Helical Screw Sense of Peptide Molecules. X-Ray Diffraction Structures of Two Oligopeptides with a Single Chiral Centre

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A crystal-state structural analysis of Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe and Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe has been performed by X-ray diffraction. Both peptides are folded into incipient 3_{10} helices stabilized by two consecutive intramolecular N–H···O=C hydrogen bonds of the C_{10} type (β-bends). While Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe gives rise to a left-handed helix, two independent molecules of opposite helical screw sense are observed in the crystals of Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe. The latter compound represents the first example of screw sense indifference shown in the crystal state by a peptide containing a single chiral C$^{\alpha}$-*tri*substituted α-amino acid residue.

A program is currently under way in our laboratory aimed at synthesizing and examining the 3D-structure of peptides based on the highly helicogenic α-aminoisobutyric acid (Aib) residue[1–5] as well organized molecular scaffolds and carrying side-chain functionalized α-amino acids as guest residues, as potential tools for studies of molecular recognition. We have so far investigated Aib-rich peptides containing L-Dap(*p*BrBz) or L-Dab(*p*BrBz) [L-Dap(*p*BrBz), N$^{\beta}$-*p*-bromobenzoyl-L-α,β-diaminopropionic acid; L-Dab(*p*BrBz), N$^{\gamma}$-*p*-bromobenzoyl-L-α,γ-diaminobutyric acid] as the guest residues. In the present contribution the X-ray diffraction analysis of the two N$^{\alpha}$-protected tripeptide methylamides Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**) and Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe (**2**) (Z, benzyloxycarbonyl; NHMe, methylamino) are reported as an interesting case of different helix screw sense preference.

Experimental

Materials.—Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**) was synthesized in 73% yield by reacting Z-L-Dap(*p*BrBz)-OH with H-Aib)$_2$-NHMe [prepared, in turn, by catalytic hydrogenation of Z-(Aib)$_2$-NHMe] in anhydrous MeCN in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride and *N*-methylmorpholine: m.p. 223–225 °C (from ethyl acetate); $[\alpha]_D^{20}$ − 14.3° (*c* 0.5, MeOH); TLC (silica gel plates 60F-254, Merck) R_{f1} (CHCl$_3$–EtOH 9:1) 0.55; R_{f2} (1-BuOH–AcOH–water 60:20:20) 0.90; ν_{max}(KBr disk)/cm^{-1} 3343, 3282, 1708, 1658, 1542; δ_H(200 MHz; Me$_2$SO) 8.55 (1 H, m, Dap β-NH), 8.47 (1 H, s, Aib NH), 7.71 (4 H, m, *p*BrBz), 7.64 (1 H, d, Dap α-NH), 7.31 (5 H, m, Z-aromatic), 7.25 (1 H, q, N*H*CH$_3$), 7.14 (1 H, s, Aib NH), 5.01 (2 H, m, Z-CH$_2$), 4.17 (1 H, m, Dap α-CH), 3.55 (2 H, m, Dap β-CH$_2$), 2.52 (3 H, d, NHC*H*$_3$), 1.30 (3 H, s, Aib β-CH$_3$), 1.26 (6 H, s, Aib β-CH$_3$), 1.23 (3 H, s, Aib β-CH$_3$). Amino acid analysis (C. Erba model 3A 27): Dap 0.96, Aib 2.04.

Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe (**2**) was obtained in 68% yield from Z-L-Dap(*p*BrBz)-OH and H-(Aib)$_2$-NHMe as described above for Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe: m.p. 154–156 °C (from MeOH–diethyl ether); $[\alpha]_D^{20}$-17.6° (*c* 0.5, MeOH); R_{f1} 0.40; R_{f2} 0.85; ν_{max}(KBr disk)/cm^{-1} 3368, 3353, 3310, 1708, 1669, 1626, 1547; δ_H(200 MHz; Me$_2$SO) 8.61 (1 H, s, Aib NH), 8.57 (1 H, m, Dab γ-NH), 7.74 (1 H, d, Dab α-NH), 7.73 (4 H, m, *p*BrBz), 7.32 (5 H, m, Z-aromatic), 7.25 (1 H, q, N*H*CH$_3$), 7.09 (1 H, s, Aib NH), 4.99 (2 H, m, Z-CH$_2$), 3.99 (1 H, m, Dab α-CH), 3.31 (2 H, m, Dab γ-CH$_2$), 2.52 (3 H, d, NHC*H*$_3$), 1.83 (2 H, m, Dab β-CH$_2$), 1.32 (3 H, s, Aib β-CH$_3$), 1.30 (6 H, s, Aib β-CH$_3$), 1.28 (3 H, s, Aib β-CH$_3$). Amino acid analysis: Dab 1.03, Aib 1.97.

Crystal Data for Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**).—C$_{27}$H$_{34}$N$_5$O$_6$Br, *M* = 604.5. Orthorhombic, *a* = 18.155(2), *b* = 16.027(2), *c* = 10.240(2) Å, *V* = 2979.5(8) Å^3, space group $P2_12_12_1$, *Z* = 4, D_c = 1.348 g cm^{-3}. Crystal dimensions: 0.20 × 0.20 × 0.25 mm, μ(Mo-Kα) = 14.09 cm^{-1}. Final *R*-value 0.056, final R_w-value 0.057.

Crystal Data for Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe *Monohydrate* (**2**).—C$_{28}$H$_{36}$N$_5$O$_6$Br·H$_2$O, *M* = 636.5. Triclinic, *a* = 14.512(2), *b* = 14.227(2), *c* = 8.202(2) Å, α = 92.7(2)°, β = 94.3(2)°, γ = 105.7(2)°, *V* = 1622(2) Å^3, space group $P1$, *Z* = 2, D_c = 1.304 g cm^{-3}. Crystal dimensions: 0.16 × 0.24 × 0.40 mm, μ(Mo-Kα) = 13.00 cm^{-1}. Final *R*-value 0.073.

X-Ray Structure Determination of Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe (**1**) *and* Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe *Monohydrate* (**2**).—Colourless crystals of **1** and **2** were grown from ethyl acetate–light petroleum (b.p. 60–80 °C) and methanol–diethyl ether solutions, respectively. Philips PW 1100 four-circle diffractometer; *θ–2θ* scan mode up to 2*θ* = 56°; graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å); 3879 and 7778 unique reflections for **1** and **2**, respectively, were corrected for Lorentz and polarization effects but not for absorption. 1116 Reflections with $F \geqslant 7\sigma(F)$ for **1**, and 3674 reflections with $F \geqslant 6\sigma(F)$ for **2**, respectively, were considered observed. Both structures were solved by direct methods using SHELXS-86.[6] Refinement was carried out by blocked least-squares, with weight $w = 1/[\sigma^2(F) + 0.0021 F^2]$ for **1**, and unit weight for **2**. The thermal parameters were anisotropic for all non-hydrogen atoms. Hydrogen atoms of both structures were in part located on a difference Fourier map and in part calculated, and they were not refined. All calculations were performed on a MicroVAX 3400 Digital Computer with SHELX-76 software.[7]

Tables of fractional atomic co-ordinates, positional parameters of hydrogen atoms, anisotropic thermal parameters, bond distances, and bond angles for **1** and **2** are available from the Cambridge Crystallographic Data Centre.†

Results

The molecular structures of Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**) and of the two crystallographically independent molecules (indicated as **A** and **B**, respectively) of Z-L-Dab(*p*BrBz)-(Aib)$_2$-

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† See 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1993, issue 1.

NHMe monohydrate (**2**), determined by X-ray diffraction, are illustrated in Figs. 1 and 2, respectively. Relevant torsion angles[8] are reported in Table 1. Geometrical parameters for intra- and inter-molecular hydrogen bonds[9-13] are summarized in Table 2.

Bond distances and bond angles for **1** and **2** (deposited) are in general agreement with previously reported values for the geometry of the Z-urethane moiety,[14] the secondary amide[15,16] and peptide[17] groups, and the Aib[18,19] residue.

The conformation of the Z-urethane group in both **1** and **2** is the usual *trans*, *trans* (θ^1 and ω_0 torsion angles) or type-*b* conformation.[14] All secondary amide and peptide groups are *trans*, but some distortion from planarity is observed.

The backbone of Z-L-Dap(*p*BrBz)-(Aib)$_2$NHMe (**1**) is folded into two consecutive β-bends stabilized by intramolecular hydrogen bonds between the NH group of Aib(3) and the carbonyl oxygen of the urethane moiety, and between the NH group of the C-terminal methylamido moiety and the carbonyl oxygen of L-Dap(1), respectively. Both β-bends are (left-handed helical) type-III′, having the backbone torsion angles in the ranges 63–54° (φ), and 47–16° (ψ).[20-22] A $C_1^\beta \cdots O_1$ short distance (2.79 Å) is observed in the L-Dap residue. The conformation of the L-Dap side chain, defined by rotations about the C^α–C^β and C^β–N^β bonds, is *gauche*$^-$, *gauche*$^-$.

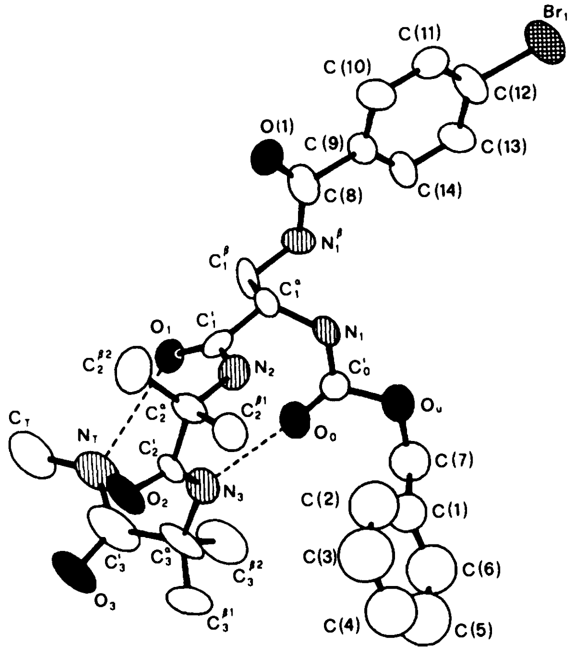

Fig. 1 X-Ray diffraction structure of Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**) with atom numbering. The intramolecular hydrogen bonds are indicated as dashed lines.

Similarly to **1**, both independent molecules A and B of Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe monohydrate (**2**) are folded into two consecutive β-bends stabilized by two intramolecular hydrogen bonds, between the NH group of Aib(3) and the carbonyl oxygen of the urethane moiety, and between the NH group of the C-terminal methylamido moiety and the carbonyl oxygen of L-Dab(1), respectively. The N-terminal hydrogen bond is weaker in molecule A than in molecule B.[9-11]

In both molecules the sets of φ, ψ torsion angles are close to those of an ideal 3_{10}-helix,[23,24] but they have negative signs, corresponding to the right-handed helical screw sense, in molecule A, while positive in molecule B, giving rise to a left-handed 3_{10}-helix. The $C_1^\beta \cdots O_1$ short contact, observed in the left-handed helical L-Dap-containing peptide **1**, is also found in the L-Dab residue of the left-handed molecule B of **2** (2.75 Å), but not in the right-handed molecule A (3.21 Å). The torsion angles about the C^α–C^β, C^β–C^γ, and C^γ–N^γ bonds of the L-Dab side chain are *gauche*$^-$, *trans*, and *skew*$^-$, respectively, in molecule A, but *gauche*$^-$, *gauche*$^-$, and *trans*, respectively, in molecule B. These values should be compared with the *trans*, *trans* disposition of the side chain in the crystal structure of L-Dab hydrochloride.[25,26] As a result, in both molecules A and B the carbonyl group of the *p*-bromobenzoyl moiety is oriented on the same side of the molecule as the Z-urethane N^α-protecting group. Overall, a pseudo-symmetry, violated essentially by the identical L-configuration of the Dab C^α atom, relates molecule A to molecule B.

In the packing mode of Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**) the N_1–H and N_2–H groups are hydrogen-bonded to the O_2=C_2' and O_3 = C_3', respectively, of a $(-x, -1/2 + y, 1/2 - z)$ symmetry-related molecule. The geometry of the N_2–H $\cdots$

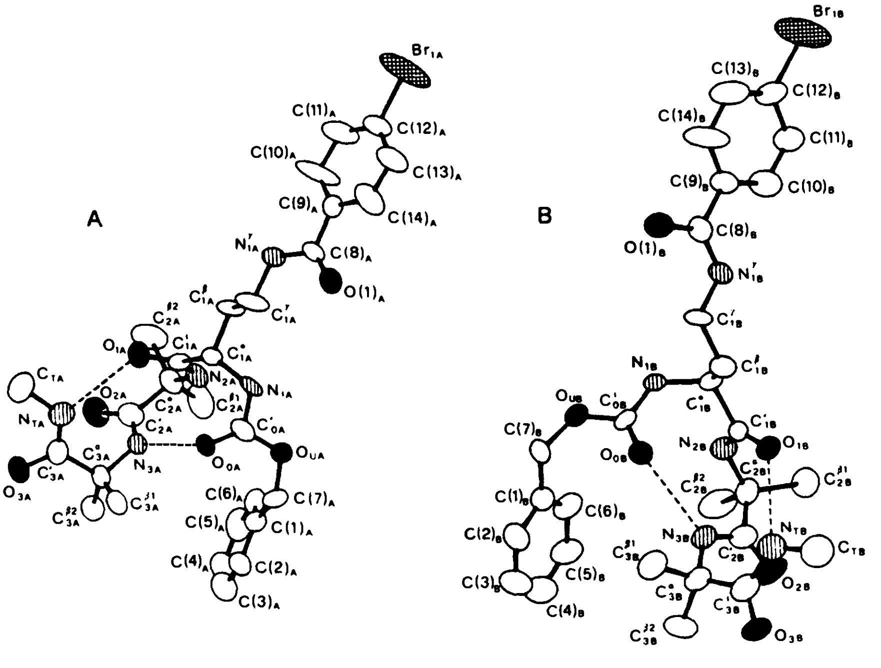

Fig. 2 X-Ray diffraction structure of Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe monohydrate (**2**) with atom numbering. The two crystallographically independent molecules are indicated as A and B, respectively. The intramolecular hydrogen bonds are indicated as dashed lines.

Table 1 Selected torsion angles (°) with estimated standard deviations in parentheses

Angle		Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**)	Z-L-Dab-(*p*BrBz)-(Aib)$_2$-NHMe (**2**)	
			Molecule **A**	Molecule **B**
$C(1)–C(7)–O_u–C_o'$	θ^2	−90(1)	80(2)	−82(2)
$C(7)–O_u–C_o–N_1$	θ^1	180(1)	175(1)	−177(1)
$O_u–C_o'–N_1–C_1^\alpha$	ω_0	174(1)	−179(1)	−177(1)
$C_o'–N_1–C_1^\alpha–C_1'$	φ_1	54(2)	−67(2)	53(2)
$N_1–C_1^\alpha–C_1'–N_2$	ψ_1	47(1)	−27(2)	42(2)
$C_1^\alpha–C_1'–N_2–C_2^\alpha$	ω_1	174(1)	180(2)	175(2)
$C_1'–N_2–C_2^\alpha–C_2'$	φ_2	63(2)	−57(2)	57(2)
$N_2–C_2^\alpha–C_2'–N_3$	ψ_2	16(2)	−28(2)	25(2)
$C_2^\alpha–C_2'–N_3–C_3^\alpha$	ω_2	−176(1)	180(1)	180(2)
$C_2'–N_3–C_3^\alpha–C_3'$	φ_3	54(2)	−57(2)	58(2)
$N_3–C_3^\alpha–C_3'–N_T$	ψ_T	38(2)	−33(2)	34(2)
$C_3^\alpha–C_3'–N_T–C_T$	ω_T	−177(2)	−179(2)	174(2)
$N_1–C_1^\alpha–C_1^\beta–N_1^\beta$		−49(2)	—	—
$C_1^\alpha–C_1^\beta–N_1^\beta–C(8)$		−80(1)	—	—
$C_1^\beta–N_1^\beta–C(8)–C(9)$		172(1)	—	—
$N_1^\beta–C(8)–C(9)–C(10)$		−165(1)	—	—
$N_1–C_1^\alpha–C_1^\beta–C_1^\gamma$		—	−72(2)	−53(2)
$C_1^\alpha–C_1^\beta–C_1^\gamma–N_1^\gamma$		—	174(1)	−70(2)
$C_1^\beta–C_1^\gamma–N_1^\gamma–C(8)$		—	−145(2)	175(2)
$C_1^\gamma N_1^\gamma–C(8)–C(9)$		—	179(1)	172(1)
$N_1^\gamma–C(8)–C(9)–C(14)$		—	172(2)	−169(2)

Table 2 Intra- and inter-molelcular hydrogen bond parameters for Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**) and Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe monohydrate (**2**)

Compound	Donor D–H	Acceptor A	Symmetry equivalence of A	Distance/Å D···A	Distance/Å H···A	Angle/° D–H···A
Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**)	N_3–H	O_0	x, y, z	3.08	2.01	156
	N_T–H	O_1	x, y, z	3.07	2.01	159
	N_1–H	O_2	$-x, -1/2 + y, 1/2 - z$	2.79	1.73	164
	N_2–H	O_3	$-x, -1/2 + y, 1/2 - z$	2.98	2.34	116
	N_1^β–H	O(1)	$1/2 - x, 1 - y, -1/2 + z$	2.96	1.90	163
Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe Monohydrate (**2**)	N_{3A}–H	O_{0A}	x, y, z	3.22	2.25	149
	N_{TA}–H	O_{1A}	x, y, z	2.94	1.93	151
	N_{3B}–H	O_{0B}	x, y, z	3.10	2.11	150
	N_{TB}–H	O_{1B}	x, y, z	3.08	2.05	153
	N_{1A}–H	$O(1)_B$	$x, y, -1 + z$	2.98	1.93	162
	N_{1B}–H	$O(1)_A$	x, y, z	2.83	1.80	154
	N_{2A}–H	$O(2)_w$	$x, 1 + y, -1 + z$	2.91	1.93	148
	N_{2B}–H	$O(1)_w$	$1 + x, y, z$	2.85	1.84	151
	N_{1A}^γ–H	O_{3B}	$x, 1 + y, z$	3.04	2.05	148
	N_{1B}^γ–H	O_{3A}	$1 + x, y, 1 + z$	3.08	2.21	135
	$O(1)_w–H_1$	O_{3A}	x, y, z	2.76	1.84	177
	$O(1)_w–H_2$	$O(1)_A$	$-1 + x, y, z$	2.79	1.84	178
	$O(2)_w–H_1$	O_{3B}	x, y, z	2.85	1.89	179
	$O(2)_w–H_2$	$O(1)_B$	$x, -1 + y, z$	2.79	1.88	176

O_3 interaction is rather distorted.[9-11] Thus, along the *b* direction rows of molecules are generated, which are also linked in the *c* direction through N_1^β–H···O(1)=C(8) ($1/2 - x, 1 - y, -1/2 + z$) hydrogen bonds. Packing is then completed through van der Waals interactions.

A complex network of hydrogen bonds characterizes the packing mode of Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe monohydrate (**2**). Molecule **B** is linked to molecule **A** of the same asymmetric unit by a hydrogen bond between the N_{1B}–H and $O(1)_A$=$C(8)_A$ groups, while the N_{1A}–H group is hydrogen-bonded to the $O(1)_B$=$C(8)_B$ group of a ($x, y, -1 + z$) symmetry-related molecule. In the same asymmetric unit the two co-crystallized water molecules act as hydrogen bond donors to the O_{3A}=C_{3A}' and O_{3B}=C_{3B}' groups, respectively. In addition, the $O(1)_W$ is hydrogen-bonded to the $O(1)_A$=$C(8)_A$ group of a ($-1 + x, y, z$) symmetry-related molecule, and the $O(2)_W$ is hydrogen-bonded to the $O(1)_B$=$C(8)_B$ group of a ($x, -1 + y, z$) symmetry-related molecule. Both water molecules also act as hydrogen bond acceptors: the N_{2B}–H group is linked to a ($1 + x, y, z$) $O(1)_W$ and the N_{2A}–H group is linked to a ($x, 1 + y, -1 + z$) $O(2)_W$. Finally, the $N_{1A}\gamma$–H group is hydrogen-bonded to a ($x, 1 + y, z$) O_{3B}=C_{3B}' group and the $N_{1B}\gamma$–H group is hydrogen-bonded to a ($1 + x, y, 1 + z$) O_{3A}=C_{3A}' group, respectively.

Interestingly, in the packing mode of Z-L-Dap(*p*BrBz)-(Aib)$_2$-NHMe (**1**) only backbone-to-backbone and side chain-to-side chain intermolecular hydrogen bonds are observed. Conversely, the packing of Z-L-Dab(*p*BrBz)-(Aib)$_2$-NHMe monohydrate (**2**) is characterized by intermolecular hydrogen bonds between the side-chain N–H groups and backbone C=O groups, while the backbone N–H groups are hydrogen-bonded either to side-chain C=O groups or to water molecules.

Discussion

It is well established that it is the right-handed α-helical screw sense that is favoured by C^α-trisubstituted L-α-amino acids.

This finding has been mainly ascribed to the unfavourable steric interaction occurring between the side-chain C^{β} atom and the carbonyl oxygen of the same residue in the left-handed helical conformation.[27–30] A similar $C_i{}^{\beta}\cdots O_i$ short distance is experienced by either the *pro*-L or *pro*-D C^{β} atom of the Aib residue in the 3_{10}-helical conformation, depending on whether the helix is left- or right-handed, respectively. Such an interaction cannot be avoided by a C^{α}-tetrasubstituted α-amino acid, irrespective of the helix handedness,[18] but its effect is not large enough to prevent the Aib residue from being the strongest known helix inducer.[1–5] In this paper we have shown that a short $C_i{}^{\beta}\cdots O_i$ distance is also observed when a C^{α}-trisubstituted L-α-amino acid residue is present in a left-handed 3_{10}-helix. However, despite this unfavourable contact, the L-Dap-containing peptide **1** adopts exclusively the left-handed helical screw sense in the crystal state, while both screw senses are seen in the X-ray structure of the L-Dab-containing peptide **2**.

In this connection, it is worth pointing out that a reversal of the usual relationship between amino acid configuration and helical handedness was also shown to occur in poly-α-amino acids, such as poly(β-benzyl)-L-aspartate and some related compounds.[31–34] Such behaviour was explained by an energetic balance of side-chain nonbonded interactions (which are less unfavourable in the right-handed helix) and backbone–side chain electrostatic interactions which, given a proper orientation of the side chain, may favour the left-handed screw sense.[35,36]

In peptides **1** and **2**, although packing effects could not be ruled out, intermolecular interactions analogous to those operative for poly(β-benzyl)-L-aspartate may play a role in determining the observed helical screw senses. Unfortunately, experimental data on poly(N^{β}-*p*BrBz)-L-Dap or poly(N^{γ}-*p*BrBz)-L-Dab are not available, while a right-handed helical conformation has been determined for poly(N^{δ}-*p*BrBz)-L-Orn (Orn, ornithine, which differs from Dab and Dap by one and two additional methylene groups, respectively, in the side chain) on the basis of a X-ray diffraction study of oriented films.[37] In the light of the results reported in the present contribution poly(N^{β}-*p*BrBz)-L-Dap and poly(N^{γ}-*p*BrBz)-L-Dab may well deserve a detailed conformational study.

The first occurrence of a chiral peptide assuming both helical screw senses in the crystal state has been documented in our laboratory for Ac-$(Aib)_2$-L-Iva-$(Aib)_2$-OMe (Ac, acetyl; Iva, isovaline; OMe, methoxy), where the only chiral centre is the quaternary Iva C^{α} atom.[38] Additional examples of chiral peptides showing both helical screw senses in the crystal state have been recently found by us in some Aib-rich peptides containing other chiral C^{α}-tetrasubstituted amino acid residues, namely C^{α}-methylphenylalanine and C^{α}-methylleucine.[39–41]

On the other hand, a number of crystal structures indicate that a single chiral C^{α}-trisubstituted amino acid residue is sufficient to impart only one helical screw sense when incorporated into an Aib-rich peptide sequence.[42–47] The only occurrence of both helical screw senses in a peptide containing Aib and C^{α}-trisubstituted protein amino acids has been recently reported for Z-D-Val-$(Aib)_2$-L-Phe-OMe, where the two chiral residues have opposite configuration and hence opposite screw sense preferences.[48]

To the best of our knowledge, the structure of Z-L-Dab(*p*BrBz)-$(Aib)_2$-NMHe (**2**) described here represents the first observation of a peptide containing a single chiral C^{α}-trisubstituted amino acid residue assuming both helical screw senses in the crystal state.

In addition, the present structural investigation suggests that the incorporation of a side-chain-functionalized amino acid residue, bearing potential hydrogen-bonding donor and acceptor groups, into a short Aib sequence does not interfere with the intramolecular hydrogen-bonding scheme typical of 3_{10}-helical Aib-rich peptides.

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