Linear Oligopeptides. Part 227.[1] X-Ray Crystal and Molecular Structures of Two α-Helix-forming (Aib-L-Ala) Sequential Oligopeptides, *p*BrBz-(Aib-L-Ala)$_5$-OMe and *p*BrBz-(Aib-L-Ala)$_6$-OMe

Ettore Benedetti,* Benedetto Di Blasio, Vincenzo Pavone, Carlo Pedone, and Antonello Santini
Department of Chemistry, University of Naples, 80134 Naples, Italy
Alfonso Bavoso
Department of Chemistry, University of Basilicata, 85100 Potenza, Italy
Claudio Toniolo,* Marco Crisma, and Luciana Sartore
Biopolymer Research Centre, C.N.R., Department of Organic Chemistry, University of Padova, 35131, Padova, Italy

A crystal-state structural analysis of *p*BrBz-(Aib-L-Ala)$_5$-OMe tetrahydrate and *p*BrBz-(Aib-L-Ala)$_6$-OMe dihydrate has been performed by X-ray diffraction. The decapeptide and dodecapeptide molecules are both basically α-helical with five and seven 1 ⟵ 5 intramolecular H-bonds, respectively. A similarity between the two structures is also seen near the *C*-terminus, where regularity of the α-helix is disrupted in favour of formation of intramolecular H-bonds of the 1 ⟵ 4 and 1 ⟵ 6 types. A brief comparison with parameters and interactions characteristic of the helices present in globular proteins has been made.

Only recently have efforts been made to establish experimentally the factors governing transitions between 3_{10}- and α-helices in polypeptides.[1–4] This phenomenon is of great relevance not only to the specific problem of the nature of the helical structure adopted by the transmembrane channel-forming, ion-transporting peptaibol antibiotics,[5,6] but also to the more general biochemical problem of the relative stability of 3_{10}- and α-helices in proteins as well.[7]

In order to delineate the effect induced by peptide main-chain lengthening on the 3_{10} ⟶ α-helix conformational interconversion, we have recently synthesized the terminally blocked sequential oligopeptides *p*BrBz-(Aib-L-Ala)$_n$-OMe (n = 1–6) (where *p*BrBz is *p*-bromobenzoyl; Aib, α-aminoisobutyric acid; OMe, methoxy). These peptides all contain the same fraction of the highly helicogenic Aib[8–12] and Ala residue. We have already shown by X-ray diffraction that, while the hexapeptide (n = 3) is a complete 3_{10}-helix in the crystal state, the octapeptide (n = 4) has an α-helical region six residues long spanning the central and *C*-terminal parts.[1–3] In this paper we describe the results of an X-ray diffraction analyses of the deca- and dodeca-peptides (n = 5 and 6, respectively) which confirm that the (Aib-L-Ala)$_n$ peptides preferentially fold into an α-helical structure when the number of repeating dipeptide units exceeds three. A preliminary account of part of this work has been reported.[2]

Experimental

Materials.—*p*BrBz-(Aib-L-Ala)$_5$-OMe was synthesized in 74% yield from the oxazol-5(4*H*)-one obtained from *p*BrBz-Aib-OH[13,14] and H-L-Ala-(Aib-L-Ala)$_4$-OMe [prepared, in turn, by catalytic hydrogenation of Z-L-Ala-(Aib-L-Ala)$_4$-OMe, where Z is benzyloxycarbonyl] in anhydrous acetonitrile under reflux for 40 h: m.p. 276–278 °C (from chloroform–diethyl ether); $[\alpha]_D$ −8.3° (*c* 0.18, CF_3CH_2OH); TLC (silica gel plates 60F-254, Merck) R_{f1} ($CHCl_3$–EtOH, 9:1) 0.10, R_{f2} (BuOH–AcOH–water 3:1:1) 0.85. Amino acid analysis (C. Erba model 3A 29): Ala 0.99, Aib 1.01.

*p*BrBz-(Aib-L-Ala)$_6$-OMe was synthesized in 55% yield from the oxazol-5(4*H*)-one from *p*BrBz-Aib-OH and H-L-Ala-(Aib-L-Ala)$_5$-OMe [prepared, in turn, by catalytic hydrogenation of Z-L-Ala-(Aib-L-Ala)$_5$-OMe] in anhydrous acetonitrile under reflux for 40 h: m.p. 264–266 °C (from MeCN); $[\alpha]_D$ −12.0° (*c* 0.5, CF_3CH_2OH); R_{f1} 0.1, R_{f2} 0.85. Amino acid analysis: Ala 0.99, Aib 1.01.

Crystal Data for pBrBz-(Aib-L-Ala)$_5$-OMe *Tetrahydrate.*—$C_{43}H_{69}BrN_{10}O_{12}\cdot 4H_2O$, M = 1 068.0. Monoclinic, a = 10.172(1), b = 15.812(12), c = 17.042(4) Å, β = 90.78(16)°, V = 2 740.6 Å^3, space group $P2_1$, Z = 2, D_c = 1.294 g cm^{-3}, D_m = 1.29 g cm^{-3}, final R-value 0.068, final R_w-value 0.073.

Crystal Data for pBrBz-(Aib-L-Ala)$_6$-OMe *Dihydrate.*—$C_{50}H_{79}BrN_{12}O_{14}\cdot 2H_2O$, M = 1 188.2. Orthorhombic, a = 10.328(17), b = 18.131(3), c = 34.995(9) Å, V = 6 555.5 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.204 g cm^{-3}, D_m = 1.20 g cm^{-3}, final R-value 0.083, final R_w-value 0.091.

X-Ray Structure Determination of pBrBz-(Aib-L-Ala)$_5$-OMe *Tetrahydrate and* pBrBz-(Aib-L-Ala)$_6$-OMe *Dihydrate.*—Colourless crystals of *p*BrBz-(Aib-L-Ala)$_5$OMe tetrahydrate (*a*) and of *p*BrBz-(Aib-L-Ala)$_6$-OMe dihydrate (*b*) were grown by slow evaporation of methanol solutions. Enraf Nonius CAD4 diffractometer, ω–2θ scan mode up to θ = 70°; Ni-filtered Cu-K_α (λ 1.541 84 Å); 5 001 and 6 045 unique reflections for (*a*) and (*b*) were corrected for Lorentz and polarization, respectively; 1 623 and 2 027 reflections with $I > 3\sigma(I)$ were considered observed and used for the refinement of (*a*) and (*b*), respectively. Both structures were solved by the Patterson heavy-atom (bromine) method. Subsequent Fourier synthesis revealed the whole structure. Refinement for both the structures was performed by a full-matrix least-squares procedure minimizing the quantity $\Sigma w(F_o - F_c)^2$, with weight equal to $1/\sigma(F_o^2)$. The hydrogen atoms were introduced in their stereochemically expected positions and were not refined. The atomic scattering factors, with the real and imaginary dispersion corrections, were calculated for all atomic species according to International Tables.[15] All calculations were performed on a MicroVAX Digital Computer at the *Centro di Metodologie Chimico Fisiche* at the University of Naples, using the SDP package.[16] Full details of the experimental procedure are given in ref. 1. A Table of isotropic and

anisotropic refinements for *p*BrBz-(Aib-L-Ala)$_5$-OMe tetrahydrate and *p*BrBz-(Aib-L-Ala)$_6$-OMe dihydrate are available from the Cambridge Crystallographic Data Centre. Fractional atomic co-ordinates, bond lengths and bond angles are given in Tables 1–3.

Results

The molecular structures of the terminally blocked sequential oligopeptides *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O and *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O, determined by X-ray diffraction, are illustrated in Figures 1 and 2, respectively. Tables 4 and 5 report a selection of torsion angles,[17] while deviations of the backbone values from the ideal values for 3_{10}- and α-helices are shown in Figure 3. In Tables 6 and 7 the intra- and inter-molecular H-bonds are given, while Figures 4 and 5 illustrate the crystal-packing modes of the deca- and dodeca-peptides, respectively.

The backbone of the decapeptide folds into an α-helix for most of its length. The helix is initiated by the Aib residue at the *N*-terminus. Peptide groups N_4–H to N_8–H participate in five consecutive 1 ⟵ 5 (C_{13}-type or α-bend)[18] intramolecular H-bonds, typical of an α-helical structure. The regularity of the α-helix is disrupted at the *C*-end, where the -Aib^5-Ala^6-Aib^7- sequence exhibits a mixed α-/3_{10}-helical character. The -Aib^7-Ala^8- sequence is folded into a type-I β-bend.[18–20] The φ,ψ torsion angles for Aib^9 have changed sign, corresponding to a change in the handedness of the helix, a common observation near the *C*-terminus of 3_{10}-helices.[8–12] The last residue in the chain (Ala^{10}) is *semi*-extended. Accordingly, peptide groups N_8–H and N_9–H form two consecutive 1 ⟵ 4 (C_{10}-type or β-bend)[18–20] H-bonds, and peptide group N_{10}–H is part of an unusual 1 ⟵ 6 (C^{16}-type or π-bend) H-bond.[7] Therefore, the peptide oxygen O_5 is an acceptor for two H-bonds[1,3,21] (a 1 ⟵ 4 type from N_8–H and a 1 ⟵ 6 from N_{10}–H) and the peptide group N_8–H forms three-centre H-bonds[22] (a 1 ⟵ 5 type with O_4 and a 1 ⟵ 4 type with O_5). The average values of the φ, ψ torsion angles for the seven α-helical residues (from Aib^1 to Aib^7) are −63°, −42°. In particular, the informative ψ-value is much closer to the value for an idealized α-helix (−45°) than to that for a 3_{10}-helix (−30°).[7,12,21]

The peptide groups ω_1, ω_8, and ω_9 deviate significantly from planarity. The helix screw-sense is right-handed, as expected on the basis of the L-configuration of the five Ala residues. The methyl ester conformation with respect to the C–N bond is intermediate between the *synplanar* and *synclinal* conformations,[23] the N_{10}–C^{α}_{10}–C'_{10}–O_{10} torsion angle being −32°.

The mode of packing of the *p*BrBz-(Aib-L-Ala)$_5$-OMe molecules is shown in Figure 4. In the crystal state the helical molecules are held together in a rather complex scheme by intermolecular H-bonds with the N–H groups not involved in the intramolecular H-bonds and the water O–H groups as donors. Each helical molecule, which has the *C*-terminus bent away from the helix axis, is weakly but directly H-bonded to a

Table 1. Positional parameters and their estimated standard deviations.

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
*p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O							
Br	0.133 5(2)	0.000	−0.010 4(2)	C'_5	−0.671(2)	0.617(1)	0.294 9(9)
C(1)	−0.010(2)	0.054(1)	0.035(1)	O_5	−0.728(1)	0.687 3(9)	0.299 2(7)
C(2)	−0.104(2)	0.011(2)	0.077(1)	N_6	−0.555(1)	0.604 1(7)	0.330 1(7)
C(3)	−0.213(2)	0.054(1)	0.103(1)	C^{α}_6	−0.500(2)	0.666 6(1)	0.380(1)
C(4)	−0.237(2)	0.135(1)	0.088(1)	C^{β}_6	−0.382(2)	0.630(1)	0.423(1)
C(5)	−0.145(2)	0.181(2)	0.046(1)	C'_6	−0.451(2)	0.744(1)	0.333(1)
C(6)	−0.028(2)	0.138(1)	0.019(1)	O_6	−0.468(1)	0.816 8(7)	0.362 1(7)
C(7)	−0.355(2)	0.181(1)	0.112(1)	N_7	−0.395(1)	0.733 6(9)	0.266 8(8)
O(1)	−0.360(1)	0.259 1(8)	0.111 9(7)	C^{α}_7	−0.352(2)	0.803(1)	0.217(1)
N_1	−0.460(1)	0.136(1)	0.134 1(8)	$C^{\beta L}_7$	−0.237(2)	0.852(2)	0.256(1)
C^{α}_1	−0.591(2)	0.180(1)	0.150(1)	$C^{\beta D}_7$	−0.310(2)	0.762(1)	0.141(1)
$C^{\beta D}_1$	−0.680(2)	0.110(1)	0.180(1)	C'_7	−0.472(2)	0.859(1)	0.199(1)
$C^{\beta L}_1$	−0.645(2)	0.216(1)	0.074(1)	O_7	−0.458(1)	0.937 4(9)	0.187 5(8)
C'_1	−0.566(2)	0.247(1)	0.213(1)	N_8	−0.587(1)	0.824(1)	0.192 6(8)
O_1	−0.621(1)	0.316 8(9)	0.203 0(7)	C^{α}_8	−0.709(2)	0.867(1)	0.172(1)
N_2	−0.503(1)	0.224(1)	0.277 6(8)	C^{β}_8	−0.784(3)	0.807(2)	0.116(1)
C^{α}_2	−0.502(2)	0.284(1)	0.341(1)	C'_8	−0.788(2)	0.893(1)	0.238(1)
C^{β}_2	−0.437(3)	0.235(2)	0.413(1)	O_8	−0.907(2)	0.918(1)	0.226(1)
C'_2	−0.410(2)	0.360(1)	0.322(1)	N_9	−0.738(2)	0.896(1)	0.309 7(9)
O_2	−0.443(1)	0.429 6(8)	0.347 2(7)	C^{α}_9	−0.797(2)	0.936(2)	0.382(1)
N_3	−0.306(1)	0.345 9(9)	0.280 8(8)	$C^{\beta L}_9$	−0.711(3)	0.922(2)	0.445(2)
C^{α}_3	−0.217(2)	0.413(1)	0.258(1)	$C^{\beta D}_9$	−0.840(3)	1.026(2)	0.365(2)
$C^{\beta L}_3$	−0.149(2)	0.455(1)	0.327(1)	C'_9	−0.918(2)	0.884(1)	0.405(1)
$C^{\alpha D}_3$	−0.110(2)	0.374(1)	0.202(1)	O_9	−1.016(2)	0.916(1)	0.439(1)
C'_3	−0.296(2)	0.478(1)	0.210(1)	N_{10}	−0.919(2)	0.799(1)	0.389(1)
O_3	−0.284(1)	0.556 5(9)	0.221 5(7)	C^{α}_{10}	−1.020(2)	0.746(2)	0.428(1)
N_4	−0.373(1)	0.449 2(9)	0.152 2(8)	C^{β}_{10}	−0.996(3)	0.655(2)	0.405(2)
C^{α}_4	−0.450(2)	0.506(2)	0.101(1)	C'_{10}	−1.012(2)	0.753(2)	0.517(1)
C^{β}_4	−0.511(2)	0.458(1)	0.034(1)	O_{10}	0.916(1)	0.264(1)	0.445 8(9)
C'_4	−0.554(2)	0.553(1)	0.148(1)	O^*_{10}	−1.129(1)	0.741(1)	0.548 3(8)
O_4	−0.573(1)	0.629 6(8)	0.139 7(7)	C(8)	−1.132(2)	0.744(2)	0.633(1)
N_5	−0.623(1)	0.509(1)	0.199 1(7)	Ow(1)	−0.241(3)	0.020(2)	0.439(2)
C^{α}_5	−0.729(2)	0.542(1)	0.249(1)	Ow(2)	0.825(3)	0.175(2)	0.289(1)
$C^{\beta L}_5$	−0.840(2)	0.571(1)	0.195(1)	Ow(3)	0.602(2)	0.054(1)	0.313(1)
$C^{\beta D}_5$	−0.772(2)	0.474(1)	0.307(1)	Ow(4)	−0.371(4)	0.915(3)	0.499(3)

Table 1 (*continued*)

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
*p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O							
Br	0.369 3(4)	1.320 9(2)	−0.128 0(1)	C'_6	1.516(2)	1.010(1)	0.084 1(5)
C(1)	0.480(2)	1.244(1)	−0.112 6(6)	O'_6	1.611(1)	0.992 4(7)	0.103 4(3)
C(2)	0.449(2)	1.173(1)	−0.124 7(6)	N_7	1.412(2)	1.043 8(8)	0.098 9(4)
C(3)	0.528(2)	1.115(1)	−0.115 0(6)	C^{α}_7	1.404(2)	1.061(1)	0.139 6(5)
C(4)	0.634(2)	1.130(1)	−0.090 5(5)	$C^{\beta L}_7$	1.268(2)	1.089(1)	0.147 1(6)
C(5)	0.660(2)	1.199(1)	−0.080 0(6)	$C^{\beta D}_7$	1.498(2)	1.117(1)	0.150 7(6)
C(6)	0.581(2)	1.258(1)	−0.091 9(6)	C'_7	1.420(2)	0.989(1)	0.161 8(5)
C(7)	0.726(2)	1.067(1)	−0.077 4(5)	O'_7	1.493(1)	0.985 1(7)	0.190 5(4)
O(1)	0.801(1)	1.077 4(7)	−0.049 9(4)	N_8	1.356(2)	0.929 9(8)	0.151 0(4)
N_1	0.718(1)	1.003 3(8)	−0.095 4(4)	C^{α}_8	1.362(2)	0.861(1)	0.171 6(5)
C^{α}_1	0.789(2)	0.937(1)	−0.081 7(5)	C^{β}_8	1.251(2)	0.811(1)	0.159 2(7)
$C^{\beta D}_1$	0.725(2)	0.912(1)	−0.041 9(7)	C'_8	1.487(2)	0.822(1)	0.167 3(5)
$C^{\beta L}_1$	0.782(2)	0.877(1)	−0.110 2(6)	$0'_8$	1.533(1)	0.786 1(7)	0.194 7(3)
C'_1	0.925(2)	0.953(1)	−0.074 7(5)	O'_8	1.549(1)	0.823 7(8)	0.133 6(4)
O'_1	0.979(1)	0.928 7(7)	−0.044 3(4)	C^{α}_9	1.675(2)	0.787 8(9)	0.128 3(5)
N_2	0.993(1)	0.987 4(8)	−0.100 0(4)	$C^{\beta D}_9$	1.717(2)	0.810(1)	0.087 3(6)
C^{α}_2	1.132(2)	0.994(1)	−0.095 8(5)	$C^{\beta L}_9$	1.660(2)	0.705(1)	0.129 6(6)
C^{β}_2	1.194(2)	1.017(1)	−0.133 2(6)	C'_9	1.775(2)	0.816(1)	0.155 2(5)
C'_2	1.171(2)	1.044(1)	−0.062 5(5)	O'_9	1.864(2)	0.776 4(8)	0.165 2(4)
O'_2	1.272(1)	1.029 7(7)	−0.044 4(4)	N_{10}	1.763(2)	0.885 7(8)	0.167 4(4)
N_3	1.100(1)	1.103 2(8)	−0.056 9(4)	C^{α}_{10}	1.854(2)	0.921(1)	0.193 6(6)
C^{α}_3	1.129(2)	1.154(1)	−0.024 8(5)	C^{β}_{10}	1.869(2)	1.001(1)	0.182 6(6)
$C^{\beta D}_3$	1.255(2)	1.193(1)	−0.030 9(6)	C'_{10}	1.812(2)	0.912(1)	0.235 3(5)
$C^{\beta L}_3$	1.016(2)	1.210(1)	−0.024 5(6)	O'_{10}	1.869(1)	0.950 7(7)	0.258 8(4)
C'_3	1.128(2)	1.109(1)	0.012 7(5)	N_{11}	1.710(2)	0.868 8(8)	0.243 9(4)
O'_3	1.214(1)	1.114 5(7)	0.035 7(4)	C^{α}_{11}	1.664(2)	0.859(1)	0.283 3(5)
N_4	1.025(1)	1.066 5(8)	0.017 6(4)	$C^{\beta L}_{11}$	1.542(2)	0.810(1)	0.282 3(6)
C^{α}_4	1.016(2)	1.026(1)	0.052 7(6)	$C^{\beta D}_{11}$	1.774(2)	0.828(1)	0.308 6(6)
C^{β}_4	0.870(3)	0.994(2)	0.056 0(8)	C'_{11}	1.614(2)	0.933(1)	0.296 2(5)
C'_4	1.107(2)	0.962(1)	0.054 4(6)	O'_{11}	1.615(1)	0.950 8(8)	0.332 2(4)
O'_4	1.163(1)	0.947 6(7)	0.086 2(4)	N_{12}	1.567(2)	0.982 8(9)	0.272 7(4)
N_5	1.141(2)	0.923 5(9)	0.023 6(5)	C^{α}_{12}	1.511(2)	1.053(1)	0.279 9(6)
C^{α}_5	1.240(2)	0.868(1)	0.023 0(6)	C^{β}_{12}	1.585(2)	1.116(1)	0.267 9(6)
$C^{\beta D}_5$	1.189(3)	0.800(2)	0.044 3(8)	C'_{12}	1.351(3)	1.054(1)	0.267 0(7)
$C^{\beta L}_5$	1.264(3)	0.847(1)	−0.019 0(7)	O'_{12}	1.321(2)	1.111(1)	0.256 3(6)
C'_5	1.360(2)	0.900(1)	0.038 1(6)	O'_{12}*	1.317(2)	0.986(1)	0.267 5(5)
O'_5	1.430(2)	0.861 2(8)	0.061 0(4)	C(8)	1.174(4)	0.984(2)	0.257(1)
N_6	1.403(2)	0.964 0(8)	0.028 6(4)	Ow(1)	0.919(2)	0.027 4(8)	0.328 8(4)
C^{α}_6	1.521(2)	0.996(1)	0.041 7(5)	Ow(2)	0.561(3)	0.352(2)	0.697 0(8)
C^{β}_6	1.539(2)	1.074(1)	0.020 2(7)				

Table 2. Bond distances.[a]

Atom 1	Atom 2	Distance/Å	Atom 1	Atom 2	Distance/Å	Atom 1	Atom 2	Distance/Å
*p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O								
Br	C(1)	1.86(2)	N_2	C^{α}_2	1.43(2)	N_5	C^{α}_5	1.48(2)
C(1)	C(2)	1.38(3)	C^{α}_2	C^{β}_2	1.60(3)	C_5	$C^{\beta L}_5$	1.52(3)
C(1)	C(6)	1.37(3)	C^{α}_2	C'_2	1.55(3)	C_5	$C^{\beta D}_5$	1.52(3)
C(2)	C(3)	1.38(3)	C'_2	O_2	1.23(2)	C^{α}_5	C'_5	1.53(2)
C(3)	C(4)	1.34(3)	C'_2	N_3	1.30(2)	C'_5	O_5	1.26(2)
C(4)	C(5)	1.39(3)	N_3	C^{α}_3	1.45(2)	C'_5	N_6	1.33(2)
C(4)	C(7)	1.47(3)	C^{α}_3	$C^{\beta L}_3$	1.51(3)	N_6	C^{α}_6	1.41(2)
C(5)	C(6)	1.44(3)	C^{α}_3	$C^{\beta D}_3$	1.58(3)	C^{α}_6	C^{β}_6	1.50(3)
C(7)	O(1)	1.23(2)	C^{α}_3	C'_3	1.54(3)	C^{α}_6	C'_6	1.56(3)
C(7)	N_1	1.34(2)	C'_3	O_3	1.27(2)	C'_6	O_6	1.27(2)
N_1	C^{α}_1	1.53(2)	C'_3	N_4	1.32(2)	C'_6	N_7	1.28(2)
C^{α}_1	$C^{\beta D}_1$	1.53(3)	N_4	C^{α}_4	1.48(2)	N_7	C^{α}_7	1.46(2)
C^{α}_1	$C^{\beta L}_1$	1.52(3)	C^{α}_4	C^{β}_4	1.50(3)	C^{α}_7	$C^{\beta L}_7$	1.54(3)
C^{α}_1	C'_1	1.52(3)	C^{α}_4	C'_4	1.52(3)	C^{α}_7	$C^{\beta D}_7$	1.52(3)
C'_1	O_1	1.25(2)	C'_4	O_4	1.24(2)	C^{α}_7	C'_7	1.54(3)
C'_1	N_2	1.31(2)	C'_4	N_5	1.33(2)	C'_7	O_7	1.26(2)

Table 2 (*continued*)

Atom 1	Atom 2	Distance/Å	Atom 1	Atom 2	Distance/Å	Atom 1	Atom 2	Distance/Å
*p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O								
C′$_7$	N$_8$	1.30(2)	N$_9$	C$^{\alpha}_9$	1.51(3)	N$_{10}$	C$^{\alpha}_{10}$	1.49(3)
N$_8$	C$^{\alpha}_8$	1.47(2)	C$^{\alpha}_9$	C$^{\beta L}_9$	1.40(3)	C$^{\alpha}_{10}$	C$^{\beta}_{10}$	1.51(4)
C$^{\alpha}_8$	C$^{\beta}_8$	1.54(3)	C$^{\alpha}_9$	C$^{\beta D}_9$	1.53(4)	C$^{\alpha}_{10}$	C′$_{10}$	1.52(3)
C$^{\alpha}_8$	C′$_8$	1.45(3)	C$^{\alpha}_9$	C′$_9$	1.54(3)	C′$_{10}$	O$^{*}_{10}$	1.33(3)
C$_8$	O$_8$	1.29(3)	C′$_9$	O$_9$	1.27(3)	O$^{*}_{10}$	C(8)	1.45(3)
C′$_8$	N$_9$	1.32(3)	C′$_9$	N′$_{10}$	1.37(3)			
*p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O								
Br	C(1)	1.88(2)	C′$_3$	O′$_3$	1.20(2)	C$^{\alpha}_8$	C$^{\beta}_8$	1.53(3)
C(1)	C(2)	1.39(3)	C′$_3$	N$_4$	1.32(3)	C$^{\alpha}_8$	C′$_8$	1.49(3)
C(1)	C(6)	1.29(3)	N$_4$	C$^{\alpha}_4$	1.44(3)	C′$_8$	O′$_8$	1.25(2)
C(2)	C(3)	1.38(3)	C$^{\alpha}_4$	C$^{\beta}_4$	1.62(4)	C′$_8$	N$_9$	1.34(2)
C(3)	C(4)	1.41(3)	C$^{\alpha}_4$	C′$_4$	1.48(3)	N$_9$	C$^{\alpha}_9$	1.46(2)
C(4)	C(5)	1.34(3)	C′$_4$	O′$_4$	1.29(2)	C$^{\alpha}_9$	C$^{\beta D}_9$	1.55(3)
C(4)	C(7)	1.55(3)	C′$_4$	N′$_5$	1.33(3)	C$^{\alpha}_9$	C$^{\beta L}_9$	1.51(3)
C(5)	C(6)	1.40(3)	N$_5$	C$^{\alpha}_5$	1.43(3)	C$^{\alpha}_9$	C′$_9$	1.49(3)
C(7)	O$_1$	1.25(2)	C$^{\alpha}_5$	C$^{\beta D}_5$	1.54(4)	C′$_9$	O′$_9$	1.22(3)
C(7)	N$_1$	1.32(2)	C$^{\alpha}_5$	C$^{\beta L}_5$	1.54(3)	C′$_9$	N′$_{10}$	1.33(3)
N$_1$	C$^{\alpha}_1$	1.49(2)	C$^{\alpha}_5$	C′$_5$	1.48(3)	N$_{10}$	C$^{\alpha}_{10}$	1.46(3)
C$^{\alpha}_1$	C$^{\beta L}_1$	1.60(3)	C′$_5$	O′$_5$	1.29(3)	C$^{\alpha}_{10}$	C$^{\beta}_{10}$	1.51(3)
C$^{\alpha}_1$	C$^{\beta D}_1$	1.47(3)	C′$_5$	N$_6$	1.28(3)	C$^{\alpha}_{10}$	C′$_{10}$	1.53(3)
C$^{\alpha}_1$	C′$_1$	1.46(3)	N$_6$	C$^{\alpha}_6$	1.43(3)	C′$_{10}$	O′$_{10}$	1.23(2)
C′$_1$	O′$_1$	1.28(2)	C$^{\alpha}_6$	C$^{\beta}_6$	1.61(3)	C′$_{10}$	N$_{11}$	1.35(3)
C′$_1$	N$_2$	1.29(2)	C$^{\alpha}_6$	C′$_6$	1.51(3)	N$_{11}$	C$^{\alpha}_{11}$	1.47(2)
N$_2$	C$^{\alpha}_2$	1.45(3)	C′$_6$	O′$_6$	1.24(2)	C$^{\alpha}_{11}$	C$^{\beta L}_{11}$	1.55(3)
C$^{\alpha}_2$	C$^{\beta}_2$	1.51(3)	C′$_6$	N$_7$	1.34(2)	C$^{\alpha}_{11}$	C$^{\beta D}_{11}$	1.54(3)
C$^{\alpha}_2$	C′$_2$	1.54(3)	N$_7$	C$^{\alpha}_7$	1.46(2)	C$^{\alpha}_{11}$	C′$_{11}$	1.51(3)
C′$_2$	O$_2$	1.25(2)	C$^{\alpha}_7$	C$^{\beta L}_7$	1.52(3)	C′$_{11}$	O′$_{11}$	1.30(2)
C′$_2$	N$_3$	1.31(2)	C$^{\alpha}_7$	C$^{\beta D}_7$	1.46(3)	C′$_{11}$	N$_{12}$	1.31(3)
N$_3$	C$^{\alpha}_3$	1.48(2)	C$^{\alpha}_7$	C′$_7$	1.53(3)	N$_{12}$	C$^{\alpha}_{12}$	1.42(3)
C$^{\alpha}_3$	C$^{\beta D}_3$	1.49(3)	C′$_7$	O′$_7$	1.26(2)	C$^{\alpha}_{12}$	C$^{\beta}_{12}$	1.43(3)
C$^{\alpha}_3$	C$^{\beta L}_3$	1.55(3)	C′$_7$	N′$_8$	1.32(2)	C$^{\alpha}_{12}$	C′$_{12}$	1.71(3)
C$^{\alpha}_3$	C′$_3$	1.54(3)	N$_8$	C$^{\alpha}_8$	1.44(2)	C′$_{12}$	O′$_{12}$	1.15(3)
C′$_{12}$	O$^{*}_{12}$	1.28(3)	O$^{*}_{12}$	C(8)	1.52(4)			

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 3. Bond angles.[a]

Atom 1	Atom 2	Atom 3	Angle/°	Atom 1	Atom 2	Atom 3	Angle/°	Atom 1	Atom 2	Atom 3	Angle/°
*p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O											
Br	C(1)	C(1)	123.(2)	C$^{\alpha}_1$	C′$_1$	O$_1$	116.(1)	N$_3$	C$^{\alpha}_3$	C$^{\beta D}_3$	108.(2)
Br	C(1)	C(6)	118.(1)	C$^{\alpha}_1$	C′$_1$	N′$_2$	118.(2)	N$_3$	C$^{\alpha}_3$	C′$_3$	108.(1)
C(2)	C(1)	C(6)	119.(2)	O$_1$	C′$_1$	N$_2$	125.(2)	C$^{\beta L}_3$	C$^{\alpha}_3$	C$^{\beta D}_3$	110.(2)
C(1)	C(2)	C(3)	120.(2)	C′$_1$	N$_2$	C$^{\alpha}_2$	116.(2)	C$^{\beta L}_3$	C$^{\alpha}_3$	C′$_3$	110.(2)
C(2)	C(3)	C(4)	124.(2)	N$_2$	C$^{\alpha}_2$	C$^{\beta}_2$	105.(2)	C$^{\beta D}_3$	C$^{\alpha}_3$	C′$_3$	107.(1)
C(3)	C(4)	C(5)	118.(2)	N$_8$	C$^{\alpha}_8$	C$^{\beta}_8$	106.(2)	C$^{\alpha}_3$	C′$_3$	O$_3$	121.(2)
C(3)	C(4)	C(7)	125.(2)	N$_8$	C$^{\alpha}_8$	C′$_8$	115.(2)	C$^{\alpha}_3$	C′$_3$	N$_4$	118.(2)
C(5)	C(4)	C(7)	117.(2)	C$^{\beta}_8$	C$^{\alpha}_8$	C′$_8$	112.(2)	O$_3$	C′$_3$	N$_4$	121.(2)
C(4)	C(5)	C(6)	119.(2)	C$^{\alpha}_8$	C′$_8$	O$_8$	119.(2)	C′$_3$	N$_4$	C$^{\alpha}_4$	122.(2)
C(1)	C(6)	C(5)	120.(2)	C$^{\alpha}_8$	C′$_8$	N$_9$	122.(2)	N$_4$	C$^{\alpha}_4$	C$^{\beta}_4$	110.(2)
C(4)	C(7)	O(1)	122.(2)	O$_8$	C′$_8$	N$_9$	117.(2)	N$_4$	C$^{\alpha}_4$	C′$_4$	111.(1)
C(4)	C(7)	N$_1$	118.(2)	C′$_8$	N$_9$	C$^{\alpha}_9$	128.(2)	C$^{\beta}_4$	C$^{\alpha}_4$	C′$_4$	111.(1)
O(1)	C(7)	N$_1$	120.(2)	N$_9$	C$^{\alpha}_9$	C$^{\beta L}_9$	108.(2)	C$^{\alpha}_4$	C′$_4$	O$_4$	122.(2)
C(7)	N$_1$	C$^{\alpha}_1$	121.(2)	N$_2$	C$^{\alpha}_2$	C$^{1}_2$	111.(2)	C$^{\alpha}_4$	C′$_4$	N$_5$	118.(2)
N$_1$	C$^{\alpha}_1$	C$^{\beta D}_1$	105.(1)	C$^{\beta}_2$	C$^{\alpha}_2$	C$^{1}_2$	106.(2)	O$_4$	C′$_4$	N$_5$	120.(2)
N$_1$	C$^{\alpha}_1$	C$^{\beta L}_1$	108.(1)	C$^{\alpha}_2$	C′$_2$	O$_2$	117.(2)	C′$_4$	N$_5$	C$^{\alpha}_5$	126.(2)
N$_1$	C$^{\alpha}_1$	C′$_1$	108.(1)	C$^{\alpha}_2$	C′$_2$	N$_3$	119.(2)	N$_5$	C$^{\alpha}_5$	C$^{\beta L}_5$	107.(1)
C$^{\beta L}_1$	C$^{\alpha}_1$	C$^{\beta D}_1$	110.(2)	O$_2$	C′$_2$	N$_3$	125.(2)	N$_5$	C$^{\alpha}_5$	C$^{\beta D\alpha}_5$	110.(1)
C$^{\beta L}_1$	C$^{\alpha}_1$	C′$_1$	111.(1)	C′$_2$	N$_3$	C$^{\alpha}_3$	123.(2)	N$_9$	C$^{\alpha}_9$	C$^{\beta}_9$	110.(2)
C$^{\beta D}_1$	C$^{\alpha}_1$	C′$_1$	114.(2)	N$_3$	C$^{\alpha}_3$	C$^{\beta L}_3$	113.(2)	N$_9$	C$^{\alpha}_9$	C′$_9$	109.(2)

Table 3 (*continued*)

Atom 1	Atom 2	Atom 3	Angle/°	Atom 1	Atom 2	Atom 3	Angle/°	Atom 1	Atom 2	Atom 3	Angle/°
*p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O											
$C_9^{\beta L}$	C_9^{α}	$C_9^{\beta D}$	118.(2)	C'_5	N_6	C_6^{α}	121.(1)	$C_7^{\beta D}$	C_7^{α}	C'_7	108.(2)
$C_9^{\beta L}$	C_9^{α}	C'_9	102.(2)	N_6	C_6^{α}	C_6^{β}	110.(2)	C_7^{α}	C'_7	O_7	120.(2)
$C_9^{\beta D}$	C_9^{α}	C'_9	109.(2)	N_6	C_6^{α}	C'_6	111.(1)	C_7^{α}	C'_7	N_8	118.(2)
C_9^{α}	C'_9	O_9	123.(2)	C_6^{β}	C_6^{α}	C'_6	107.(1)	O_7	C'_7	N_8	121.(2)
C_9^{α}	C'_9	N_{10}	119.(2)	C_6^{α}	C'_6	O_6	118.(1)	C'_7	N_8	C_8^{α}	125.(2)
O_9	C'_9	N_{10}	118.(2)	C_6^{α}	C'_6	N_7	120.(2)	C'_9	N_{10}	C_{10}^{α}	118.(2)
N_5	C_5^{α}	C'_5	107.(1)	O_6	C'_6	N_7	122.(2)	N_9	C_{10}^{α}	C_{10}^{β}	108.(2)
$C_5^{\beta L}$	C_5^{α}	$C_5^{\beta D}$	113.(2)	C'_6	N_7	C_7^{α}	124.(2)	N_{10}	C_{10}^{α}	C'_{10}	112.(2)
$C_5^{\beta L}$	C_5^{α}	C'_5	111.(2)	N_7	C_7^{α}	$C_7^{\beta L}$	111.(2)	C_{10}^{β}	C_{10}^{α}	C'_{10}	109.(2)
$C_5^{\beta D}$	C_5^{α}	C'_5	109.(1)	N_7	C_7^{α}	$C_7^{\beta D}$	106.(2)	C_{10}^{α}	C'_{10}	O_{10*}	111.(2)
C_5^{α}	C'_5	O_5	122.(1)	N_7	C_7^{α}	C'_7	108.(1)	C'_{10}	O_{10*}	C(8)	115.(2)
C_5^{α}	C'_5	N_6	117.(1)	$C_7^{\beta L}$	C_7^{α}	$C_7^{\beta D}$	111.(2)				
O_5	C'_5	N_6	121.(1)	$C_7^{\beta L}$	C_7^{α}	C'_7	113.(2)				
*p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O											
Br	C(1)	C(2)	117.(2)	N_2	C_2^{α}	C'_2	112.(2)	N_5	C_5^{α}	C'_5	109.(2)
Br	C(1)	C(6)	120.(2)	C_2^{β}	C_2	C'_2	112.(2)	$C_5^{\beta D}$	C_5^{α}	$C_5^{\beta L}$	108.(2)
C(2)	C(1)	C(6)	122.(2)	C_2^{α}	C'_2	O_2	119.(2)	$C_5^{\beta D}$	C_5^{α}	C'_5	116.(2)
C(1)	C(2)	C(3)	120.(2)	C_2^{α}	C'_2	N_3	117.(2)	$C_5^{\beta L}$	C_5^{α}	C'_5	108.(2)
C(2)	C(3)	C(4)	117.(2)	O'_2	C'_2	N_3	124.(2)	C_5^{α}	C'_5	O'_5	118.(2)
C(3)	C(4)	C(5)	120.(2)	C'_2	N_3	C_3^{α}	120.(1)	C_5^{α}	C'_5	N_6	124.(2)
C(3)	C(4)	C(7)	120.(2)	N_3	C_3^{α}	$C_3^{\beta D}$	111.(2)	O'_5	C'_6	N_6	118.(2)
C(5)	C(4)	C(7)	119.(2)	N_3	C_3^{α}	$C_3^{\beta L}$	105.(2)	C'_5	N_6	C_6^{α}	125.(2)
C(4)	C(5)	C(6)	121.(2)	N_3	C_3^{α}	C'_3	108.(1)	N_6	C_6^{α}	C_6^{β}	108.(2)
C(1)	C(6)	C(5)	119.(2)	$C_3^{\beta D}$	C_3^{α}	$C_3^{\beta L}$	110.(2)	N_6	C_6^{α}	C'_6	111.(2)
C(4)	C(7)	O(1)	120.(2)	$C_3^{\beta D}$	C_3^{α}	C'_3	112.(2)	C_6^{β}	C_6^{α}	C'_6	108.(2)
C(4)	C(7)	N_1	118.(2)	$C_3^{\beta L}$	C_3^{α}	C'_3	109.(2)	C_6^{α}	C'_6	O'_6	118.(2)
O(1)	C(7)	N_1	122.(2)	C_3^{α}	C'_3	O'_3	121.(2)	C_6^{α}	C'_6	N_7	119.(2)
C(7)	N_1	C_1	122.(1)	C_3^{α}	C'_3	N_4	115.(2)	O'_6	C'_6	N_7	123.(2)
N_1	C_1^{α}	$C_1^{\beta L}$	108.(1)	O'_3	C'_3	N_4	123.(2)	C'_6	N_7	C_7^{α}	121.(2)
N_1	C_1^{α}	$C_1^{\beta D}$	111.(2)	C'_3	N_4	C_4^{α}	118.(2)	N_7	C_7^{α}	$C_7^{\beta L}$	107.(2)
N_1	C_1^{α}	C'_1	111.(1)	N_4	C_4^{α}	C_4^{β}	108.(2)	N_7	C_7^{α}	$C_7^{\beta D}$	112.(2)
$C_1^{\beta L}$	C_1^{α}	$C_1^{\beta D}$	111.(2)	N_4	C_4^{α}	C'_4	113.(2)	N_7	C_7^{α}	C'_7	108.(1)
$C_1^{\beta L}$	C_1^{α}	C'_1	108.(2)	C_4^{β}	C_4^{α}	C'_4	108.(2)	$C_7^{\beta L}$	C_7^{α}	$C_7^{\beta D}$	109.(2)
$C_1^{\beta D}$	C_1^{α}	C'_1	108.(2)	C_4^{α}	C'_4	O'_4	119.(2)	$C_7^{\beta L}$	C_7^{α}	C'_7	107.(2)
C_1^{α}	C'_1	O'_1	119.(2)	C_4^{α}	C'_4	N_5	123.(2)	$C_7^{\beta D}$	C_7^{α}	C'_7	113.(2)
C_1^{α}	C'_1	N_2	121.(2)	O'_4	C'_4	N_5	118.(2)	C_7^{α}	C'_7	O'_7	121.(2)
O_1^{α}	C'_1	N_2	120.(2)	C'_4	N_5	C_5^{α}	125.(2)	C_7^{α}	C'_7	N_8	120.(2)
C'_1	N_2	C_2^{α}	121.(2)	N_5	C_5^{α}	$C_5^{\beta D}$	108.(2)	O'_7	C'_7	N_8	119.(2)
N'_2	C_2^{α}	C_2^{β}	111.(2)	N_5	C_5^{α}	$C_5^{\beta L}$	108.(2)	C'_7	N_8	C_8^{α}	123.(1)
N_8	C_8^{α}	C_8^{β}	110.(2)	C_9^{α}	C'_9	N_{10}	118.(2)	$C_{11}^{\beta L}$	C_{11}^{α}	C'_{11}	104.(2)
N_8	C_8^{α}	C'_8	114.(2)	O'_9	C'_9	N_{10}	123.(2)	$C_{11}^{\beta D}$	C_{11}^{α}	C'_{11}	114.(2)
C_8^{β}	C_8^{α}	C'_8	109.(2)	C'_9	N_{10}	C_{10}^{α}	124.(2)	C_{11}^{α}	C'_{11}	O'_{11}	120.(2)
C_8^{α}	C'_8	O'_8	120.(2)	N_{10}	C_{10}^{α}	C_{10}^{β}	109.(2)	C_{11}^{α}	C'_{11}	N_{12}	124.(2)
C_8^{α}	C'_8	N_9	119.(2)	N_{10}	C_{10}^{α}	C'_{10}	112.(2)	O'_{11}	C'_{11}	N_{12}	116.(2)
O'_8	C'_8	N_9	121.(2)	C_{10}^{β}	C_{10}^{α}	C'_{10}	112.(2)	C'_{11}	N_{12}	C_{12}^{α}	131.(2)
C'_8	N'_9	C_9^{α}	122.(1)	C_{10}^{α}	C'_{10}	O'_{10}	117.(2)	N_{12}	C_{12}^{α}	C_{12}^{β}	116.(2)
N_9	C_9^{α}	$C_9^{\beta D}$	104.(1)	C_{10}^{α}	C'_{10}	N_{11}	119.(2)	N_{12}	C_{12}^{α}	C'_{12}	111.(2)
N_9	C_9^{α}	$C_9^{\beta L}$	110.(2)	O'_{10}	C'_{10}	N_{11}	124.(2)	C_{12}^{β}	C_{12}^{α}	C'_{12}	116.(2)
N_9	C_9^{α}	C'_9	112.(1)	C'_{10}	N_{11}	C_{11}^{α}	122.(2)	C_{12}^{α}	C'_{12}	O'_{12}	111.(2)
$C_9^{\beta D}$	C_9^{α}	$C_9^{\beta L}$	109.(2)	N_{11}	C_{11}^{α}	$C_{11}^{\beta L}$	108.(2)	C_{12}^{α}	C'_{12}	O_{12}^{*}	105.(2)
$C_9^{\beta D}$	C_9^{α}	C'_9	107.(2)	N_{11}	C_{11}^{α}	$C_{11}^{\beta D}$	110.(2)	O'_{12}	C'_{12}	O_{12}^{*}	143.(3)
$C_9^{\beta L}$	C_9^{α}	C'_9	114.(2)	N_{11}	C_{11}^{α}	C'_{11}	106.(2)	C'_{12}	O_{12}^{*}	C(8)	107.(2)
C_9^{α}	C'_9	O'_9	120.(2)	$C_{11}^{\beta L}$	C_{11}^{α}	$C_{11}^{\beta D}$	114.(2)				

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

molecule translated along the *b* axis [N(1)–H · · · O(7)=C′(7) 3.27 (Å]. The bending of the *C*-terminus with the disruption of the helix should be directly linked to the extent of hydration and/or the need for packing of the hydrated helices. Other H-bonds between helices are observed, but they are mediated by water molecules Ow(1), Ow(2), and Ow(3), which interconnect the helices. Columns of molecules are then formed along the *b* direction, packed head-to-tail and parallel to each other. Each of these columns, by means of H-bonds of the O–H · · · O type with the co-crystallized water molecules, pack with an iso-

Table 4. Selected torsion angles for *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O.

	Residue									
	1	2	3	4	5	6	7	8	9	10
(*a*) Main-chain torsion angles (°) (σ 1)										
φ_i	−56[a]	−73	−59	−65	−56	−72	−57	−96	68	−57
ψ_i	−50	−32	−48	−44	−48	−39	−33	16	31	151[b]
ω_i	−169	−179	−179	−173	−173	177	−177	168	166	179[c]

(*b*) Torsion angles (°) for the *N*- and *C*-terminal blocking groups (or 1°)

O(1)–C(7)–C(4)–C(3)		164	N_{10}–C^{α}_{10}–C'_{10}–O_{10}	−32
O(1)–C(7)–C(4)–C(5)		−16		
N_1–C(7)–C(4)–C(3)	θ_1	−17		
N_1–C(7)–C(4)–C(5)	θ'_1	163		
C^{α}_1–N_1–C(7)–C(4)	ω_0	−172		

[a] C(7)–N_1–C^{α}_1–C'_1. [b] N_{10}–C^{α}_{10}–C'_{10}–O^{*}_{10}. [c] C^{α}_{10}–C'_{10}–O^{*}_{10}–C(8).

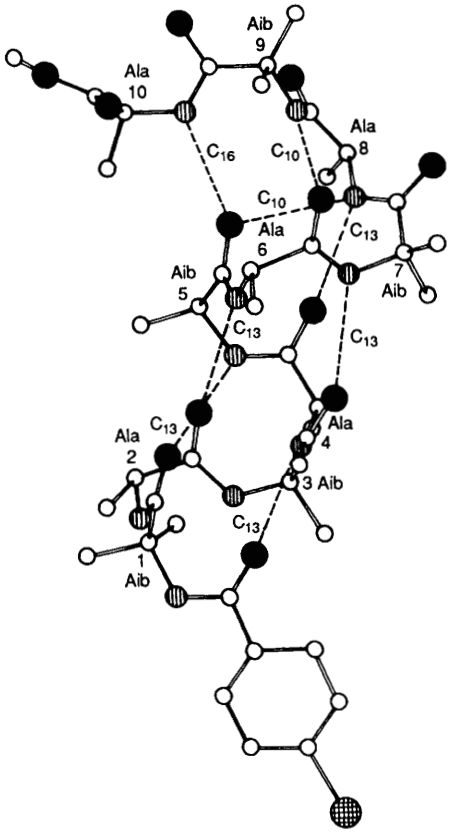

Figure 1. Molecular structure of *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O. The eight intramolecular H-bonds of the C_{10}-, C_{13}-, and C_{16}-types are indicated as dashed lines.

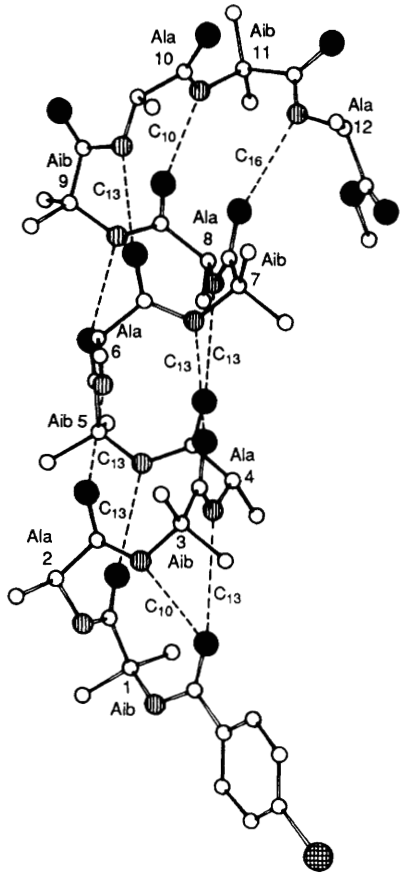

Figure 2. Molecular structure of *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O. The ten intromolecular H-bonds of the C_{10}-, C_{13}-, and C_{16}-types are indicated as dashed lines.

oriented parallel column of helical molecules along the *c* axis. The resulting double column of molecules then packs with similar columns in a parallel fashion by means of van der Waals interactions between facing hydrophobic groups. The details of each H-bond are given in Table 6. All possible donors are involved in the H-bonding scheme, while among the acceptors only the O_8 atom is not involved. Analogous packings of helical molecules with or without the presence of hydration have been described earlier. In general, the N–H • • • O and the O–H • • • O distances are in reasonable agreement with literature data.[24–27]

The general features of the helical structure formed by the dodecapeptide closely parallel those described above for the decapeptide. In particular (i) the α-helix spans the Aib^1-to-Aib^9 segment with seven 1 ⟵ 5 intramolecular H-bonds. (ii) Near the *C*-terminus the -Aib^9-Ala^{10}- sequence forms a type-I β-bend, the Aib^{11} residue has a *left*-handed helical character, and the Ala^{12} residue is *semi*-extended. Consequently, peptide groups N_{11}–H and N_{12}–H are involved in 1 ⟵ 4 and 1 ⟵ 6 H-bonds, respectively. (iii) The average values of the φ,ψ torsion angles (−62°, −41°) are approximately those expected for an idealized α-helix. (iv) The helix screw-sense is right-handed.

Minor changes from the structure of the decapeptide are seen near the *N*-terminus [the amide oxygen O(1) is an acceptor for two H-bonds, a 1 ⟵ 4 type from N_3–H and a 1 ⟵ 5 type from N_4–H] and near the *C*-terminus as well [the methyl

Table 5. Selected torsion angles for *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O.

	Residue											
	1	2	3	4	5	6	7	8	9	10	11	12
(*a*) Main-chain torsion angles (°) (σ 2–4)												
φ_i	−50[a]	−69	−56	−74	−54	−65	−57	−72	−58	−92	65	−114
ψ_i	−48	−38	−49	−33	−44	−48	−45	−36	−28	7	28	22[b]
ω_i	−170	178	−177	172	−178	−178	−177	178	180	−179	177	179[c]

(*b*) Torsion angles (°) for the *N*- and *C*-terminal blocking groups (σ 2–4°)				
O(1)–C(7)–C(4)–C(3)		−165	N_{12}–C^{α}_{12}–C'_{12}–O_{12}	−148
O(1)–C(7)–C(4)–C(5)		18		
N_1–C(7)–C(4)–C(3)	θ_1	13		
N_1–C(7)–C(4)–C(5)	θ'_1	−163		
C^{α}_1–N_1–C(7)–C(4)	ω_0	−172		

[a] C(7)–N_1–$C_1{}^{\alpha}$–C'_1. [b] N_{12}–$C_{12}{}^{\alpha}$–C'_{12}–O_{12}*. [c] $C_{12}{}^{\alpha}$–C'_{12}–O_{12}*–C(8).

Table 6. Intramolecular H-bonds for *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O and *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O.

	1 ⟵ 4 H-bonds				1 ⟵ 5 H-bonds			
	Donor	Acceptor	Distance/Å N···O	Angle/° N···O=C	Donor	Acceptor	Distance/Å N···O	Angle/° N···O=C
(*a*) *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O	N_3	O_1	3.23	114.4	N_4	O_1	3.09	166.8[a]
	N_4	O_1	3.40	104.3	N_5	O_1	3.03	152.9[a]
	N_5	O_2	3.34	102.8	N_6	O_2	3.00	153.6[a]
	N_6	O_3	3.42	102.8	N_7	O_3	3.12	157.2[a]
	N_7	O_4	3.25	109.5	N_8	O_4	3.20	156.2[a]
	N_8	O_5	3.17	110.9[a]	N_9	O_5	3.31	154.6
	N_9	O_6	3.14	112.1[a]	N_{10}[b]	O_6	4.63	97.1
	N_{10}[b]	O_7	6.25	59.0				
(*b*) *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O	N_3	O_1	3.14	125.2[a]	N_4	O_1	3.32	166.9[a]
	N_4	O_1	3.42	110.1	N_5	O_1	2.91	160.2[a]
	N_5	O_2	3.35	98.3	N_6	O_2	3.12	149.0[a]
	N_6	O_3	3.34	108.1	N_7	O_3	3.27	151.8[a]
	N_7	O_4	3.14	112.3	N_8	O_4	3.03	165.3[a]
	N_8	O_5	3.47	104.0	N_9	O_5	2.90	155.4[a]
	N_9	O_6	3.30	105.1	N_{10}	O_6	3.35	152.6[a]
	N_{10}	O_7	3.42	109.2	N_{11}	O_7	3.60	145.1
	N_{11}	O_8	2.93	114.8[a]	N_{12}[c]	O_8	4.50	94.7
	N_{12}[c]	O_9	6.13	55.9				

[a] Considered observed. [b] N_{10} forms a 1 ⟵ 6 (C_{16}) H-bond with O_5 (N···O distance 3.06 Å. N···O=C angle 146.7°). [c] N_{12} forms a 1 ⟵ 6 (C_{16}) H-bond with O_7 (N···O distance 2.98 Å. N···O=C angle 158.0°).

Table 7. Intermolecular H-bonds for *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O and *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O.

	Donor	Acceptor	Distance/Å N···O	Angle/° N···O=C	Symmetry operation
(*a*) *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H$_2$O	N_1	O_7	3.27	170.3	$x, y-1, z$[a]
	N_2	Ow(3)	2.96		$x, y-1, z$[a]
	N_3	Ow(2)	3.01		$x-1, y-1, z$[a]
	Ow(1)*	O_9	2.82	151.2	$x-1, y+1, z$[b]
	Ow(1)	Ow(4)*	2.36		$x, y-1, z$[b]
	Ow(2)*	O_{10}	3.14	129.1	x, y, z[b]
	Ow(2)	Ow(3)*	3.00		$x, y-1, z$[b]
	Ow(3)*	O_7	2.88	122.4	$x-1, y+1, z$[b]
	Ow(3)*	Ow(1)	2.72		$x-1, y, z$[b]
	Ow(4)*	O_6	2.96	137.7	x, y, z[b]
(*b*) *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H$_2$O	N_1	Ow(1)	3.06		$-x+\frac{3}{2}, -y+1, -z-\frac{1}{2}$[a]
	N_2	O_{11}	2.85	153.9	$-x+\frac{5}{2}, -y+2, -z-\frac{1}{2}$[a]
	Ow(1)	O^*_{11}	2.86	159.3	$x+1, y-1, z$[b]
	Ow(2)	O(9)	2.70	147.8	$-x+\frac{5}{2}, -y+\frac{1}{2}, z-\frac{1}{2}$[b]
	Ow(1)	Ow(2)*	2.77		$-x, y+\frac{1}{2}, -z+\frac{3}{2}$[b]

[a] Symmetry operation refers to the oxygen atom. [b] Symmetry operation refers to the starred water oxygen atom.

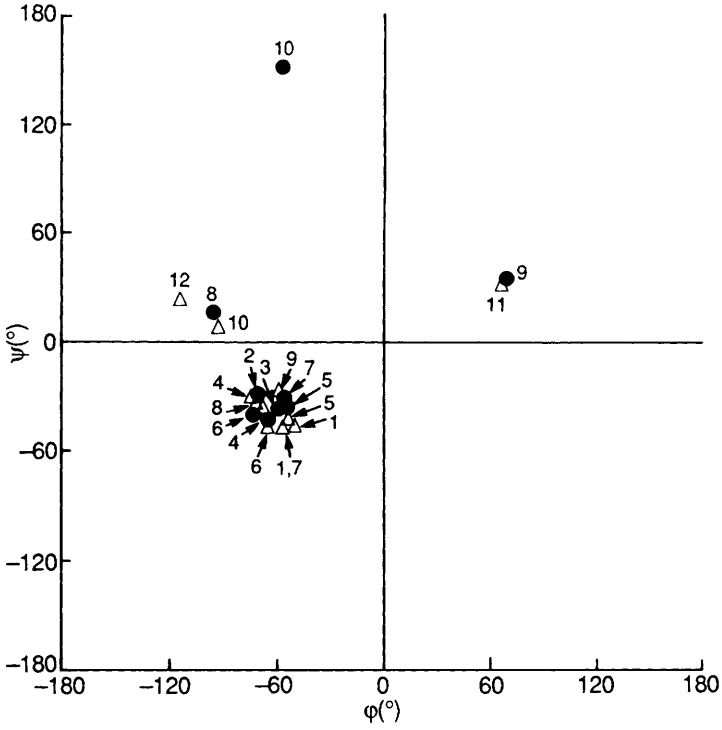

Figure 3. A graph of the φ_i, ψ_i torsion angles for *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H_2O (–●–) and *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H_2O (–△–). Numbers define the position of the residue in the sequence.

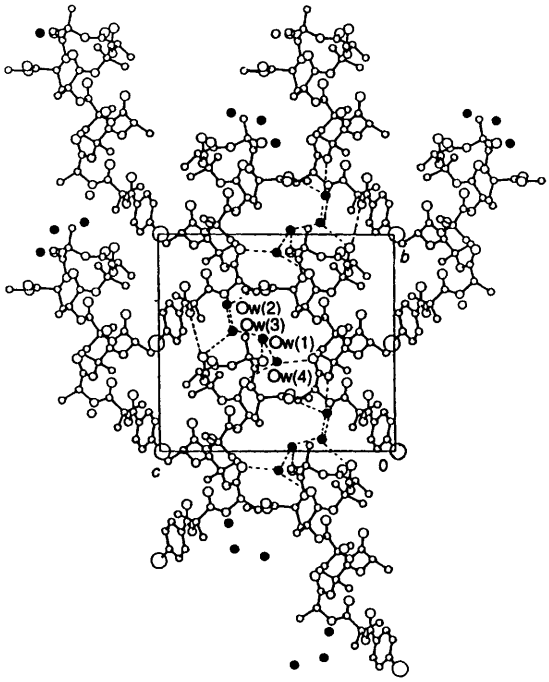

Figure 4. Crystal packing of the molecules of *p*BrBz-(Aib-L-Ala)$_5$-OMe·4H_2O viewed down the *a* axis. Intermolecular H-bonds are represented as dashed lines and the co-crystallized water molecules as full circles.

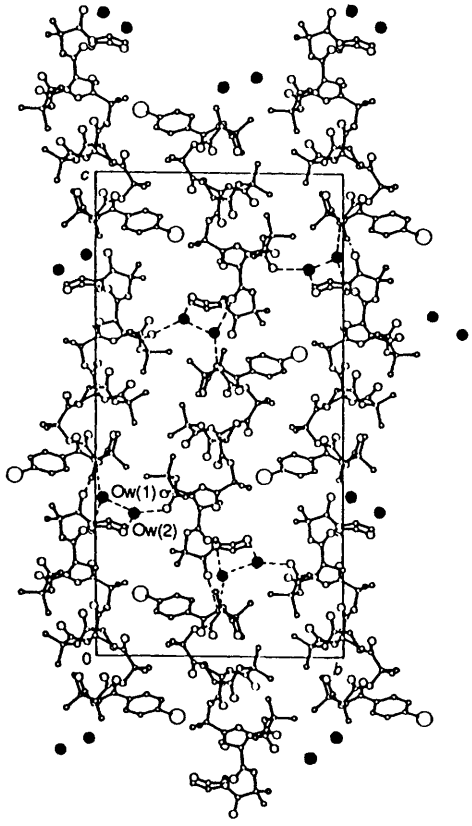

Figure 5. Crystal packing of the molecules of *p*BrBz-(Aib-L-Ala)$_6$-OMe·2H_2O viewed down the *a* axis. Intermolecular H-bonds are represented as dashed lines and the co-crystallized water molecules as full circles.

ester conformation is *anticlinal/antiplanar*, the N_{12}–C^{α}_{12}–C'_{12}– O_{12} torsion angle being −148°]. In no case did the deviation from planarity for the ω torsion angles exceed |10°|.

The mode of packing of the *p*BrBz-(Aib-L-Ala)$_6$-OMe molecules is shown in Figure 5. As in the case of the decapeptide we observed the formation of columns of helical molecules packed head-to-tail; however, at variance with the decapeptide, in the dodecapeptide each column packs in an antiparallel fashion with the neighbouring columns. Only one N–H • • • O=C

H-bond links together the helices along a column; in addition, two water molecules link molecules in the same column and between columns. Again, the distances of the N–H · · · O and O–H · · · O H-bonds are, in general, in good agreement with literature data,[24–27] but in a few instances the distances observed are larger than usual although with the correct geometry. Details of the intermolecular H-bonds are given in Table 7. It is worth noting that in this structure the co-crystallized solvent molecules are located near $\frac{1}{4}$ and $\frac{3}{4}$ of the *c* axis.

Discussion

We have recently reported the first experimental proof of a 3_{10}-helix ⟶ α-helix conformational transition in the crystal state induced by peptide main-chain lengthening only.[1–3] In fact, while the sequential hexapeptide *p*BrBz-(Aib-L-Ala)$_n$-OMe (n = 3) is a complete 3_{10}-helix, the octapeptide (n = 4) is essentially an α-helix. The results of the present work on the decapeptide (n = 5) and dodecapeptide (n = 6) molecules of this series confirm that the (Aib-L-Ala)$_n$ peptides tend to adopt an α-helical structure when the number of repeating dipeptide units (n) exceeds three.

The mean values of the φ,ψ torsion angles experimentally found in the right-handed helical residues of the two peptides described here, $-62 \pm 0.5°$ and $-41.5 \pm 0.5°$, are the same as those observed in globular proteins.[7,28,29] However, an alternation of φ,ψ-values is noted along the chain, reflecting different contributions of the Aib (odd residues) and L-Ala (even residues) amino acids. In particular, the Aib residues have lower φ and higher ψ absolute values compared with the L-Ala residues.

The finding that the α-helix (1 ⟵ 5 H-bonds) switches to 1 ⟵ 4 or 1 ⟵ 4, 1 ⟵ 6 H-bonding patterns at the *N*- and *C*-terminus, the 1 ⟵ 6 H-bonded form including a left-handed, achiral helical residue, well documented in protein structures,[30–32] is also typical of the (Aib-L-Ala)$_n$ deca- and dodeca-peptide. These results, characteristic of a relatively short peptide, may indicate that such terminating conformations are intrinsic to the α-helix and not a consequence of the need for a long polypeptide chain to change direction.

The intramolecular H-bonds are considered observed on the basis of a combined analysis of N · · · O distances and N · · · O=C angles (Table 3). Interestingly, the mean N · · · O=C bond angle of a 1 ⟵ 4 H-bond is significantly smaller than those of 1 ⟵ 5 and 1 ⟵ 6 H-bonds. A possible correlation between intramolecular N · · · O distances and N · · · O=C[28] angles is that the shorter the N · · · O distance, the larger the N · · · O=C angle (which is always greater than 120° and lies mostly in the range 150–160°).

In the two (Aib-L-Ala)$_n$ peptides water–peptide interactions[7,28,33] take place only at the *N*-terminus (with the peptide N–H groups) and at the *C*-terminus (with the peptide C=O groups) of the chain. With one exception (the C=O group of L-Ala[6] of the decapeptide), the (externally) hydrated N–H and C=O groups are among those not involved in the intramolecular N–H · · · O=C H-bonding schemes. No internally hydrated peptide segments, commonly found in globular proteins[34] and Aib-containing sequential *tri*peptides,[35] have been observed. It is clear that the bending of the *C*-ends of the Aib-containing deca- and dodeca-peptides with disruption of the helices are intimately connected with -CONH- hydration and/or the need for packing of the hydrated peptides. Interestingly, in this series of four (Aib-L-Ala)$_n$ peptides (n 3–6) structurally determined at atomic resolution only the completely 3_{10}-helical hexapeptide (n = 3) crystallizes in the anhydrous form.[1–3]

References

1 Part 226, V. Pavone, E. Benedetti, B. Di Blasio, C. Pedone, A. Santini, A. Bavoso, C. Toniolo, M. Crisma, and L. Sartore, *J. Biomol. Struct. Dyn.*, 1990, **7**, 1321.
2 E. Benedetti, B. Di Blasio, V. Pavone, C. Pedone, A. Santini, A. Bavoso, C. Toniolo, M. Crisma, and L. Sartore, in 'Peptides 1988,' eds. G. Jung and E. Bayer, de Gruyter, Berlin, 1989, p. 465.
3 E. Benedetti, A. Bavoso, B. Di Blasio, V. Pavone, C. Pedone, A. Santini, C. Toniolo, and M. Crisma, *Z. Kristall.*, 1988, **185**, 40.
4 I. L. Karle, J. L. Flippen-Anderson, K. Uma, H. Balaram, and P. Balaram, *Proc. Natl. Acad. Sci. USA*, 1989, **86**, 765.
5 R. Nagaraj and P. Balaram, *Acc. Chem. Res.*, 1981, **14**, 356.
6 E. Benedetti, A. Bavoso, B. Di Blasio, V. Pavone, C. Pedone, C. Toniolo, and G. M. Bonora, *Proc. Natl. Acad. Sci. USA*, 1982, **79**, 7951.
7 D. J. Barlow and J. M. Thornton, *J. Mol. Biol.*, 1988, **201**, 601.
8 C. Toniolo, G. M. Bonora, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, and C. Pedone, *Biopolymers*, 1983, **22**, 205.
9 B. V. V. Prasad and P. Balaram, *CRC Crit. Rev. Biochem.*, 1984, **16**, 307.
10 C. Toniolo, *Br. Polym. J.*, 1986, **18**, 221.
11 C. Toniolo, E. Benedetti, and C. Pedone, *Gazz. Chim. Ital.*, 1986, **116**, 355.
12 C. Toniolo and E. Benedetti, 'ISI Atlas of Science: Biochemistry,' 1988, vol. 1, p. 225.
13 C. Toniolo, G. M. Bonora, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, and C. Pedone, *Macromolecules*, 1986, **19**, 472.
14 G. Valle, M. Crisma, and C. Toniolo, *Z. Kristallogr.*, 1986, **175**, 73.
15 D. T. Cromer and J. T. Waber, in 'International Tables for X-Ray Crystallography,' The Kynoch Press, Birmingham, 1974, vol. 4, Table 2.2.B.
16 Enraf-Nonius (1979). Structure Determination Package, Enraf Nonius, Delft, The Netherlands.
17 IUPAC–IUB Commission on Biochemical Nomenclature, *Biochemistry*, 1970, **9**, 3471.
18 C. Toniolo, *CRC Crit. Rev. Biochem.*, 1980, **9**, 1.
19 C. Venkatachalam, *Biopolymers*, 1968, **6**, 1425.
20 G. D. Rose, L. M. Gierasch, and J. A. Smith, *Adv. Protein Chem.*, 1985, **37**, 1.
21 I. L. Karle, M. Sukumar, and P. Balaram, *Proc. Natl. Acad. Sci. USA*, 1986, **83**, 9284.
22 R. Taylor, O. Kennard, and W. Versichel, *J. Am. Chem. Soc.*, 1984, **106**, 244.
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 C. Ramakrishnan and N. Prasad, *Int. J. Protein Res.*, 1971, **3**, 209.
25 R. Taylor, O. Kennard, and W. Versichel, *Acta Crystallogr., Sect. B*, 1984, **40**, 280.
26 I. D. Brown, *Acta Crystallogr., Sect. A*, 1976, **32**, 24.
27 J. Mitra nd C. Ramakrishnan, *Int. J. Pept. Protein Res.*, 1977, **9**, 27.
28 T. Blundell, D. Barlow, N. Borkakoti, and J. Thornton, *Nature (London)*, 1983, **306**, 281.
29 L. G. Presta and G. D. Rose, *Science*, 1988, **240**, 1632.
30 C. Schellman, in 'Protein Folding,' ed. R. Jaenicke, Elsevier, Amsterdam, The Netherlands, 1980, p. 53.
31 E. N. Baker and R. E. Hubbard, *Prog. Biophys. Mol. Biol.*, 1984, **33**, 97.
32 K. Henrick, C. A. Collyer, and D. M. Blow, *J. Mol. Biol.*, 1989, **209**, 129.
33 C. H. Yang, J. N. Brown, and K. D. Kopple, *Int. J. Pept. Protein Res.*, 1979, **14**, 12.
34 M. Sundaralingam and Y. C. Sekharudu, *Science*, 1989, **244**, 1333.
35 I. L. Karle, *Biopolymers*, 1989, **28**, 1.

Paper 9/04799I
Received 9th *November* 1989
Accepted 22nd *May* 1990