrum is characterized by two strong bands at 1 748 cm^{-1} (C=O stretching mode of weakly intramolecularly hydrogen-bonded carboxylic acid groups)[30] and 1 680 cm^{-1} (C=O stretching mode of free amide groups),[31–33] accompanied by a weaker band at 1 714 cm^{-1}, the intensity of which increases with increasing concentration (C=O stretching mode of strongly intermolecularly hydrogen-bonded carboxylic acid groups).[11] The i.r. absorption properties of mClAc-Dpg-OH are similar to those of mClAc-Deg-OH, but the latter shows a slightly enhanced self-association tendency.

Interestingly, the nature of the intermolecular hydrogen bonds occurring in the more concentrated $CDCl_3$ solution (involving the carboxylic acid C=O group as the hydrogen-bonding acceptor) seem to differ from that found in the crystal state (involving the amide C=O group as the hydrogen-bonding acceptor). However, the characteristic intramolecular Cl$\cdots$H(N)$\cdots$O interaction (C_5,C_5 conformer) appears to survive to a high extent in $CDCl_3$ solution.

The significantly lower tendency of mClAc-Aib-OH to give the C_5,C_5 conformer is illustrated in Figure 4, where the relative intensity of the two N–H bands is reversed compared with mClAc-Deg-OH (and mClAc-Dpg-OH). In parallel, the strong band at *ca.* 1 750 cm^{-1} undergoes a 6 cm^{-1} shift to higher frequency. The propensity of mClAc-Aib-OH to self-associate *via* O–H$\cdots$O=C (carboxylic acid) intermolecular hydrogen bonds is even larger than that of mClAc-Deg-OH. The i.r. absorption spectrum of Ac-Aib-OH (not shown) exhibits two bands in the N–H stretching region. From literature data[34,35] and a concentration study the stronger absorption at 3 434 cm^{-1} is assigned to free N–H groups, and the weaker absorption at 3 338 cm^{-1} to N–H groups involved in intermolecular hydrogen bonds of moderate strength. The positions of these two bands indirectly corroborate our assignments of the Cl$\cdots$HN and Cl$\cdots$H(N)$\cdots$O N–H stretching vibrations. In fact, the inductive effect of the Cl-substituent is known to increase the N–H stretching frequency, but it is more than compensated for by the effect of the Cl$\cdots$HN intramolecular hydrogen bond,[31–34] thereby producing a net shift to lower frequency from 3 434 cm^{-1} (Ac-Aib-OH) to 3 420 cm^{-1} (*N*-monochloroacetylated derivatives). The effect of the additional intramolecular hydrogen bond (N–H$\cdots$O=C) is to decrease further the frequency[1,36] (to 3 384 cm^{-1}).

A ^{1}H n.m.r. investigation confirmed the similar behaviour of mClAc-Deg-OH and mClAc-Dpg-OH. In $CDCl_3$ solution the peak of the NH proton of the former is seen at δ 7.43, while that of the latter is near δ 7.45. Conversely, mClAc-Aib-OH shows its NH proton at significantly higher field, δ 7.12 (in the non-halogenated derivative Ac-Aib-OH the corresponding peak is visible at δ 5.85). These chemical shifts values are only slightly altered by heating or by changing concentration. The addition of the strong hydrogen-bonding acceptor solvent dimethyl sulphoxide (DMSO)[37] again emphasized the parallelism between mClAc-Deg-OH and mClAc-Dpg-OH. The $\Delta\delta$ values between the two solvents are 0.45 (to lower fields from $CDCl_3$ to DMSO solution) for mClAc-Deg-OH and 0.44 for mClAc-Dpg-OH. For mClAc-Aib-OH and Ac-Aib-OH, on the other hand, this parameter is dramatically enhanced to δ 1.29 and 2.18, respectively.

From the above results it seems reasonable to conclude that the three-centre, doubly intramolecular hydrogen-bonded C_5,C_5 structure (Figure 1a), found for mClAc-Deg-OH as well as mClAc-Dpg-OH in the crystal state, is still present to a significant extent in $CDCl_3$ solution as a remarkably stable conformer. It is noteworthy that also in solution the behaviour of the monochloroacetylated derivatives of these two glycine residues dialkylated at α-carbon is markedly different from that of their lower homologue (mClAc-Aib-OH) which does not tend to adopt a fully extended conformation in its amino acid part.

References

1 C. Toniolo, *CRC Crit. Rev. Biochem.*, 1980, **9**, 1.
2 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.
3 G. M. Bonora, C. Toniolo, B. Di Blasio, V. Pavone, C. Pedone, E. Benedetti, I. Lingham, and P. Hardy, *J. Am. Chem. Soc.*, 1984, **106**, 8152.
4 E. Benedetti, B. Di Blasio, C. Pedone, A. Bavoso, C. Toniolo, G. M. Bonora, M. T. Leplawy, and P. M. Hardy, in 'Proceedings of the International Symposium in Biomolecular Structure and Interactions,' ed. V. Sasisekharan, Indian Institute of Science, Bangalore, 1985, vol. 8, p. 253.
5 C. Toniolo, G. M. Bonora, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, and C. Pedone, *Biopolymers*, 1983, **22**, 205.
6 G. R. Marshall, in 'Intra-science Chemistry Reports,' ed. N. Kharasch, Gordon and Breach, New York, 1971, vol. 5, p. 305.
7 G. Jung, H. Brückner, and H. Schmitt, in 'Structure and Activity of Natural Peptides,' eds. G. Voelter and G. Weitzel, de Gruyter, Berlin, 1981, p. 75.
8 B. V. Venkataram Prasad and P. Balaram, *CRC Crit. Rev. Biochem.*, 1984, **16**, 307.
9 R. Bosch, H. Brückner, G. Jung, and W. Winter, *Tetrahedron*, 1982, **38**, 3579.
10 G. Valle, G. M. Bonora, and C. Toniolo, *Gazz. Chim. Ital.*, 1984, **114**, 481.
11 G. Valle, C. Toniolo, and G. M. Bonora, *Acta Crystallogr.*, 1985, **C41**, 235.
12 J. W. Keller and C. S. Day, *Acta Crystallogr.*, 1984, **C40**, 1224.
13 J. E. Baldwin, R. M. Adlington, B. J. Rawlings, and R. H. Jones, *Tetrahedron Lett.*, 1985, **26**, 485.
14 G. A. Jeffrey and H. Maluszynska, *Int. J. Biol. Macromol.*, 1982, **4**, 173.
15 R. Taylor, O. Kennard, and W. Versichel, *J. Am. Chem. Soc.*, 1984, **106**, 244.
16 P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, 1931, **93**, 581.
17 T. M. Balasubramanian, N. C. E. Kendrick, M. Taylor, G. R. Marshall, J. E. Hale, I. Vodyanoy, and F. Reusser, *J. Am. Chem. Soc.*, 1981, **103**, 6127.
18 D. Leibfritz, E. Haupt, N. Dubischar, H. Lachmann, R. Oekonomopoulos, and G. Jung, *Tetrahedron*, 1982, **38**, 2165.
19 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,' University of York, and University of Louvain, 1980.
20 L. Pauling, in 'The Nature of the Chemical Bond,' Cornell University Press, Ithaca, 1960, 3rd edn., p. 438.
21 C. S. Chen and R. Parthasarathy, *Int. J. Pept. Protein Res.*, 1978, **11**, 9.
22 IUPAC-IUB Commission on Biochemical Nomenclature, *J. Mol. Biol.*, 1970, **52**, 1.
23 J. D. Dunitz and P. Strickler, in 'Structural Chemistry and Molecular Biology,' eds. A. Rich and N. Davidson, Freeman, San Francisco, 1968, p. 595.
24 E. Benedetti, in Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins,' ed. B. Weinstein, Dekker, New York, 1982, p. 105.
25 R. Taylor, O. Kennard, and W. Versichel, *Acta Crystallogr.*, 1984, **B40**, 280.
26 Z. Berkovitch-Yellin, S. Ariel, and L. Leiserowitz, *J. Am. Chem. Soc.*, 1983, **105**, 765.

27 I. D. Brown, *Acta Crystallogr.*, 1976, **B32**, 24.
28 J. Mitra and C. Ramakrishnan, *Int. J. Pep. Protein Res.*, 1977, **9**, 27.
29 G. Valle, G. M. Bonora, and C. Toniolo, *Gazz. Chim. Ital.*, 1984, **114**, 341.
30 G. Valle, G. M. Bonora, and C. Toniolo, *Gazz. Chim. Ital.*, 1984, **114**, 487.
31 R. A. Nyquist, *Spectrochim. Acta*, 1963, **19**, 509.
32 P. J. Krueger and D. W. Smith, *Can. J. Chem.*, 1967, **45**, 1611.
33 I. M. Ginzburg, *J. Gen. Chem. USSR*, 1983, **53**, 2311.
34 E. Benedetti, B. Di Blasio, V. Pavone, C. Pedone, C. Toniolo, and G. M. Bonora, *J. Biol. Chem.*, 1981, **256**, 9229.
35 M. Palumbo, S. Da Rin, G. M. Bonora, and C. Toniolo, *Makromol. Chem.*, 1976, **177**, 1477.
36 A. Aubry, J. Protas, E. Boussard, M. Marraud, and J. Neel, *Biopolymers*, 1978, **17**, 1693.
37 D. Martin and H. G. Hauthal, in 'Dimethyl Sulphoxide,' van Nostrand-Reinhold, Wokingham, 1975.

Received 8*th May* 1985; *Paper* 5/767