and $Pb(2,2,2)^{2+}$ to form the intermediate $(2,1,1)Pb^{2+}(2,2,2)$ to take place. Pb^{2+} is located very probably inside the (2,2,2) cavity. Therefore the (2,1,1) ligand could hardly interact with the metal ion.

Finally, the activation parameters for the $Pb(2,1,1)^{2+}$ exchange reactions studied here are given in Table II. When (2,2,1) is the exchanged ligand, the entropy of activation has a large negative value, while when (2,2,2) is the incoming ligand $\Delta S^{\ddagger}$ is fairly large and positive. The $\Delta H^{\ddagger}$ value for the (2,1,1)–(2,2,2) exchange is about twice as larger as that for the (2,1,1)–(2,2,1) exchange reaction. Although not much information can be drawn from the values of these activation paarameters, the very different $\Delta S^{\ddagger}$ values may suggest that two very different steps are responsible for the observed kinetic behavior of (2,2,1) and (2,2,2) in the exchange reaction with $Pb(2,1,1)^{2+}$.

Registry No. $Ca(^2B,2,2)^{2+}$, 80679-40-9; $Tl(2,2,2)^{+}$, 51156-84-4; $Pb(2,1,1)^{2+}$, 80679-41-0; (2,2,1), 31364-42-8; (2,2,2), 23978-09-8.

Solid-State and Solution Conformation of Homo Oligo(α-aminoisobutyric acids) from Tripeptide to Pentapeptide: Evidence for a 3_{10} Helix[1a]

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Abstract: The X-ray diffraction and IR absorption conformational analysis in the solid state of the *N*-benzyloxycarbonyl homotri-, tetra-, and pentapeptides from α-aminoisobutyric acid has shown the occurrence of incipient 3_{10} helices, formed by one, two, and three type III (or type III′) β turns, respectively. α-Helical structures, although having closely related pairs of ϕ,ψ torsional angles, are not compatible with the observed intramolecular N—H···O=C hydrogen-bonding schemes of the tetra- and pentapeptides. In solvents of low polarity, the IR absorption data are in favor of the occurrence of the same intramolecular hydrogen-bonded forms as found in the solid state. Aggregation of these structures takes place at high concentrations. Since segments containing up to four α,α-dialkylated, α-amino acid residues in a row have been found in the transmembrane channel-forming peptide antibiotics of the alamethicin family, it is clear that the 3_{10}-helical structure must be taken into account in postulating[a] the model of folding of those parts of their sequences containing a high proportion of these residues.

The α,α-dialkylated, α-amino acid residues Aib[2] and Iva occur extensively in the transmembrane channel-formining peptide antibiotics of the alamethicin family.[3-7] According to a number of theoretical analyses, replacement of the hydrogen atom at the C^{α} carbon atom in the Ala residue by a methyl group produces severe restriction of the conformational freedom of the resulting Aib residue.[8-14]

We have begun an investigation of the conformational preferences of segments of the antibiotics, both in the solid state and in solution. Our initial objective is the study of segments containing exclusively α,α-dialkylated, α-amino acid residues, namely, $-(Aib)_{2,4}-$ and $-(Aib)_{1,3}$-Iva.[3-7]

We have synthesized and examined by X-ray diffraction and IR absorption the complete homoligopeptide series (to the pentapeptide) formed by the achiral Aib residue having the general formula Z-$(Aib)_n$-OX (n = 1–5; X = H, *t*-Bu). In this paper we describe in detail the results of our conformational analysis of the N-protected homotri-, tetra-, and pentapeptides, i.e., those peptides having folded structures with at least one intramolecular N—H···O=C hydrogen bond. IR absorption data[15] and preliminary crystallographic results[16] of the lower homologue Z-$(Aib)_2$-OH have already been reported. The complex phenomenon exhibited by Z-Aib-OH in the solid state (possibly polymorphism), first

(1) (a) This is part 81 of the *Linear Oligopeptides* series; for part 80 see G. M. Bonora and C. Toniolo, *Gazz. Chim. Ital.*, **111**, 239 (1981). (b) University of Naples. (c) University of Padua.

(2) The following abbreviation are used in the text: Aib, α-aminoisobutyric acid or α-methylalanine; Iva, isovaline or α-ethylalanine; Ala, alanine; Leu, leucine; Val, valine; Pro, proline; Ac, acetyl; *t*-Boc, *tert*-butyloxycarbonyl; Z, benzyloxycarbonyl; Piv, pivaloyl; Tos, tosyl or *p*-toluenesulfonyl; OMe, methoxy; OBzl, benzyloxy; OEt, ethoxy; O-*t*-Bu, *tert*-butoxy; NHMe, methylamino; MeOH, methanol.

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Table I. Crystallographic Data for Z-(Aib)$_3$-O-*t*-Bu, Z-(Aib)$_4$-OH, and Z-(Aib)$_5$-O-*t*-Bu

parameter	Z-(Aib)$_3$-O-*t*-Bu	Z-(Aib)$_4$-OH	Z-(Aib)$_5$-O-*t*-Bu
mol formula	$C_{24}H_{37}N_3O_6$	$C_{24}H_{36}N_4O_7$	$C_{32}H_{51}N_5O_8$
mol wt	463.58	492.58	633.79
cryst system	monoclinic	monoclinic	triclinic
space group	$P2_1/c$	$P2_1/n$	$P\bar{1}$
Z	4	4	2
a, Å	9.540	16.678	9.185
b, Å	26.026	17.891	11.540
c, Å	11.006	9.016	18.737
α, deg	90.00	90.00	105.79
β, deg	106.72	95.92	93.92
γ, deg	90.00	90.00	102.98
V, Å^3	2617.2	2675.9	1844.4
d(calcd), g/cm^3	1.176	1.223	1.141
d(exptl), g/cm^3	1.17	1.22	1.13
radiation, Å	Cu Kα (1.5418)	Cu Kα (1.5418)	Mo Kα (0.710 73)
measured reflctns	4953	5424	6480
reflctns with $I > 3.0\sigma(I)$	2443	4189	3734
final R value	0.053	0.075	0.062
temp	ambient	ambient	ambient

discussed by McGahren and Goodman,[17] requires further study.[15]

Experimental Section

Synthesis of Peptides. Z-(Aib)$_n$-O-*t*-Bu (n = 3–5) were synthesized from the pertinent *N*-benzyloxycarbonyl oxazolones[18,19] and H-Aib-O-*t*-Bu[19] in anhydrous acetonitrile under reflux as described by Jones et al.[19] The C-deprotected derivatives Z-(Aib)$_n$-OH (n = 3–5) were obtained from the corresponding *tert*-Butyl esters using trifluoroacetic acid.[19] All compounds have melting points in agreement with those described in the literature.[19,20] Thin-layer chromatography in three different eluent systems and C, H, and N elemental analyses proved that all compounds are analytically pure.

Infrared Absorption. Infrared absorption spectra were recorded by using a Perkin-Elmer Model 580 spectrophotometer. For the solution measurements a 10-cm path length cell with KBr windows was employed at low concentrations, whereas cells with 0.1-mm path lengths and CaF_2 windows were used for measurements at high concentrations. Spectrograde deuteriochloroform (99.8% d) was purchased from Merck, Darmstadt, West Germany. For the solid-state measurements the KBr disk technique was used. The band positions are accurate to ±1 cm^{-1}.

X-ray Diffraction. Crystals of Z-(Aib)$_3$-O-*t*-Bu, Z-(Aib)$_4$-OH, and Z-(Aib)$_5$-O-t-Bu were grown from MeOH or H_2O/MeOH solution by slow evaporation at room temperature. Details of the procedures used in the unit cell determination and intensity data collection are similar to those recently reported by us.[21] A summary of crystallographic data and other relevant parameters is given in Table I.

All three structures were solved by means of a straightforward application of direct methods, using MULTAN in the form programmed by Germain et al.[22] In all cases, the E map of the set of phases having the best combined figures of merit revealed all C, N, and O atoms. The structures were then refined with standard least-squares procedures. Fianl R values of 0.053, 0.075, and 0.062 for Z-(Aib)$_3$-O-*t*-Bu, Z-(Aib)$_4$-OH, and Z-(Aib)$_5$-O-*t*-Bu, respectively, were obtained. The final atomic parameters for the three structures are reported in Table II.

Results and Discussion

Solid-State Analysis. The modes of folding and self-association of the Z-(Aib)$_n$-OX (n = 3–5; X = *t*-Bu, H) peptides were first examined by IR absorption in the most informative frequency ranges: (i) 3450–3270 cm^{-1}, corresponding to the peptide and urethane N–H stretching vibrations, and (ii) 1800–1600 cm^{-1}, corresponding to the C=O stretching vibrations of the ester (or carboxylic acid), urethane, and peptide groups. In the –COOH compounds it is possible that also the O–H stretching vibration would contribute to the observed absorptions in the 3450–3270-cm^{-1} range. The results obtained are listed in Table III.

In the 3450–3270-cm^{-1} region a band of low intensity is seen at a frequency of ≥3408 cm^{-1} in most cases, the position of which is indicative of the occurrence of free (or extremely weak hydrogen-bonded) N–H groups. In addition, more intense bands, related to the N–H groups involved in hydrogen bonds of divergent strength, are visible below 3370 cm^{-1}. In this spectral region a single absorption at 3275 cm^{-1} is shown by the strongly bonded N–H groups of poly(Aib),[23] whereas the corresponding absorptions of the peptide antibiotics alamethicin and suzukacillin fall at 3300 cm^{-1}.[3]

In the 1800–1600 cm^{-1} region the spectra of these Aib homooligopeptides are even more complex. The absorptions of the *tert*-butyl ester groups are in the 1732–1725-cm^{-1} range, whereas those of the carboxylic acid groups are in the 1746–1728-cm^{-1} range. The absorptions at 1711–1697 cm^{-1} are assigned to the C=O vibrations of weak hydrogen-bonded urethane groups. In fact, free urethane groups show bands at frequencies of >1715 cm^{-1}.[24–26] Several bands associated with the peptide C=O groups are seen in the 1683–1635-cm^{-1} region. The band of the bonded peptide C=O groups of poly(Aib),[23] alamethicin,[3] and suzukacillin[3] appears near 1655 cm^{-1}, whereas that of the Aib-containing oligopeptide H-L-Pro-L-Val-Aib-Aib-OMe appears at 1675 cm^{-1}.[27]

To ascertain unambiguously the molecular structures and the packing modes of the homo oligo(α-aminoisobutyric acids) from tripeptide to pentapeptide in the solid state, we examined some representative examples by X-ray diffraction. In this paper the results obtained for Z-(Aib)$_3$-O-*t*-Bu, Z-(Aib)$_4$-OH, and Z-(Aib)$_5$-O-*t*-Bu are described. the molecular parameters for the three peptides have been deposited as supplementary material. the final average estimated standard deviations (esd's) from bond lengths and bond angles are in the range 0.003–0.008 Å and 0.1–0.8°, respectively. The complete list of torsional angles[28] for the three molecules is reported in Table IV. Each molecule, having no chiral atoms, crystallizes with retention of the center of symmetry or glide planes; thus, in each unit cell of each structure molecules of both handedness simultaneously occur. In Table IV only the torsional angles of the right-handed molecules are listed.

In the three molecules bond lengths and bond angles can be considered unexceptional; in fact, a good agreement is found between the geometry observed in each structure for the urethane

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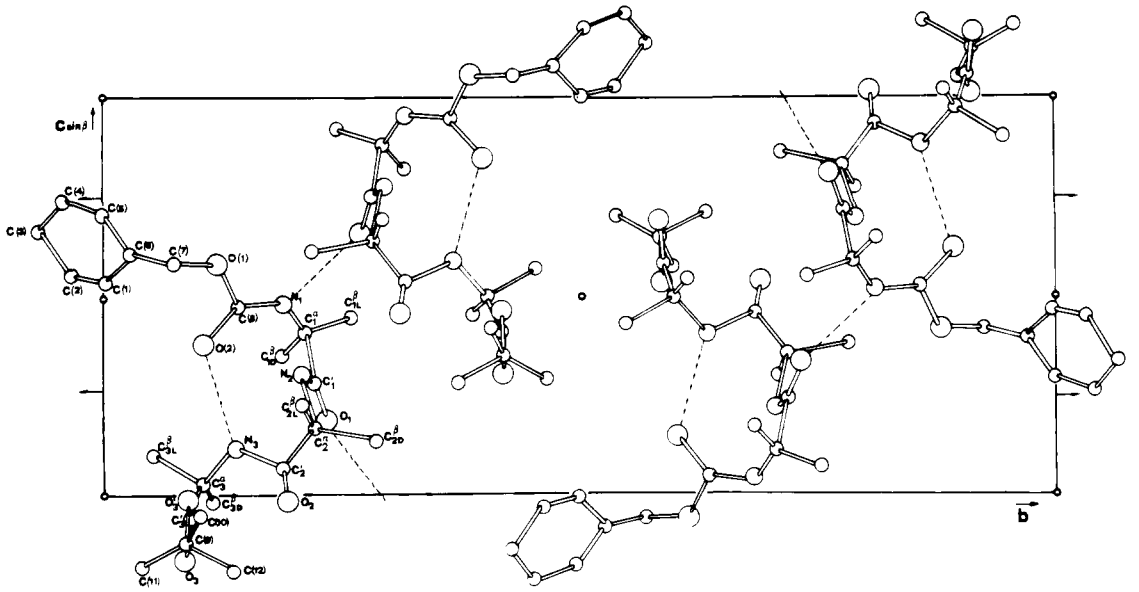

Figure 1. Intramolecular hydrogen bond and mode of packing of the Z-(Aib)$_3$-O-*t*-Bu molecules projected down the *a* axis.

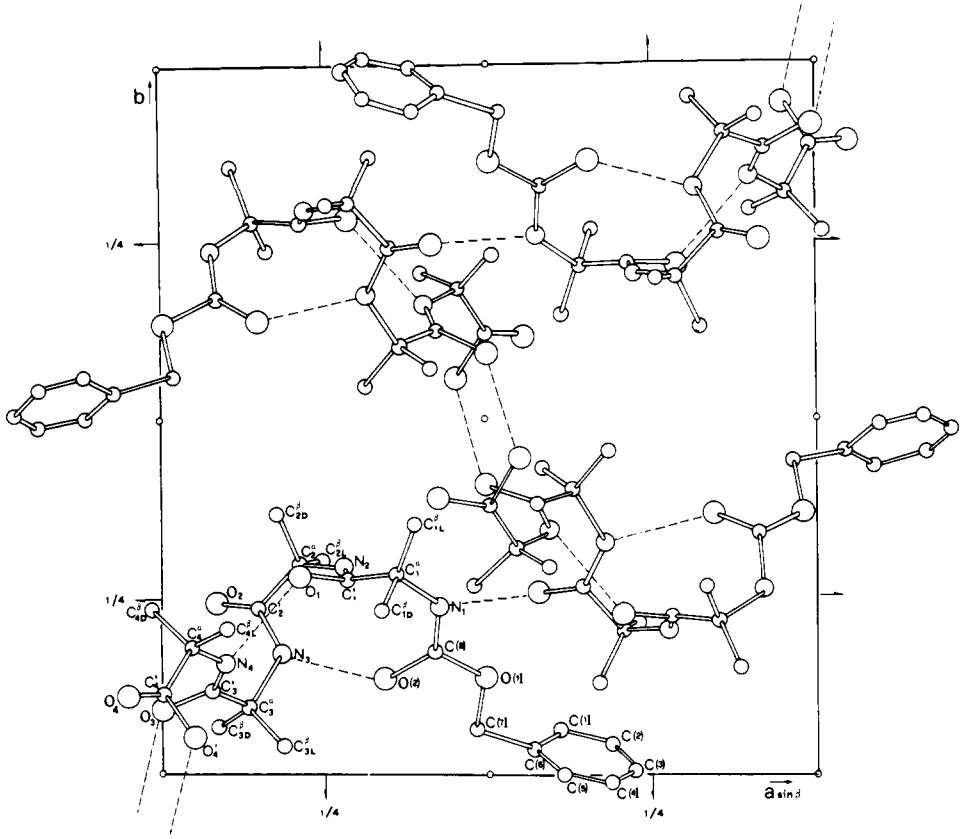

Figure 2. Intramolecular hydrogen bond and mode of packing of the Z-(Aib)$_4$-OH molecules projected down the *c* axis.

and the amide bonds, the *tert*-butyl and Z moieties, and the corresponding average geometry proposed for each of these groups in the literature.[29-31] However, the data of the present structures together with those available in the literature on other Aib residues have allowed us to calculate the average values for the bond angles involving the C$^\alpha$ atom which are correlated to the conformation assumed by the residue (see discussion below).

The succession of similar pairs of ϕ,ψ values along the chain of each peptide gives rise to helical structures, which in the present compounds (Table IV) can be described as incipient 3_{10} helices, although slightly distorted from the ideal case $(\phi,\psi) = (\pm 60°, \mp 30°)$.[32] They are formed by one, two, and three type-III (or type-III′) β bends (4 → 1 intramolecular hydrogen-bonded structures[33]) for the homotri-, tetra-, and pentapeptides, respectively (Figures 1-3).

The single intramolecular hydrogen bond in the tripeptide is seen between the N-H group of the Aib(3) residue and the C=O

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Table II. Final Atomic Parameters and Their Standard Deviations (in Parentheses)

atom	x/a	y/b	z/c	B(Eq), Å²	atom	x/a	y/b	z/c	B(Eq), Å²
				A. Z-(Aib)$_3$-O-*t*-Bu					
C(1)	−1610 (5)	−33 (2)	−7089 (4)	4.6 (2)	N_2	−687 (3)	−2253 (1)	−2826 (3)	2.7 (1)
C(2)	−2323 (6)	429 (2)	−7440 (5)	5.5 (2)	C_2^{α}	599 (4)	−2310 (1)	−1720 (4)	3.1 (2)
C(3)	−3132 (5)	640 (2)	−6712 (5)	5.4 (2)	C_2L^{β}	1936 (4)	−2122 (2)	−2099 (4)	4.0 (2)
C(4)	−3212 (6)	389 (2)	−5633 (5)	6.2 (2)	C_2D^{β}	807 (5)	−2868 (2)	−1256 (4)	4.3 (2)
C(5)	−2494 (5)	−67 (2)	−5278 (4)	5.1 (2)	C_2'	437 (4)	−1952 (1)	−641 (4)	3.3 (2)
C(6)	−1682 (4)	−287 (1)	−6008 (4)	3.5 (2)	O_2	889 (3)	−2079 (1)	478 (2)	4.2 (1)
C(7)	−818 (5)	−776 (2)	−5627 (4)	4.2 (2)	N_3	−101 (3)	−1482 (1)	−1016 (3)	3.0 (1)
O(1)	−1798 (3)	−1221 (1)	−5763 (2)	3.8 (1)	C_3^{α}	−351 (4)	−1102 (1)	−118 (4)	3.2 (2)
C(8)	−2063 (4)	−1392 (1)	−4688 (4)	3.3 (2)	C_3L^{β}	−822 (5)	−602 (2)	−855 (4)	4.3 (2)
O(2)	−1734 (3)	−1162 (1)	−3692 (3)	4.0 (1)	C_3D^{β}	−1555 (5)	−1284 (2)	448 (4)	5.0 (2)
N_1	−2724 (3)	−1854 (1)	−4900 (3)	3.1 (1)	C_3'	1042 (4)	−991 (1)	955 (4)	3.4 (2)
C_1^{α}	−3287 (4)	−2113 (1)	−3950 (4)	3.1 (2)	O_3	1017 (3)	−881 (1)	2010 (3)	5.2 (1)
C_1L^{β}	−4056 (5)	−2606 (2)	−4564 (4)	4.5 (2)	O_3'	2231 (3)	−994 (1)	555 (2)	3.6 (1)
C_1D^{β}	−4394 (5)	−1769 (2)	−3556 (4)	5.0 (2)	C(9)	3702 (4)	−913 (2)	1463 (4)	3.9 (2)
C_1'	−2064 (4)	−2263 (1)	−2763 (3)	3.0 (1)	C(10)	3990 (6)	−1323 (2)	2486 (5)	6.1 (3)
O_1	−2371 (3)	−2376 (1)	−1782 (2)	4.4 (1)	C(11)	3821 (6)	−372 (2)	1994 (6)	5.9 (3)
					C(12)	4707 (5)	−987 (2)	631 (5)	6.0 (3)
				B. Z-(Aib)$_4$-OH					
C(1)	6018 (3)	655 (3)	1057 (6)	7.1 (2)	C_2^{α}	2123 (2)	2944 (2)	1165 (3)	3.1 (1)
C(2)	6789 (4)	479 (4)	913 (7)	9.7 (3)	C_2L^{β}	2414 (2)	2923 (2)	−400 (4)	4.7 (2)
C(3)	7228 (4)	76 (4)	1929 (8)	9.4 (3)	C_2D^{β}	1685 (2)	3678 (2)	1407 (5)	4.6 (2)
C(4)	6879 (4)	−198 (3)	3127 (7)	8.7 (3)	C_2'	1527 (2)	2286 (2)	1269 (3)	2.6 (1)
C(5)	6084 (4)	−36 (3)	3278 (6)	7.4 (3)	O_2	813 (1)	2373 (1)	899 (3)	3.6 (1)
C(6)	5624 (3)	394 (2)	2215 (5)	5.2 (2)	N_3	1851 (1)	1623 (1)	1728 (3)	2.5 (1)
C(7)	4784 (3)	621 (3)	2392 (6)	6.7 (2)	C_3^{α}	1348 (2)	955 (2)	1906 (3)	2.8 (1)
O(1)	4836 (1)	1336 (1)	3172 (3)	5.0 (1)	C_3L^{β}	1909 (2)	337 (2)	2597 (4)	3.8 (1)
C(8)	4127 (2)	1632 (2)	3443 (4)	3.8 (1)	C_3D^{β}	944 (2)	695 (2)	407 (4)	3.7 (1)
O(2)	3485 (1)	1321 (1)	3175 (3)	4.5 (1)	C_3'	728 (2)	1102 (2)	3022 (3)	2.7 (1)
N_1	4234 (1)	2334 (2)	4004 (3)	3.4 (1)	O_3	77 (1)	777 (1)	2912 (2)	3.3 (1)
C_1^{α}	3594 (2)	2708 (2)	4720 (3)	3.2 (1)	N_4	967 (1)	1552 (1)	4171 (3)	3.1 (1)
C_1L^{β}	3872 (2)	3508 (2)	5060 (4)	4.6 (2)	C_4^{α}	459 (2)	1763 (2)	5333 (3)	3.2 (1)
C_1D^{β}	3441 (3)	2297 (3)	6156 (4)	5.0 (2)	C_4L^{β}	1009 (2)	2088 (2)	6642 (4)	4.0 (1)
C_1'	2801 (2)	2755 (2)	3700 (3)	2.9 (1)	C_4D^{β}	−175 (2)	2329 (2)	4717 (4)	4.8 (2)
O_1	2154 (1)	2724 (1)	4222 (2)	3.4 (1)	C_4'	40 (2)	1080 (2)	5955 (4)	3.4 (1)
N_2	2845 (1)	2862 (1)	2228 (3)	3.0 (1)	O_4	−634 (2)	1099 (2)	6291 (3)	5.4 (1)
					O_4'	537 (1)	504 (1)	6196 (3)	4.1 (1)
				C. Z-(Aib)$_5$-O-*t*-Bu					
C(1)	3922 (6)	3014 (4)	38 (3)	7.1 (2)	C_3^{α}	3471 (5)	−161 (4)	1233 (2)	5.2 (2)
C(2)	2697 (8)	2451 (5)	−443 (4)	7.7 (3)	C_3L^{β}	5086 (5)	461 (4)	1155 (2)	6.6 (2)
C(3)	1433 (6)	2967 (5)	−389 (3)	8.3 (3)	C_3D^{β}	2599 (6)	−904 (5)	465 (3)	6.7 (2)
C(4)	1570 (6)	4064 (6)	151 (3)	10.0 (3)	C_3'	3605 (5)	−1018 (4)	1725 (2)	5.0 (2)
C(5)	2908 (6)	4646 (5)	631 (3)	7.2 (3)	O_3	3579 (4)	−2116 (3)	1439 (2)	7.4 (2)
C(6)	4087 (5)	4117 (4)	574 (2)	5.0 (2)	N_4	3839 (3)	−474 (3)	2468 (2)	4.9 (1)
C(7)	5542 (6)	4758 (5)	1077 (2)	7.0 (2)	C_4^{α}	4182 (4)	−1113 (3)	3013 (3)	5.6 (2)
O(1)	5286 (4)	5207 (2)	1848 (1)	6.1 (1)	C_4L^{β}	4286 (5)	−215 (4)	3795 (3)	7.1 (2)
C(8)	4971 (5)	4336 (4)	2205 (2)	5.0 (2)	C_4D^{β}	5671 (5)	−1493 (5)	2921 (4)	7.7 (3)
O(2)	5102 (3)	3277 (2)	1960 (2)	5.6 (1)	C_4'	2894 (4)	−2257 (3)	2960 (2)	5.2 (2)
N_1	4501 (4)	4800 (3)	2860 (2)	4.8 (1)	O_4	3136 (3)	−3120 (2)	3174 (2)	7.0 (1)
C_1^{α}	4242 (5)	4085 (3)	3396 (2)	4.5 (2)	N_5	1509 (3)	−2199 (3)	2738 (2)	4.9 (1)
C_1L^{β}	3624 (6)	4853 (4)	4048 (2)	5.8 (2)	C_5^{α}	166 (4)	−3164 (3)	2733 (2)	5.0 (2)
C_1D^{β}	5712 (5)	3828 (4)	3676 (2)	6.4 (2)	C_5L^{β}	−1205 (5)	−2639 (4)	2629 (3)	6.0 (2)
C_1'	3052 (4)	2844 (3)	3055 (2)	4.1 (1)	C_5D^{β}	44 (6)	−4352 (4)	2097 (3)	6.6 (2)
O_1	3068 (3)	1941 (2)	3273 (1)	4.8 (1)	C_5'	148 (5)	−3444 (4)	3478 (2)	5.5 (2)
N_2	1981 (4)	2819 (3)	2519 (2)	4.5 (1)	O_5	−340 (4)	−4460 (3)	3540 (2)	7.9 (2)
C_2^{α}	771 (5)	1706 (4)	2141 (2)	5.0 (2)	O_5'	640 (3)	−2400 (2)	4051 (2)	5.7 (1)
C_2L^{β}	−6 (6)	1956 (4)	1466 (3)	7.1 (2)	C(9)	526 (6)	−2370 (5)	4839 (2)	6.8 (2)
C_2D^{β}	−359 (5)	1427 (5)	2674 (3)	6.9 (2)	C(10)	−1173 (7)	−2630 (8)	4911 (3)	9.9 (4)
C_2'	1432 (4)	590 (3)	1838 (2)	3.8 (1)	C(11)	1290 (7)	−1040 (6)	5265 (3)	8.6 (3)
O_2	710 (3)	−471 (2)	1794 (1)	4.9 (1)	C(12)	1452 (8)	−3216 (6)	5061 (3)	13.0 (3)
N_3	2776 (4)	832 (3)	1599 (2)	4.2 (1)					

group of the urethane moiety (the $N_3\cdots O(2)$ distance is 3.025 Å) (Figure 1). In the tetrapeptide the two intramolecular hydrogen bonds occur between the N—H groups of the Aib(3) and Aib(4) residues and the C=O groups of the urethane moiety and the first peptide unit (the $N_3\cdots O(2)$ and $N_4\cdots O_1$ distances are 2.95 and 2.88 Å, respectively) (Figure 2). In the pentapeptide the three intramolecular hydrogen bonds occur between the N—H groups of the Aib(3), Aib(4), and Aib(5) residues and the C=O groups of the urethane moiety and the first and second peptide units (the $N_3\cdots O(2)$, $N_4\cdots O_1$, and $N_5\cdots O_2$ distances are 3.01, 3.05, and 3.17 Å, respectively) (Figure 3). The observed N···O distances fall in the range 2.88–3.17 Å: the average N···O distance for an hydrogen bond involving a peptide N—H group and a peptide C=O group is 2.92 Å.[34]

Peptide sequences for which two consecutive O···N distances ($O_i\cdots N_{i+3}$ and $O_{i+1}\cdots N_{i+4}$) are both within the accepted limits for the formation of hydrogen bonds are considered a double β bend, and analogous definitions hold for higher order multiple β bends (for a complementary definition, see ref 35). With the single exception of Piv-D-Pro-L-ProL-Ala-NHMe where the presence of

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(35) Y. Isogai, G. Némethy, S. Rachovsky, S. J. Leach, and H. A. Scheraga, *Biopolymers*, **19**, 1183 (1980).

Table III. Infrared Absorption Data of the Homo Oligo(α-aminoisobutyric acid) Peptides in the Solid State

peptide	3450–3270 cm^{-1}	1800–1600 cm^{-1}
Z-$(Aib)_3$-O-*t*-Bu[a]	3408, 3329	1725, 1698, 1669, 1655
Z-$(Aib)_4$-O-*t*-Bu[a]	3429,[b] 3355, 3337	1732,[b] 1711, 1670, 1655[b]
Z-$(Aib)_5$-O-*t*-Bu[a]	3426, 3339, 3322[b]	1732, 1702, 1683,[b] 1670 1654[b]
Z-$(Aib)_3$-OH[c]	3419, 3355, 3285[d]	1738, 1705, 1683, 1648
Z-$(Aib)_4$-OH[c]	3365,[b] 3300	1727, 1705, 1659, 1635[b]
Z-$(Aib)_5$-OH[c]	3295[d]	1746, 1697, 1657[d]

[a] From methanol solution. [b] Shoulder. [c] From a methanol–water solution. [d] Broad band.

a double β bend (formed by a type-II′ β bend[33] followed by a type-I β bend[33]) is observed,[36] all other multiple β bends reported in the literature have been found in the crystal structures of peptides containing Aib residues. Actually, double β bends have been observed in Z-Aib-L-Pro-Aib-L-Ala-OMe[37,38] and *t*-Boc-L-Pro-Aib-L-Ala-Aib-OBzl[11,39] where a type-III β bend is followed by a type-I β bend, and a triple β bend (three consecutive type-I β bends) in Tos-$(Aib)_5$-OMe.[40] The structures of the tetra- and pentapeptides, described in this paper (Figures 2 and 3) represent cases of a double β bend and a triple β bend, respectively, where two and three consecutive type-III β bends occur. Interestingly, a comparison of the structures of Tos-$(Aib)_5$-OMe[40] and Z-$(Aib)_5$-O-*t*-Bu (Table IV and Figures 3) reveals that the influence of different N- and C-terminal blocking groups on the conformational preferences and the intramolecular hydrogen-bonding scheme of the Aib homooligopentapeptide is negligible.

α-Helical structures, although having pairs of φ,ψ torsional angles (φ,ψ) = (∓55°,∓45°) closely related to those of the 3_{10} helices, are not compatible with the observed hydrogen-bonding schemes of the tetra- and pentapeptides, being characterized by $5 \rightarrow 1$ intramolecular hydrogen-bonded peptide forms.

The deviations of the ω angles of the nine Aib–Aib bonds from the ideal value of the trans planar peptide unit (180°) are rather small (the average $|\Delta\omega|$ is around 4°) (Table IV). The effect of the nonplanar distorsion of the peptide unit on the stability of the 3_{10}-helical structure of poly(Aib) has recently been discussed.[12]

The signs of the φ,ψ torsional angles of the last Aib residue in the sequences of the tri-, tetra-, and pentapeptides examined in this work are opposite with respect to those of the preceding residues (Table IV), regardless of the presence or absence of a blocking group at the C-terminal end. The same phenomenon has been verified in other homopeptides from Aib, namely, Z-$(Aib)_2$-OH[16] and Tos-$(Aib)_5$-OMe.[40] The discussion of this experimental finding must take the following into account: (i) the possible involvment of the –COOH group of the C-deblocked peptides in various types of intermolecular hydrogen-bonding schemes [Strong support to the relevance of this point is given by the preliminary results obtained in our laboratories on the solid-state structure of Z-$(Aib)_3$-OH.[16]]. In this tripeptide, which crystallizes as the monohydrate, the same intramolecular hydrogen bond is seen as in Z-$(Aib)_3$-O-*t*-Bu (Figure 1); however, the –COOH group is involved in a hydrogen bond with the $C_1{=}O_1$ group through an internal water bridge,[41,42] which is responsible for the onset in the last residue of the chain of a unique feature for the homo oligo(α-aminoisobutyric acids), i.e., the same helical twist as that of the preceding residues]; (ii) the absence at the

Table IV. Torsional Angles (Deg) with Esd's for Z-$(Aib)_3$-O-*t*-Bu, Z-$(Aib)_4$-OH, and Z-$(Aib)_5$-O-*t*-Bu[a]

angle		Z-$(Aib)_5$-O-*t*-Bu	Z-$(Aib)_4$-OH	Z-$(Aib)_3$-O-*t*-Bu
O(1)–C(7)–C(6)–C(1)		−135.2 (6)	−83.8 (7)	−111.9 (6)
O(1)–C(7)–C(6)–C(5)	θ^3	46.5 (4)	89.9 (7)	71.3 (6)
C(8)–O(1)–C(7)–C(6)	θ^2	77.2 (5)	−179.7 (6)	−99.5 (6)
O(2)–C(8)–O(1)–C(7)		10.7 (6)	5.3 (6)	11.6 (6)
N_1–C(8)–O(1)–C(7)	θ^1	−169.3 (6)	−172.5 (7)	−167.8 (7)
$C_1{}^{\alpha}$–N_1–C(8)–O(1)	ω_0	−173.3 (6)	−165.2 (6)	−173.4 (6)
$C_1{}^{\alpha}$–N_1–C(8)–O(2)		6.8 (5)	17.0 (5)	7.1 (6)
C_1L^{β}–$C_1{}^{\alpha}$–N_1–C(8)		−176.4 (6)	−173.8 (6)	176.0 (6)
C_1D^{β}–$C_1{}^{\alpha}$–N_1–C(8)		63.0 (5)	65.5 (5)	56.8 (5)
$C_1{}'$–$C_1{}^{\alpha}$–N_1–C(8)	ϕ_1	−59.1 (5)	−56.2 (5)	−65.2 (5)
O_1–$C_1{}'$–$C_1{}^{\alpha}$–N_1		152.0 (6)	146.9 (6)	163.7 (7)
O_1–$C_1{}'$–$C_1{}^{\alpha}$–C_1L^{β}		−90.7 (6)	−95.5 (6)	−78.1 (6)
O_1–$C_1{}'$–$C_1{}^{\alpha}$–C_1D^{β}		29.0 (5)	24.3 (5)	40.6 (6)
N_2–$C_1{}'$–$C_1{}^{\alpha}$–N_1	ψ_1	−29.5 (4)	−35.7 (5)	−14.5 (5)
N_2–$C_1{}'$–$C_1{}^{\alpha}$–C_1L^{β}		87.8 (5)	81.9 (5)	103.7 (6)
N_2–$C_1{}'$–$C_1{}^{\alpha}$–C_1D^{β}		−152.5 (6)	−158.3 (6)	−137.6 (7)
$C_2{}^{\alpha}$–N_2–$C_1{}'$–$C_1{}^{\alpha}$	ω_1	180.0 (6)	−177.6 (6)	170.2 (6)
$C_2{}^{\alpha}$–N_2–$C_1{}'$–O_1		−1.5 (5)	−0.2 (5)	−7.9 (6)
C_2L^{β}–$C_2{}^{\alpha}$–N_2–$C_1{}'$		−168.2 (5)	−170.8 (5)	−163.5 (6)
C_2D^{β}–$C_2{}^{\alpha}$–N_2–$C_1{}'$		70.9 (5)	68.5 (5)	74.6 (5)
$C_2{}'$–$C_2{}^{\alpha}$–N_2–$C_1{}'$	ϕ_2	−51.6 (4)	−53.7 (4)	−47.6 (5)
O_2–$C_2{}'$–$C_2{}^{\alpha}$–N_2		149.0 (6)	154.1 (5)	144.6 (7)
O_2–$C_2{}'$–$C_2{}^{\alpha}$–C_2L^{β}		−94.4 (6)	−89.5 (6)	−99.0 (7)
O_2–$C_2{}'$–$C_2{}^{\alpha}$–C_2D^{β}		26.4 (5)	30.6 (5)	21.5 (6)
N_3–$C_2{}'$–$C_2{}^{\alpha}$–N_2	ψ_2	−33.8 (4)	−28.4 (4)	−41.4 (5)
N_3–$C_2{}'$–$C_2{}^{\alpha}$–C_2L^{β}		82.8 (5)	88.0 (5)	75.0 (6)
N_3–$C_2{}'$–$C_2{}^{\alpha}$–C_2D^{β}		−156.5 (6)	−152.0 (5)	−164.4 (7)
$C_3{}^{\alpha}$–N_3–$C_2{}'$–$C_2{}^{\alpha}$	ω_2	−174.3 (6)	178.7 (5)	178.7 (6)
$C_3{}^{\alpha}$–N_3–$C_2{}'$–O_2		2.8 (5)	−3.9 (5)	−7.4 (6)
C_3L^{β}–$C_3{}^{\alpha}$–N_3–$C_2{}'$		−171.0 (5)	−174.1 (5)	174.7 (6)
C_3D^{β}–$C_3{}^{\alpha}$–N_3–$C_2{}'$		69.0 (5)	66.3 (4)	−65.6 (5)
$C_3{}'$–$C_3{}^{\alpha}$–N_3–$C_2{}'$	ϕ_3	−55.1 (5)	−58.4 (4)	56.6 (5)
O_3–$C_3{}'$–$C_3{}^{\alpha}$–N_3		151.1 (6)	150.5 (5)	−148.0 (7)
O_3–$C_3{}'$–$C_3{}^{\alpha}$–C_3L^{β}		−92.3 (6)	−93.1 (5)	94.3 (7)
O_3–$C_3{}'$–$C_3{}^{\alpha}$–C_3D^{β}		27.2 (6)	26.3 (5)	−25.0 (6)
N_4–$C_3{}'$–$C_3{}^{\alpha}$–N_3	ψ_3	−32.7 (5)	−34.6 (4)	36.7 (5)[c]
N_4–$C_3{}'$–$C_3{}^{\alpha}$–C_3L^{β}		83.9 (5)	81.7 (5)	−81.0 (6)[c]
N_4–$C_3{}'$–$C_3{}^{\alpha}$–C_3D^{β}		−156.6 (6)	−158.9 (5)	159.7 (6)[c]
$C_4{}^{\alpha}$–N_4–$C_3{}'$–$C_3{}^{\alpha}$	ω_3	−172.1 (6)	179.3 (6)	
$C_4{}^{\alpha}$–N_4–$C_3{}'$–O_3		4.0 (6)	−6.0 (5)	
C_4L^{β}–$C_4{}^{\alpha}$–N_4–$C_3{}'$		−177.0 (6)	164.3 (5)	
C_4D^{β}–$C_4{}^{\alpha}$–N_4–$C_3{}'$		62.5 (5)	−74.2 (5)	
$C_4{}'$–$C_4{}^{\alpha}$–N_4–$C_3{}'$	ϕ_4	−61.2 (5)	47.9 (4)	
O_4–$C_4{}'$–$C_4{}^{\alpha}$–N_4		156.0 (6)	−142.2 (6)	
O_4–$C_4{}'$–$C_4{}^{\alpha}$–C_4L^{β}		−87.3 (6)	100.5 (6)	
O_4–$C_4{}'$–$C_4{}^{\alpha}$–C_4D^{β}		31.5 (6)	−19.9 (6)	
N_5–$C_4{}'$–$C_4{}^{\alpha}$–N_4	ψ_4	−30.1 (5)	43.7 (4)[b]	
N_5–$C_4{}'$–$C_4{}^{\alpha}$–C_4L^{β}		86.6 (5)	−73.7 (5)[b]	
N_5–$C_4{}'$–$C_4{}^{\alpha}$–C_4D^{β}		−154.6 (6)	165.9 (6)[b]	
$C_5{}^{\alpha}$–N_5–$C_4{}'$–$C_4{}^{\alpha}$	ω_4	−173.8 (6)		
$C_5{}^{\alpha}$–N_5–$C_4{}'$–O_4		0.0 (5)		
C_5L^{β}–$C_5{}^{\alpha}$–N_5–$C_4{}'$		166.9 (5)		
C_5D^{β}–$C_5{}^{\alpha}$–N_5–$C_4{}'$		−72.9 (5)		
$C_5{}'$–$C_5{}^{\alpha}$–N_5–$C_4{}'$	ϕ_5	50.7 (5)		
O_5–$C_5{}'$–$C_5{}^{\alpha}$–N_5		−144.7 (7)		
O_5–$C_5{}'$–$C_5{}^{\alpha}$–C_5L^{β}		98.8 (7)		
O_5–$C_5{}'$–$C_5{}^{\alpha}$–C_5D^{β}		−20.8 (6)		
$O_5{}'$–$C_5{}'$–$C_5{}^{\alpha}$–N_5	$\psi_5{}^*$	39.9 (4)		
$O_5{}'$–$C_5{}'$–$C_5{}^{\alpha}$–C_5L^{β}		−76.6 (5)		
$O_5{}'$–$C_5{}'$–$C_5{}^{\alpha}$–C_5D^{β}		163.9 (6)		
C(9)–$O_5{}'$–$C_5{}'$–$C_5{}^{\alpha}$		170.4 (6)		−177.7 (6)[d]
C(9)–$O_5{}'$–$C_5{}'$–O_5		−4.9 (6)		7.1 (6)[d]
C(10)–C(9)–$O_5{}'$–$C_5{}'$		61.7 (6)		58.6 (6)[d]
C(11)–C(9)–$O_5{}'$–$C_5{}'$		176.9 (6)		175.8 (7)[d]
C(12)–C(9)–$O_5{}'$–$C_5{}'$		−67.9 (6)		66.0 (6)[d]

[a] The nomenclature adopted for the C-terminal oxygen atoms is as follows: the double-bonded oxygen atom is denoted with a subscript corresponding to the sequence number of the residue while to the single bonded (hydroxil or esterified) oxygen atom a prime superscript is added: i.e. $C_n{}'{=}O_n$ and $C_n{}'{-}O_n{}'$, respectively. [b] In Z-$(Aib)_4$-OH for these three angles N_5 must be read as $O_4{}'$. [c] In Z-$(Aib)_3$-O*t*Bu for these angles N_4 must be read as $O_3{}'$. [d] In Z-$(Aib)_3$-O*t*Bu, $C_5{}'$ must be read as $C_3{}'$, $C_5{}^{\alpha}$ as $C_3{}^{\alpha}$, O_5 as O_3 and $O_5{}'$ as $O_3{}'$.

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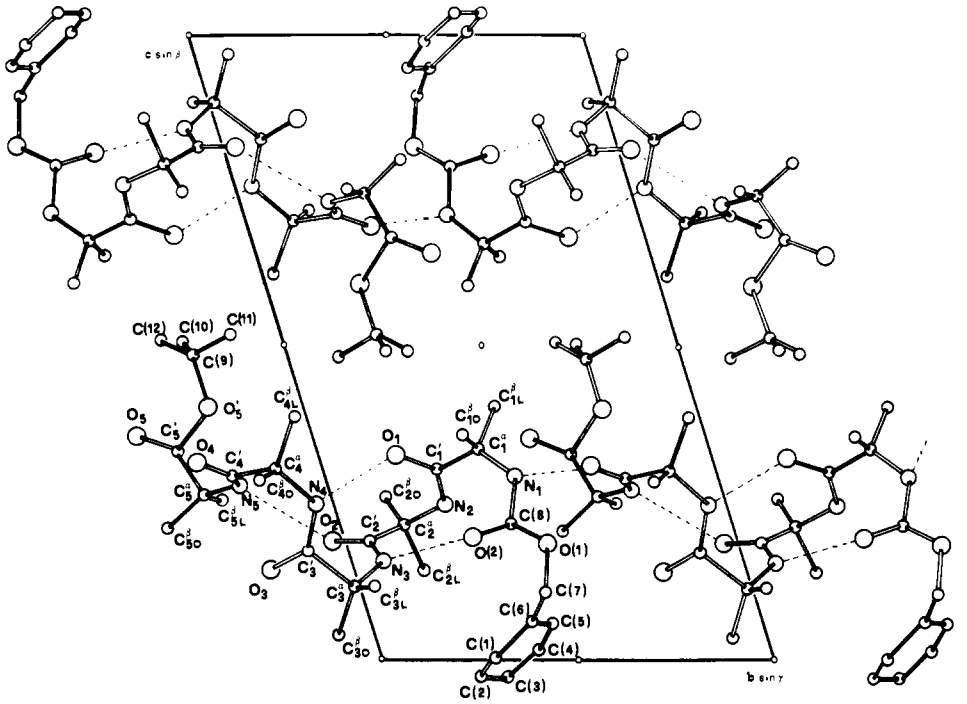

Figure 3. Intramolecular hydrogen bond and mode of packing of the Z-(Aib)$_5$-O-*t*-Bu molecules projected down the *a* axis.

C-terminal end of *Z*-(Aib)$_4$-OH (Figure 2), as in Z-(Aib)$_2$-OH[16] and Z-(Aib)$_3$-OH·H$_2$O,[16] of the oxy analogue of the type-III (or type-III′) 4 → 1 intramolecular hydrogen-bonded conformation,[43,44] which would have imposed on the last residue the same handedness of the preceding ones; (iii) in the ester derivatives the blocked C-terminal residue does not have any hydrogen-bonding donor [As a consequence, this residue has a greater conformational freedom, which in turn (in an Aib residue) is reflected in ϕ,ψ values either both negative or both positive, corresponding to right- or left-handed twists, respectively.]. Thus, both inter- and intramolecular hydrogen bonds, involving the -COOH group and packing forces, could discriminate between the two conformations available to the last residue.

The inspection of the geometries of all Aib-containing compounds examined in our laboratories revealed the two bond angles at the C$^\alpha$ carbon atom have values systematically smaller than the tetrahedral value. From this observation the possible existence of a correlation between the conformational space of the Aib residue and its geometry at the C$^\alpha$ atom was examined in more detail.[13,16]

From our structural results, as well as from literature data on the crystal structures of other Aib-containing peptides or Aib-derivatives, an average geometry of this residue was calculated, which indeed was found to be intimately correlated to the conformation. The two methyl groups were distinguished according to their L and D position, and, correspondingly, they were labeled $C_{nL}{}^\beta$ and $C_{nD}{}^\beta$, where *n* is the sequence number. The averaging of a total of 20 Aib residues contained in accurately refined crystal structures ($R \leq 0.08$)[13] produced a set of values for bond distances very similar to those reported in the literature for the peptide unit.[34] However, peculiar values were obtained for the bond angles involving the C$^\alpha$ atom (Figure 4. For a residue *n* having a right-handed helical conformation the angles involving the $C_{nD}{}^\beta$ methyl group and the atoms of the backbone, N_n, $C_n{}^\alpha$, and C_n', tend to become larger than the tetrahedral value (the N_n–$C_n{}^\alpha$–$C_{nD}{}^\beta$ and C_n'–$C_n{}^\alpha$–$C_{nD}{}^\beta$ angles have average values of 110.7 and 110.5°, respectively, whereas those involving the $D_{NL}{}^\beta$ methyl group and the atoms of the backbone tend to become smaller (the N_n–$C_n{}^\alpha$–$C_{nL}{}^\beta$ and C_n'–$C_n{}^\alpha$–$C_{nL}{}^\beta$ and C_n'–$C_n{}^\alpha$–$C_{nL}{}^\beta$ have average values of 107.0 and 106.7°, respectively. Exactly the reverse holds true for an Aib residue in a left-handed helical conformation.

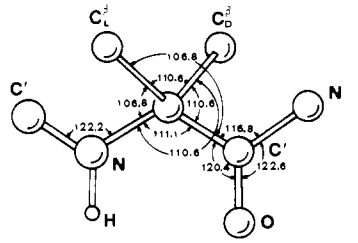

Figure 4. Averaged bond angles in an Aib residue.

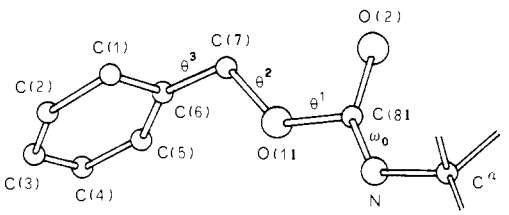

Figure 5. Numbering of atoms and definition of torsional angles of the benzyloxycarbonyl N-terminal blocking group.

Deformations of bond angles requiring little energy are, then, to be taken into account in the conformational calculations of Aib-containing peptides since they may represent the discriminating factor in fixing the overall conformation of the molecule. In a recent theoretical work the sensitivity of the conformation of Aib–containing peptides to geometry was indeed tested.[13] *Inter alia*, the results clearly indicate that for Ac-(Aib)$_3$-NHMe a tetrahedral symmetrical geometry at the C$^\alpha$ atom favors the α-helical structure (with a single 5 → 1 intramolecular hydrogen-bonded conformation), whereas with the asymmetric geometry the 3_{10}-helical structure (with a double 4 → 1 intramolecular hydrogen-bonded conformation) is preferred.

The conformation of the benzyloxycarbonyl N-terminal blocking group is fully described by the dihedral angles ω_0, θ^1, θ^2, and θ^3,[30] as illustrated in Figure 5.

In the three peptides studied in this work the values of these angles (Table IV) indicate that ω_0 and θ' are trans. The trans disposition in a secondary urethane bond (ω_0) is not surprising since it represents its minimum energy conformation;[29,30] however, for a derivative of a N-alkylated α-amino acid the energy dif-

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(44) C. Toniolo, *CRC Crit. Rev. Biochem.*, **9**, 1 (1980).

ference between the trans and cis conformations of the urethane linkage is rather small.[29,30] All the crystal structures of the *N*-benzyloxycarbonyl peptides reported in the literature have $\omega \simeq 180°$, except the structures of Z-L-Pro-L-Pro-OH[45] and Z-L-Pro-L-Leu-OEt[46] which are the only two having a N-alkylated α-amino acid residue at the N-terminal, and they both have $\omega \simeq 0°$ (3° and −11°, respectively).

The angle θ', instead, is for all *N*-benzyloxycarbonyl derivatives always trans,[30] showing a preference for the methylene C(7) atom to lie in the plane of the urethane bond with a conformation in which the C(8)=O(2) carbonyl double bond bisects the plane H–C(7)–H.

The angles θ^2 and θ^3 define the conformation of the phenyl ring with respect to the urethane moiety.[30] In the tri-, tetra-, and pentapeptide crystal structures described in this paper they assume different values. θ^2 has values of −99, 180, and 77°, while θ^3 has values of 71, 90, and 46.5°, for the tri-, tetra-, and pentapeptides, respectively (Table IV). The conformations observed for the *N*-benzyloxycarbonyl-protecting group in the three structures are similar to those usually observed in such derivatives, which have been recently analyzed.[30]

The torsion angles involving atoms at the C-terminal blocking group in Z-(Aib)$_5$-O-*t*-Bu and *Z*-(Aib)$_3$-O-*t*-Bu, reported in Table IV, clearly indicate the same conformation for these groups in both structures with the staggering of the three methyl groups around the C(9)–O_5' and C(9)–O_3' bonds, respectively, and a trans arrangement of the atoms around the C_5'–O_5' and C_3'–O_3' bonds (170 and −178°, respectively). This conformation is similar to that observed for the *t*-Boc-blocking group.[29] The carboxylic acid group in Z-(Aib)$_4$-OH assumes a conformation with respect to the C_4^α–N_4 bond which is almost half way between the *synplanar* and *synclinal* conformation:[47] in fact, the O_4'–C_4'–C_4^α–N_4 torsion angle presents a value of 44°.

The modes of packing of the three peptides are given in Figures 1–3. In Z-(Aib)$_3$-O-*t*-Bu one intermolecular hydrogen bond, N_1—H···O_1=C_1', is seen (the N_1···O_1 distance is 2.97 Å);[34] consequently, in the projection down the *a* axis (Figure 1) the molecules are linked together with the formation of long rows. Packing is obtained through van der Waals interactions between the hydrophobic groups.

In the tetrapeptide Z-(Aib)$_4$-OH one intermolecular hydrogen bond occurs between the hydroxyl group O_4'–H and the carbonyl oxygen O_3 around a crystallographic center of symmetry leading to the formation of dimers as shown in Figure 2. The O_4'···O_3 distance is 2.67 Å: the average O···O distance for a hydrogen bond involving an O–H donor and a carbonyl group as the acceptor is 2.76 Å.[48] A second intermolecular hydrogen bond is present, N_1—H···O_2=C_2' (the N_1···O_2 distance is 3.03 Å).[34]

In the crystal structure of the pentapeptide one intermolecular N—H···O=C hydrogen bond occurs between N_1—H and the C_4'=O_4 carbonyl (the N_1···O_4 distance is 2.89 Å),[34] leading, as in the case of the tripeptide, to the formation of long rows of hydrogen-bonded molecules extending along the *a* direction, as shown in Figure 3. Packing is obtained through hydrophobic interactions between methyl, benzyl, and *tert*-butyl groups. In summary, the intramolecular hydrogen bond N_3—H···O(2)=C_8 is present in all three peptides. The intramolecular hydrogen bonds N_4—H···O_1=C_1' and N_5—H···O_2=C_2' are also present whenever possible, i.e., in the tetra- and pentapeptides. The N_1—H group is involved in an intermolecular hydrogen bond in all three peptides, with O_1=C_1' in the tripeptide, O_2=C_2' in the tetrapeptide, and O_4=C_4' in the pentapeptide. Conversely, the N_2—H and the last O=C group of the chain are always free; the C-blocked peptides have an additional carbonyl group free, namely, the O_2=C_2' group in the tripeptide and the O_3=C_3' group in the pentapeptide.

Table V. Infrared Absorption Data of the Homo Oligo(α-aminoisobutyric acid) Peptides in Deuteriochloroform Solution in the 3480–3300-cm^{-1} Frequency Range

peptide	5×10^{-4} M concn: band positions	5×10^{-4} M concn: A_H/A_F	5×10^{-2} M concn: band positions	5×10^{-2} M concn: A_H/A_F
Z-(Aib)$_3$-O-*t*-Bu	3429, 3379	1.23	3428, 3374	1.68
Z-(Aib)$_4$-O-*t*-Bu	3426, 3363	2.39	3426, 3359	3.55
Z-(Aib)$_5$-O-*t*-Bu	3426, 3350	3.81	3426, 3347	5.29
Z-(Aib)$_3$-OH	3425, 3348	2.11	*a*	*a*
Z-(Aib)$_4$-OH	3426, 3338	4.41	*a*	*a*
Z-(Aib)$_5$-OH	3426, 3333	6.29	*a*	*a*

[a] Sparingly soluble.

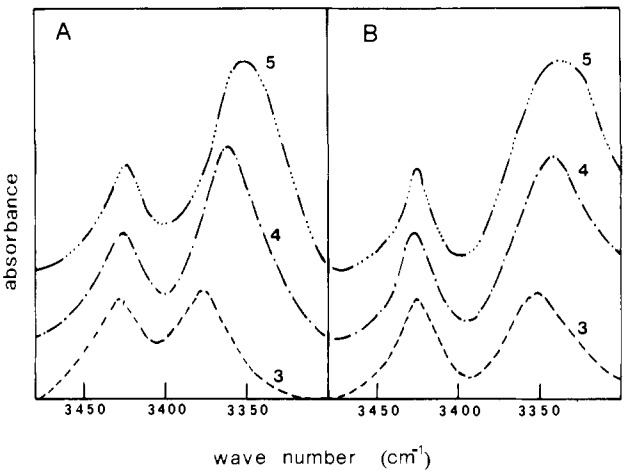

Figure 6. Infrared absorption spectra in deuteriochloroform (concentration 5×10^{-4} M) in the 3480–3300-cm^{-1} frequency range of Z-(Aib)$_n$-O-*t*-Bu (A) and Z-(Aib)$_n$-OH (B) (n = 3–5).

Solution Analysis. The conformational preferences of the Z-(Aib)$_n$-OX (n = 3–5; X = H, *t*-Bu) peptides were examined in a solvent of low polarity ($CDCl_3$) at various concentrations using IR absorption. The results obtained are reported in Table V and Figure 6.

Using the Mizushima's dilution technique,[49] we were able to show that at 5×10^{-4} M concentration intermolecular hydrogen bonding is negligible for all peptides. The band at 3429–3425 cm^{-1} is assigned to the free (solvated) urethane and amide N–H groups,[50] while the band at 3379–3333 cm^{-1} to the intramolecular hydrogen-bonded N–H groups.[50] The latter absorption shifts to lower frequencies with increasing peptide chain length and deblocking of the C-terminal group. In addition, the ratio of the integrated intensity of the band of the hydrogen-bonded N–H group to free N–H groups (A_H/A_F)[50] increases regularly from the tripeptide to the pentapeptide in both the C-blocked and C-deblocked series.

If one plots the integrated band intensity of the bonded N–H groups (at 3379–3333 cm^{-1}) as a function of the number of the intramolecular hydrogen bonds for the Z-(Aib)$_n$-O-*t*-Bu and Z-(Aib)$_n$-OH (n = 3–5) series at 5×10^{-4} M concentration, where the value of one hydrogen bond is taken for the integrated band intensity of the bonded N–H groups of the tripeptides, a good linearity is observed, which is strongly in favor of the occurrence of two intramolecular hydrogen bonds in the tetrapeptides, while it is in favor of three such bonds in the pentapeptides.[51-53] The

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more obvious consequence in terms of conformation is that the tri-, tetra-, and pentapeptides exclusively populate the single, double, and triple β-bend structures, respectively. This conclusion is supported by the excellent correlation with all the solid-state structures of homo oligo(α-aminoisobutyric acids) so far solved by X-ray diffraction (this work and ref 16 and 40), which unequivocally demonstrate that the type-III (or type-III') 4 → 1 intramolecular hydrogen-bonded conformations are those exclusively adopted whenever possible (i.e., in the N-protected tripeptides and their higher homologues). However, it is evident that the present conformational analysis in deuteriochloroform at high dilution cannot exclude categorically the occurrence of either the 3 → 1[43,44] or the 5 → 1 intramolecular hydrogen-bonded conformations (the latter at the level of the tetra- and pentapeptides). These conformations can exist either as the only species in solution or as components of the equilibrium mixtures, which could also involve the 4 → 1 intramolecular hydrogen-bonded forms.

At 5×10^{-2} M concentration the IR absorption spectral patterns in the N–H stretching region change only marginally for the C-protected peptides. The C-deblocked compounds were not examined owing to their low solubility under these experimental conditions. Interestingly, the A_H/A_F ratio of all the three C-protected peptides increases, with the 100-times increases in concentration (the bands due to the intra- and intermolecular hydrogen-bonded N–H groups overlap[50]). This result strongly supports the view that at 5×10^{-2} M concentration the N—H···O=C intermolecular hydrogen-bonded species exist in all three compounds, the extend of which is higher for the pentapeptide and lower for the tripeptide.[50] in this context, it should be recalled that the urethane N–H is the one responsible for the aggregation of the incipient 3_{10} helices of Z-(Aib)$_3$-O-*t*-Bu, Z-(Aib)$_4$-OH, and Z-(Aib)$_5$-O-*t*-Bu in the solid state.

Conclusions

The solid-state conformational anslysis, carried out by X-ray diffraction and IR absorption, of the N-benzyloxycarbonyl homotri-, and tetra-, and pentapeptides from the Aib residue has indicated the onset of incipient 3_{10} helices, formed by one, two, and three type-III (or type-III') β turns (4 → 1 intramolecular hydrogen-bonded structures), respectively. α-Helical structures, although having pairs of ϕ,ψ torsional angles close to those of the 3_{10} helices, are not compatible with the observed N—H···O=C hydrogen-bonding schemes of the tetra- and pentapeptides, being characterized by 5 → 1 intramolecular hydrogen-bonded peptide forms. The signs of the ϕ,ψ torsional angles of the last Aib residue in the sequences of the homo oligo(α-aminoisobutyric acids) are opposite to those of the preceding residues. The existence of a correlation between the conformational space of the Aib residue and its geometry at the C^α carbon atom has been discussed. The effect of the presence of a free –COOH group at the C-terminal end of the peptide chain on the type of folding was found to be negligible; however, it acts as donor in the intermolecular hydrogen-bonding scheme.

In solvents of low polarity (e.g., deuteriochloroform) the IR absorption data are in favor of the occurrence of the same intramolecular hydrogen-bonded folded forms as found in the solid state. Aggregation of these structures takes place at high concentrations.

Clearly, since segments containing up to four α, α-alkylated, α-amino acid residues in a row have been found in the peptide antibiotics of the alamethicin family, the 3_{10}-helical structure must be taken into consideration in suggesting a model of folding of these parts of their sequences containing a high proportion of Aib and Iva residues.

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Registry No. (*Z*)-Aib$_3$-O-*t*-Bu, 4512-37-2; (*Z*)-Aib$_4$-O-*t*-Bu, 4512-38-3; (*Z*)-Aib$_5$-O-*t*-Bu, 4512-39-4.

Supplementary Material Available: Tables of positional and thermal parameters, anistropic thermal parameters, and structure factor amplitudes for Z-(Aib)$_3$-O-*t*-Bu, Z-(Aib)$_4$-OH, and Z-(Aib)$_5$-O-*t*-Bu (52 pages). Ordering information is given on any current masthead page.

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Palladium-Catalyzed Cyclization of ω-Olefinic Tosamides. Synthesis of Nonaromatic Nitrogen Heterocycles

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Abstract: The cyclization of aliphatic amino olefins to nonaromatic nitrogen heterocycles has been accomplished by conversion of the amine to the corresponding *p*-toluenesulfonamide, followed by Pd(II)-catalyzed intramolecular amination of the olefin. The resulting tosylated enamines could be reduced and photolytically deprotected to give the saturated nitrogen heterocycle. The same product was obtained by reduction of the tosylated enamines with sodium bis(2-methoxyethoxy)aluminum hydride (Red-al).

Introduction

Transition metal organometallic reagents have been used extensively in the synthesis of heterocyclic compounds.[1] In our laboratories, the palladium(II)-catalyzed intramolecular amination[2] and carboxylation[3] of olefins, converting *o*-allylanilines to indoles and *o*-allylbenzoic acids to isocoumarins, have been developed. In this paper we describe the synthesis of nonaromatic nitrogen heterocycles using this approach.

Results and Discussion

Although *o*-allylanilines cyclized smoothly to indoles when treated with a catalytic amount of palladium(II) chloride under

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