Linear Oligopeptides. Part 316.[1] Conformational Characterization of Syndiotactic Homo-peptides from $C^{\alpha,\alpha}$-Disubstituted Glycines

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Terminally blocked, syndiotactic linear homo-peptides from $C^{\alpha,\alpha}$-disubstituted glycines Iva and (αMe)Val have been prepared to the hexapeptide and tripeptide amide levels, respectively, by solution methods and fully characterized. The molecular and crystal structures of *p*BrBz-(D-Iva-L-Iva)$_2$-OBu^t methanol solvate, *p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t methanol solvate, and Z-D-(αMe)Val-L-(αMe)Val-D-(αMe)Val-NHPr^i (*p*BrBz = *p*-bromobenzoyl, Z = benzyloxycarbonyl) were determined by X-ray diffraction. While the Iva pentapeptide and the (αMe)Val tripeptide amide are folded in an (incipient) left-handed 3_{10}-helical conformation, the Iva tetrapeptide adopts a double β-bend conformation of the II′–III type. The FTIR absorption and ^{1}H NMR analyses support our contention that in chloroform solution, the longest syndiotactic homo-peptides may be folded in well developed 3_{10}-helical structures. This is the first structural study reported on regularly alternating (D–L) peptides based on conformationally constrained α-amino acids.

Since the discovery of the antibiotic and ionophoric properties of gramicidin A, many theoretical and experimental studies have explored the possible structures of peptides characterized by protein amino acids with a strict alternation of L- and D-configurations (syndiotactic or heterochiral peptides).[2–19] New structures, different from those typical of poly(L-amino acid) chains (isotactic or homochiral peptides) have been proposed and identified for model peptides and gramicidin A itself. These include a variety of single- and double-stranded helices, and ribbon and sheet structures.

In our continuing investigation of the preferred conformations of isotactic peptides rich in non-coded, C^{α}-methylated amino acids ($C^{\alpha,\alpha}$-disubstituted glycines)[20] we have clearly shown that these residues are conformationally constrained, strongly preferring backbone φ, ψ torsion angles ±60, ±30°, *i.e.* in the $\alpha/3_{10}$-helical region of the conformational map (in particular, short homopeptide chains fold exclusively into 3_{10}-helices).[21] These amino acids have also been found in other regions of the conformational space (*e.g.*, in the semi-extended region, with $\varphi = \mp 60°$, $\psi = \pm 120°$), although rarely. On these bases, the most probable structures for a heterochiral –CO-D-AA^1-L-AA^2-D-AA^3-L-AA^4-D-AA^5-NH–pentapeptide sequence based on C^{α}-methylated amino acids may be envisaged as follows.

(*i*) *Right-handed* 3_{10}*-helix*,[21] with the following sequence of φ,ψ angles: D-AA^1 = 60, −120° and L-AA^2 = D-AA^3 = L-AA^4 = D-AA^5 = −60, −30°. This helix, which does not include residue D-AA^1, has a type-II′ β-bend[22–24] at the N-terminus.

(*ii*) *Left-handed* 3_{10}*-helix*,[21] with D-AA^1 = L-AA^2 = D-AA^3 = L-AA^4 = D-AA^5 = 60, 30°.

(*iii*) *Polar* 3_{10}*-pleated sheet*,[2] with D-AA^1 = D-AA^3 = D-AA^5 = 60, 30°, and L-AA^2 = L-AA^4 = −60, −30°. In this structure, no residue is able to form a C=O···H–N intramolecular hydrogen bond.

(*iv*) (LD) β*-Bend ribbon structure*,[3] with D-AA^1 = D-AA^3 = D-AA^5 = 60, −120°, and L-AA^2 = L-AA^4 = −60, −30°. This structure is generated by a series of non-consecutive type-II′ β-bends. Only D-AAs, starting from D-AA^3, form intramolecular hydrogen bonds as donors.

It is pertinent to note that D-AA residues in structures (*i*) and (*iv*), and L-AA residues in structure (*ii*), are not in their most stable left- or right-handed helical conformation, respectively. In addition, as reported above, structures (*iii*) and (*iv*) are not stabilized or only partially stabilized by intramolecular hydrogen bonds.

In the present paper we report results of the first conformational analysis of syndiotactic peptides derived from C^{α}-methylated amino acids. More specifically, the structural preferences of homo-peptides from Iva (isovaline or C^{α}-methyl-α-aminobutyric acid) to the hexapeptide level and (αMe)Val (C^{α}-methyl valine) to the tripeptide amide level have been investigated in the crystal state by X-ray diffraction and in chloroform solution by FTIR and ^{1}H NMR spectroscopies. Among the four structures listed above, only structures (*i*) and (*ii*) have been unambiguously authenticated in the peptides studied in this work.

Experimental

Materials.—The physical properties and the analytical data for the Iva and (αMe)Val syndiotactic homo-peptides discussed in this work and their synthetic intermediates are listed in Table 1.

Crystallographic Data for the Oxazol-5(4H)-*one from* pBrBz-D-Iva-L-Iva-D-Iva-OH (pBrBz, para-*bromobenzoyl*).—$C_{22}H_{30}BrN_3O_4$, M = 480.4. Orthorhombic, a = 18.695(2), b = 12.484(2), c = 10.391(2) Å, V = 2425.1(7) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.316 g cm^{-3}, $F(000)$ = 1000, μ = 17.06 cm^{-1} (MoKα), final R value 0.058, final R_w value 0.062.

Crystallographic Data for pBrBz-(D-Iva-L-Iva)$_2$-OBu^t (OBu^t, tert-*butoxy*) *Methanol Solvate*.—$C_{31}H_{49}BrN_4O_6$·CH_3OH, M = 685.7. Orthorhombic, a = 20.829(2), b = 17.760(2), c = 9.470(2) Å, V = 3503.2(9) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.30 g cm^{-3}, $F(000)$ = 1456, μ = 12.07 cm^{-1} (MoKα), final R value 0.064, final R_w value 0.071.

Table 1 Physical properties and analytical data for the syndiotactic homo-peptides from Iva and (αMe)Val

Compound	Yield (%)	M.p./°C[a]	Recryst. solvent[b]	$[\alpha]_D^{20}$[c]	$[\alpha]_{436}^{20}$[c]	TLC[e] R_f(I)	R_f(II)	R_f(III)	ν/cm^{-1}[f]
(*a*) Iva peptides									
*p*BrBz-D-Iva-L-Iva-OBu^t	94	Oil	AcOEt–PE	−10.1	−22.1	0.95	0.95	0.55	3402, 3371, 3360, 1722, 1674, 1590, 1568
*p*BrBz-D-Iva-L-Iva-OH	81	85–87	EE–PE	−6.3	−10.7	0.35	0.90	0.25	3385, 3281, 1720, 1656, 1639, 1591, 1566, 1540
Oxazol-5(4*H*)-one from *p*BrBz-D-Iva-L-Iva-OH	98	Oil	EE–PE	−14.8[d]	−31.0[d]	0.95	—	0.55	3376, 1817, 1669, 1652, 1524
*p*BrBz-D-Iva-L-Iva-D-Iva-OBu^t	69	114–115	AcOEt–PE	17.1	38.9	0.90	0.95	0.40	3427, 3376, 3303, 1731, 1720, 1683, 1639, 1588, 1566, 1536
*p*BrBz-D-Iva-L-Iva-D-Iva-OH	91	152–154	MeOH–PE–EE	12.8	27.5	0.40	0.90	0.20	3319, 1731, 1651, 1590, 1567
Oxazol-5(4*H*)-one from *p*BrBz-D-Iva-L-Iva-D-Iva-OH	92	137–138	AcOEt–PE–EE	−5.2[d]	−13.1[d]	0.90	—	0.45	3404, 3324, 1824, 1665, 1589
*p*BrBz-(D-Iva-L-Iva)$_2$-OBu^t	38	168–169	AcOEt–PE	−3.4	−7.8	0.80	0.95	0.35	3329, 1727, 1670, 1643, 1589, 1567
*p*BrBz-(D-Iva-L-Iva)$_2$-OH	98	204–206	EE–PE	−4.6	−5.2	0.45	0.90	0.20	3308, 1738, 1658, 1590, 1567
Oxazol-5(4*H*)-one from *p*BrBz-(D-Iva-L-Iva)$_2$-OH	94	63-65	AcOEt–PE	0.5[d]	0.0[d]	0.80	—	0.40	3336, 1817, 1675, 1646, 1589, 1567
*p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t	78	225–226	AcOEt	6.2	14.8	0.85	0.95	0.45	3326, 1725, 1666, 1589
*p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OH	96	274–276	EE	8.3	16.8	0.35	0.95	0.20	3303, 1737, 1656, 1590
Oxazol-5(4*H*)-one from *p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OH	92	215–217	AcOEt	−6.4[d]	−33.1[d]	0.85	—	0.45	3386, 3338, 3324, 1799, 1675, 1666, 1645, 1590
*p*BrBz-(D-Iva-L-Iva)$_3$-OBu^t	14	230–232	AcOEt–PE	−7.8	−18.1	0.95	0.95	0.40	3440, 3318, 1726, 1663, 1589
(*b*) (αMe)Val peptides									
Z-D-(αMe)Val-NHPr^i	78	94–96	AcOEt–PE	0.8	3.7	0.75	0.90	0.45	3385, 3330, 3300, 1729, 1711, 1695, 1662, 1648, 1540, 1524
Z-L-(αMe)Val-D-(αMe)Val-NHPr^i	39	53–55	AcOEt–PE	0.6	2.6	0.95	0.95	0.45	3421, 3336, 1724, 1667, 1641, 1524
Z-D-(αMe)Val-L-(αMe)Val-D-(αMe)Val-NHPr^i	10	156–158	EE–PE	−17.0	−34.8	0.95	0.95	0.40	3426, 3320, 1705, 1668, 1528

[a] Determined on a Leitz model Laborlux 12 apparatus (Wetzlar, Germany). [b] AcOEt, ethyl acetate; PE, light petroleum; EE, diethyl ether; MeOH, methanol. [c] Determined on a Perkin-Elmer model 241 polarimeter (Norwalk, CT) equipped with a Haake model L thermostat (Karlsruhe, Germany); c = 0.5 (MeOH). [d] c = 0.5 (AcOEt). [e] Silica gel plates (60F-254 (Merck, Darmstadt, Germany), using the following solvent systems: (I) chloroform–ethanol 9:1; (II) butan-1-ol–acetic acid–water 6:2:2; (III) toluene–ethanol 7:1. The compounds were revealed either with the aid of a UV lamp or with the hypochlorite–starch–iodide chromatic reaction. A single spot was observed in each case. [f] Determined in KBr pellets on a Perkin-Elmer model 580 B spectrophotometer equipped with a Perkin-Elmer model 3600 IR data station and a model 660 printer.

Crystallographic Data for pBrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t *Methanol Solvate*.—$C_{36}H_{58}BrN_5O_7 \cdot CH_3OH$, M = 784.8. Orthorhombic, a = 22.223(2), b = 18.888(2), c = 10.587(2) Å, V = 4444(1) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.173 g cm^{-3}, $F(000)$ = 1672, μ = 9.61 cm^{-1} (MoKα), final R value 0.064, final R_w value 0.071.

Crystallographic Data for Z-D-(αMe)Val-L-(αMe)Val-D-(αMe)Val-NHPr^i (Z, *benzyloxycarbonyl*; NHPr^i, *isopropylamino*).—$C_{29}H_{48}N_4O_5$, M = 532.7. Monoclinic, α = 14.130(20), b = 10.599(10), c = 10.424(10) Å, β = 98.2(1)°, V = 1545(3) Å^3, space group $P2_1$, Z = 2, D_c = 1.145 g cm^{-3}, $F(000)$ = 580, μ = 5.96 cm^{-1} (CuKα), final R value 0.063, final R_w value 0.060.

X-Ray Crystal Structure Determination of the oxazol-5(4H)-one from pBrBz-D-Iva-L-Iva-D-Iva-OH, pBrBz-(D-Iva-L-Iva)$_2$-OBu^t *Methanol Solvate*, pBrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t *Methanol Solvate*, and Z-D-(αMe)Val-L-(αMe)Val-D-(αMe)Val-NHPr^i.—Colourless crystals of the Iva tripeptide oxazolone, Iva tetrapeptide, Iva pentapeptide, and (αMe)Val tripeptide were grown by slow evaporation of diethyl ether–light petroleum, chloroform–methanol, methanol and methanol solutions, respectively. Crystal sizes were 0.15 × 0.15 × 0.40, 0.8 × 0.8 × 0.8, 0.4 × 0.6 × 0.8, 0.15 × 0.25 × 0.20 for the Iva tripeptide oxazolone, Iva tetrapeptide, Iva pentapeptide and (αMe)Val tripeptide, respectively. Philips PW 1100 diffractometer (Eindhoven, The Netherlands), θ–2θ scan mode to θ = 28° or 44° [the latter for the (αMe)Val tripeptide]; graphite monochromated MoKα radiation (λ = 0.7107 Å) or CuKα radiation (λ = 1.5418 Å) [the latter for the (αMe)Val tripeptide]; 3291 independent reflections and 1293 with $F \geqslant 4\sigma(F)$ considered observed for the Iva tripeptide oxazolone; 4719 independent reflections and 2185 with $F \geqslant 7\sigma(F)$ considered observed for the Iva tetrapeptide; 5924 independent reflections and 1916 with $F \geqslant 6\sigma(F)$ considered observed for the Iva pentapeptide; and 1278 independent reflections and 1145 with $F \geqslant 5\sigma(F)$ considered observed for the (αMe)Val tripeptide. The structures of the Iva tripeptide oxazolone and the Iva tetrapeptide were solved by direct methods using the SHELXS 86 program.[25] Refinements were carried out by full-matrix blocked least squares using the SHELX 76 program,[26] $w = 1/[\sigma^2(F) + 0.002\,98\,F^2]$ for the Iva tripeptide oxazolone and $w = 1/[\sigma^2(F) + 0.004\,F^2]$ for the Iva tetrapeptide. The thermal parameters were anisotropic for all non-hydrogen atoms, except for $C_2^{\gamma 2}$ and $C_3^{\gamma 2}$ of the Iva tripeptide oxazolone which were kept isotropic. Positional disorder was observed for the carbon atom of the methanol molecule co-crystallized with the Iva tripeptide. This carbon atom was located at two positions with population parameters 0.56 and 0.36, respectively, and subsequently isotropically refined. The structure of the Iva pentapeptide was phased by the Patterson method. Non-hydrogen atoms were located on subsequent difference Fourier maps. The structure of the (αMe)Val tripeptide was solved using the coordinates of a segment taken from the nearly isomorphous structure of Z-[D-(αMe)Val]$_3$-NHPr^i.[27] The remaining non-hydrogen atoms were located on a difference Fourier map. Refinements were carried out by full-matrix blocked least squares using the SHELX 76 program, $w = 1/[\sigma^2(F) + 0.0019\,F^2]$ for the Iva pentapeptide and $w = 1/[\sigma^2(F) + 0.019\,F^2]$ for the (αMe)Val tripeptide. The thermal parameters were anisotropic for all non-hydrogen atoms. The hydrogen atoms of the Iva tripeptide oxazolone were calculated and not refined; those of the Iva tetrapeptide were in part located on a difference Fourier map and in part calculated, and only their isotropic thermal parameters were refined; those of the Iva pentapeptide were in part located on a difference Fourier map and in part calculated, and not refined; those of the (αMe)Val tripeptide were in part located on a difference Fourier map and in part calculated, most of them being treated in the 'riding mode' with fixed U_{iso}, while the remaining were not refined. Complete lists of bond lengths, bond angles, and torsion angles, the final positional parameters of the non-hydrogen atoms along with equivalent and anisotropic thermal factors have been deposited and are available from the Cambridge Crystallographic Data Centre.*

FTIR Absorption Spectra.—FTIR absorption spectra were recorded with a Perkin-Elmer model 1720X spectrophotometer, nitrogen flushed, equipped with a sample-shuttle device, at 2 cm^{-1} nominal resolution, averaging 100 scans. Solvent (baseline) spectra were recorded under the same conditions. Cells with path lengths of 0.1, 1.0 and 10 mm (with CaF_2 windows) were used. Spectrograde [$^2H_2$]chloroform (99.8% ^2H) was purchased from Merck.

^1H *NMR Spectra*.—^1H NMR spectra were recorded with a Bruker model AM 400 spectrometer (Karlsruhe, Germany). Measurements were carried out in [$^2H_2$]chloroform (99.96% ^2H; Merck) and in [$^2H_6$]DMSO ([$^2H_6$]dimethyl sulfoxide) (99.96% $^2H_6$; Fluka, Büchs, Switzerland) with tetramethylsilane as the internal standard. The free radical TEMPO (2,2,6,6-tetramethyl-1-piperidyloxy) was purchased from Sigma (Milwaukee, WI).

Results and Discussion

Synthesis and Characterization.—For the large-scale production of the optically pure Iva and (αMe)Val enantiomers, we exploited an economically attractive, chemoenzymatic synthesis recently described by some of us.[28] Preparation and characterization of the Iva and (αMe)Val syndiotactic homopeptide series were performed to the hexapeptide and tripeptide amide levels, respectively. During coupling reactions of these sterically hindered residues (in anhydrous acetonitrile under reflux for 20–80 h), the carboxy group of the N$^\alpha$-blocked amino acid or peptide was activated using either the symmetrical anhydride [(αMe)Val peptides] or the oxazol-5(4*H*)-one (Iva peptides) method. The N$^\alpha$-blocked peptide free acids were obtained by treatment of the corresponding *tert*-butyl esters with dilute trifluoroacetic acid. Removal of the benzyloxycarbonyl N$^\alpha$-protecting group was achieved by catalytic hydrogenation.

The various peptides and their synthetic intermediates were characterized (Table 1) by melting point determination, optical rotatory power at two wavelengths (due to the usually low value of this parameter is syndiotactic peptides), TLC in three solvent systems, and solid-state IR and ^1H NMR spectroscopies (the latter data are not reported).

Final characterization of the synthetic intermediate oxazol-5(4*H*)-one from *p*BrBz-D-Iva-L-Iva-D-Iva-OH was achieved by X-ray diffraction (Fig. 1). The displacements of the atoms in the nearly planar oxazolone ring from its mean plane vary from −0.012 to 0.020 Å. The $C_3^{\beta 1}$ and $C_3^{\beta 2}$ atoms, both linked to the C_3^α atom, are displaced on the opposite sides of the average plane of the ring by −1.295 and 1.303 Å, respectively. The exocyclic O_3 and C_2^α atoms deviate from the plane by 0.068 and −0.037 Å, respectively. The C_2'–N_3 bond length, 1.268(15) Å, is appropriate for a C–N double bond. The C_2'–O_2 and C_3'–O_2 bond lengths [1.391(14) and 1.379(15) Å, respectively] indicate that the effect of the delocalization is small, though significant. The C_3^α–C_3' and C_3^α–N_3 bond lengths [1.553(18) and 1.445(15) Å, respectively] are close to those expected for an sp^3-hybridized C_3^α atom. The exocyclic bond angles about the

* For details of the CCDC deposition scheme, see 'Instructions for Authors (1994)', *J. Chem. Soc., Perkin Trans. 2*, 1994, issue 1.

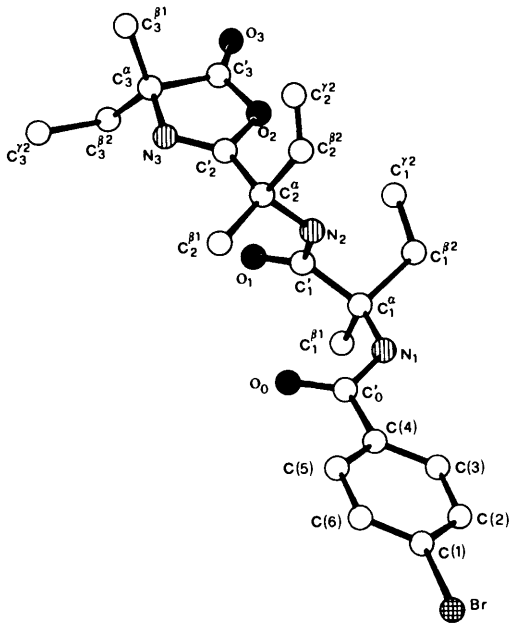

Fig. 1 X-Ray diffraction structure of the oxazol-5(4*H*)-one from *p*BrBz-D-Iva-L-Iva-D-Iva-OH with numbering of the atoms

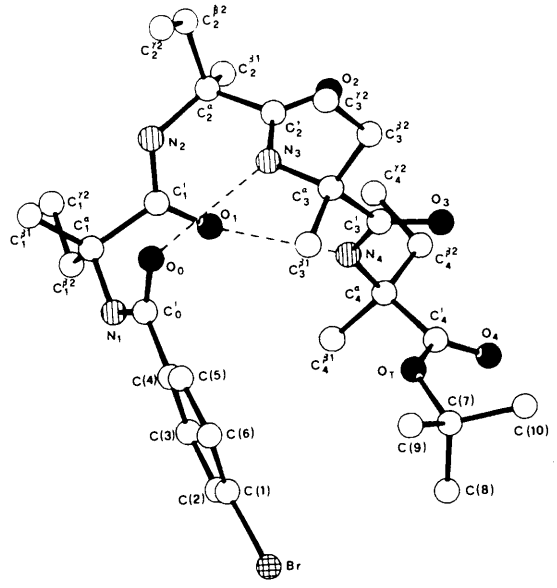

Fig. 2 X-Ray diffraction structure of *p*BrBz-(D-Iva-L-Iva)$_2$-OBu^t (methanol solvate) with numbering of the atoms. The two intramolecular hydrogen bonds are indicated by dashed lines.

carbonyl group $C_3'=O_3$ of the lactone moiety differ by 7.0°, with a larger value for the $C_3^{\alpha}-C_3'-O_3$ bond angle, 131.0(12)°. This latter value is probably the result of intramolecular interactions between the O_3 atom and the two substituents on the C_3^{α} atom. An additional relevant property is the widening of the $C_2^{\alpha}-C_2'-N_3$ bond angle to 126.0(11)°. These geometrical parameters of the oxazolone ring agree well with the corresponding mean values obtained from published X-ray diffraction structures.[29] The D-Iva^1 residue is left-handed helical with φ_1, ψ_1 torsion angles[30] of 48.8(11) and 51.9(11)°, while the L-Iva^2 residue is semi-extended [$\varphi_2 = -49.2(14)°$, $\psi_2 = 143.3(11)°$]. The values for the side-chain torsion angle χ^1 are −173.7(9)°, 167.9(5)°, and 72.5(14)° for D-Iva^1, L-Iva^2, and D-Iva^3, respectively.

Crystal-state Conformational Analysis.—We determined by X-ray diffraction the molecular and crystal structures of the following three, terminally blocked, syndiotactic homo-peptides: *p*BrBz-(D-Iva-L-Iva)$_2$-OBu^t (methanol solvate), *p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t (methanol solvate) and Z-L-(αMe)Val-D-(αMe)Val-L-(αMe)Val-NHPr^i. The *para*-bromobenzoyl group was incorporated into the longest peptides to help solve the phase problem in the X-ray diffraction analyses, since it possesses a suitable heavy atom (bromine). The molecular structures, with the atomic numbering schemes, are illustrated in Figs. 2–4. Relevant backbone and side-chain torsion angles are given in Table 2. In Table 3 the intra- and inter-molecular hydrogen bond parameters are listed.

Table 2 Selected torsion angles for *p*BrBz-(D-Iva-L-Iva)$_2$-OBu^t (methanol solvate), *p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t (methanol solvate) and Z-D-(αMe)Val-L-(αMe)Val-D-(αMe)Val-NHPr^i

Torsion angle (°)	Iva tetrapeptide	Iva pentapeptide	(αMe)Val tripeptide
θ^3	—	—	90.0(9)
θ^2	—	—	178.1(6)
θ^1	24.4(10)	−11.2(14)	177.4(6)
ω_0	−176.6(6)	168.7(9)	164.0(6)
φ_1	57.1(8)	58.2(13)	62.1(9)
ψ_1	−130.2(7)	34.8(13)	21.1(9)
ω_1	−174.7(6)	175.2(9)	−174.2(6)
φ_2	−58.8(9)	56.0(12)	37.7(9)
ψ_2	−23.1(9)	26.1(12)	39.0(8)
ω_2	178.0(6)	179.7(8)	174.7(6)
φ_3	−57.2(8)	51.6(11)	62.3(8)
ψ_3	−37.7(8)	35.3(11)	29.1(8)
ω_3	−174.1(6)	173.9(8)	−174.3(6)
φ_4	48.1(9)	62.8(11)	—
ψ_4	39.7(9)[a]	23.6(12)	—
ω_4	173.1(7)[b]	172.1(8)	—
φ_5	—	−50.5(11)	—
ψ_5	—	−45.3(11)[c]	—
ω_5	—	−174.2(8)[d]	—
$\chi_1^{1,1}$	−176.9(7)	178.6(14)	−62.6(7)
$\chi_1^{1,1'}$	—	—	175.2(6)
$\chi_2^{1,1}$	52.6(10)	−56.5(13)	−61.2(9)
$\chi_2^{1,1'}$	—	—	62.8(9)
$\chi_3^{1,1}$	59.5(9)	177.9(8)	68.4(7)
$\chi_3^{1,1'}$	—	—	−167.2(6)
$\chi_4^{1,1}$	−59.8(9)	−56.3(11)	—
$\chi_5^{1,1'}$	—	56.6(11)	—

[a] $N_4-C_4^{\alpha}-C_4'-O_T$. [b] $C_4^{\alpha}-C_4'-O_T-C(7)$. [c] $N_5-C_5^{\alpha}-C_5'-O_T$. [d] $C_5^{\alpha}-C_5'-O_T-C(7)$.

Bond lengths and bond angles (deposited) are in general agreement with previously reported values for the geometry of the *para*-bromobenzamido[31] and benzyloxycarbonylamino[32] moieties, the *tert*-butyl ester[33] and isopropylamido[27,34] groups, the peptide unit[35] and Iva[36–42] and (αMe)Val[27,43] residues.

The Iva tetrapeptide forms a slightly distorted type-II′ β-turn followed by a regular type-III β-turn. The two 1←4 C=O···H–N intramolecular hydrogen bonds have $N_3\cdots O_0$ and $N_4\cdots O_1$ distances within the range expected (2.8–3.1 Å).[44–46] The molecules of the Iva pentapeptide are folded in a regular, left-handed 3_{10}-helical structure, characterized by three intramolecular hydrogen bonds ($N_3\cdots O_0$, $N_4\cdots O_1$, and $N_5\cdots O_2$) of normal strength. The opposite handedness of the C-terminal residue of the tetra- and penta-peptides with respect to that of the preceding ones is a common observation for (incipient) 3_{10}-helix forming peptide esters.[47] The (αMe)Val tripeptide amide adopts an incipient, left-handed 3_{10}-helical structure, somewhat distorted at the central residue. The two type-III′ β-turns are characterized by intramolecular hydrogen bonds, one very weak ($N_3\cdots O_0$) and one of normal strength ($N_T\cdots O_1$).

The distribution of the ethyl side-chain χ^1 torsion angles for the five D-Iva residues of the tetra- and penta-peptides is 3*t* (*trans*) and 2g^+ (*gauche*$^+$), while that for the four L-Iva residues

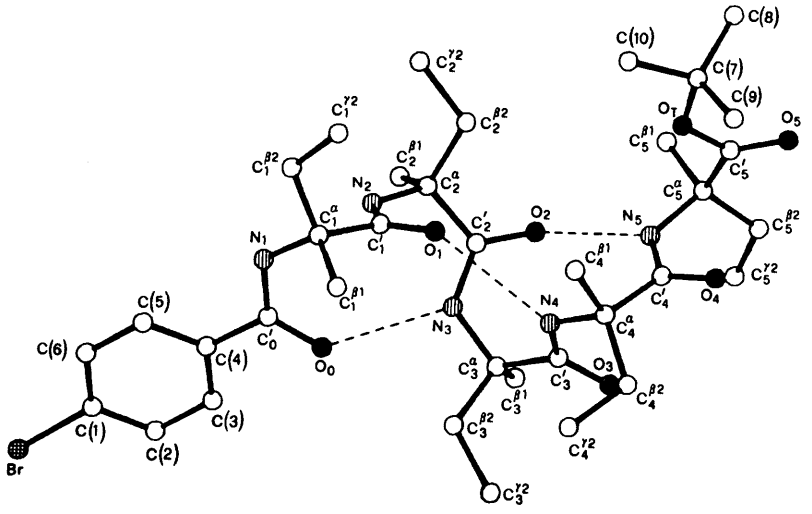

Fig. 3 X-Ray diffraction structure of *p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t (methanol solvate) with numbering of the atoms. The three intramolecular hydrogen bonds are indicated by dashed lines.

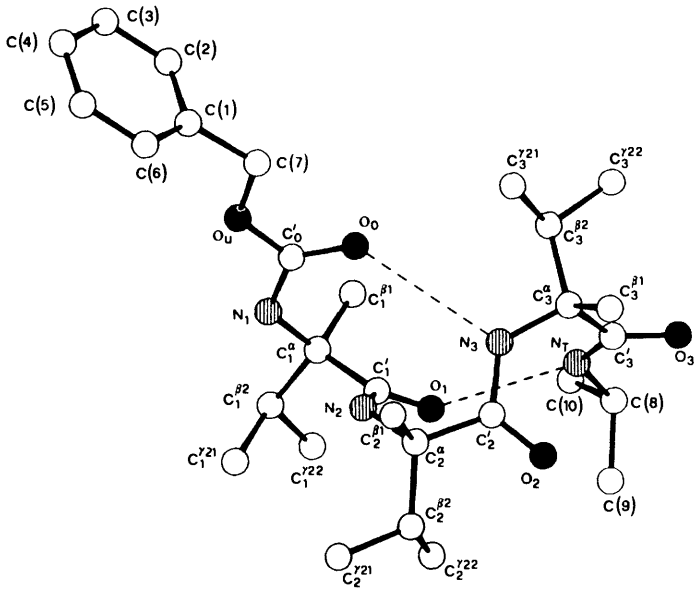

Fig. 4 X-Ray diffraction structure of Z-D-(αMe)Val-L-(αMe)Val-D-(αMe)Val-NHPr^i with numbering of the atoms. The two intramolecular hydrogen bonds are indicated by dashed lines.

Table 3 Intra- and inter-molecular hydrogen bond parameters for *p*BrBz-(D-Iva-L-Iva)$_2$-OBu^t (methanol solvate), *p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t (methanol solvate) and Z-D-(αMe)Val-L-(αMe)Val-D-(αMe)Val-NHPr^i

Peptide	Donor D–H	Acceptor A	Symmetry operations of A	Distance/Å D···A	Distance/Å H···A	Angle (°) D–H···A
Iva tetrapeptide	N_3–H	O_0	x, y, z	3.055(8)	2.048(6)	156.8(3)
	N_4–H	O_1	x, y, z	2.940(7)	1.963(5)	150.4(4)
	N_1–H	O_M	x, y, z	3.050(9)	2.059(7)	154.5(4)
	O_M–H	O_3	$-x - 1/2, y - 1/2, -z - 1$	2.716(9)	1.808(5)	179.3(5)
Iva pentapeptide	N_3–H	O_0	x, y, z	3.055(10)	2.14	162
	N_4–H	O_1	x, y, z	3.051(9)	2.24	163
	N_5–H	O_2	x, y, z	2.959(10)	1.89	164
	N_2–H	O_M	x, y, z	3.005(11)	1.94	164
	O_M–H	O_4	$x - 1/2, -y - 1, -z - 1/2$	2.714(10)	1.81	179
(αMe)Val tripeptide	N_3–H	O_0	x, y, z	3.255(6)	2.176(6)	178.0(6)
	N_T–H	O_1	x, y, z	2.857(7)	1.906(7)	144.9(7)
	N_1–H	O_3	$x, y, z - 1$	2.885(6)	1.962(6)	141.2(6)

is $3g^-$ and $1g^+$.[36–42] The three (αMe)Val side-chain conformations of the tripeptide are (t, g^-) for (αMe)Val^1, (g^-, g^+) for (αMe)Val^2 and (g^+, t) for (αMe)Val^3.[27,43]

All amide, urethane, peptide and ester groups are *trans* (ω torsion angles), as expected, with only one amide bond (ω_0 for the Iva pentapeptide) and one urethane bond [ω_0 for the (αMe)Val tripeptide] deviating more than 8° from planarity.[35,48] The θ^1 torsion angle of the *p*-bromobenza-

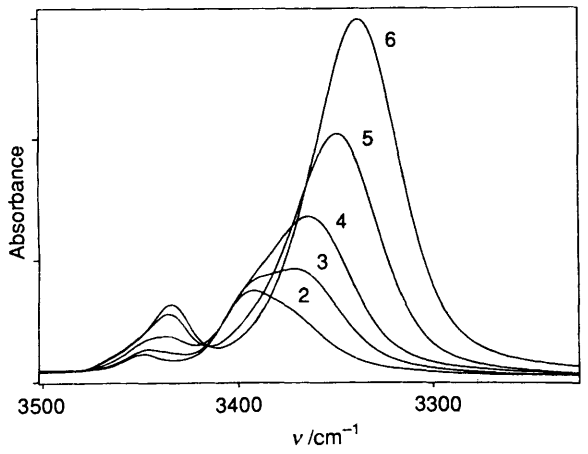

Fig. 5 FTIR absorption spectra (3500–3250 cm^{-1} region) of the Iva syndiotactic homo-peptide series from dimer through hexamer in $CDCl_3$ solution. Numbers refer to peptide main-chain length.

mido group, giving the orientation of the aromatic ring relative to the amide plane, is 24.4(10)° in the Iva tetrapeptide, while it is −11.2(14)° in the Iva pentapeptide. The conformation of the benzyloxycarbonylamido group of the (αMe)Val tripeptide (θ^1 and ω_0 torsion angles) is the usual *trans–trans* or type-b conformation.[32] The ester dispositions with respect to the C^{α}–N bond are close to the anticlinal conformation,[49] the N_4–C_4^{α}–C_4'–O_4 torsion angle of the Iva tetrapeptide and the N_5–C_5^{α}–C_5'–O_5 torsion angle of the Iva pentapeptide being −147.0(8)° and 137.4(10)°, respectively. The C-terminal *tert*-butyl ester groups of the two Iva peptides are observed in a conformation in which the three methyl substituents of the quaternary carbon atom are staggered with respect to the plane of the –C^{α}–C′(=O)–O– moiety, as usually found in ester groups from tertiary alcohols.[33] The conformation of the isopropylamido group of the (αMe)Val tripeptide allows the C–C bonds of the alkyl substituents to avoid the synperiplanar orientation with respect to the amide C′–N bond, as commonly observed.[27,34]

The molecules of both Iva tetra- and penta-peptides pack into the unit cell without any stabilization arising from (peptide) C=O · · · H–N (peptide) intermolecular hydrogen bonds. Rather, the co-crystallized methanol molecules of the tetra- and penta-peptides play the role of acceptors of the hydrogen bonds from the (amide) N_1–H and (peptide) N_2–H groups, respectively, and donors of the hydrogen bonds to the (peptide) C_3'=O_3 and (peptide) C_4'=O_4 groups, respectively. In the packing mode of the (αMe)Val tripeptide, we find a linear array of molecules in the *z*-direction, linked together by (urethane) N_1–H · · · O_3=C_3' (amide) intermolecular hydrogen bonds. All the N · · · O and O · · · O intermolecular separations are in the ranges typically shown by such hydrogen bonds.[44–46,50,51]

Solution Conformational Analysis.—The conformational preferences of the Iva and (αMe)Val syndiotactic homo-peptides in solution were determined in the turn- and helix-supporting solvent $CDCl_3$ by FTIR and ^1H NMR spectroscopies as a function of concentration (over the range 10^{-2} to 10^{-4} mol dm^{-3}). Fig. 5 illustrates the FTIR absorption spectra (N–H stretching region) of the Iva series from the di- to the hexapeptide.

The curves are characterized by two broad bands at 3440–3434 (free NH groups) and 3398–3335 cm^{-1} (hydrogen-bonded NH groups), respectively.[52] The intensity of the low-frequency band relative to the high-frequency band (A_H/A_F ratio) significantly increases as main-chain length increases; concomitantly, the absorption maximum shifts markedly to lower wavenumber. Using Mizushima's dilution method,[53] we have been able to show that even at 10^{-2} mol dm^{-3} concentration, self-association *via* N–H · · · O=C intermolecular hydrogen-bonding is absent for the tri- and tetra-peptides, and of limited significance (less than 10%) for the penta- and hexa-peptides (results not shown). Therefore, the observed hydrogen bonding should be interpreted as arising almost exclusively from intramolecular N–H · · · O=C interactions. In any event, even at the highest dilution examined, the intensity of the band of the longest oligomers related to hydrogen-bonded NH groups is remarkable, suggesting the occurrence of large populations of highly intramolecularly hydrogen bonded species. The results obtained for the syndiotactic (αMe)Val homo-peptide amides to the trimer level (not shown) strictly parallel those reported above for the analogous Iva peptides and those already published for the isomeric, isotactic (αMe)Val peptides.[27] The present FTIR absorption investigation has provided convincing evidence that main-chain length dependent intramolecular hydrogen bonding is an important factor for the structural stabilization of the terminally blocked Iva and (αMe)Val syndiotactic homo-peptides in $CDCl_3$ solution.

To get more detailed information on the preferred conformation of these peptides in this halocarbon, we carried out a 400 MHz ^1H NMR investigation. The delineation of inaccessible (or intramolecularly hydrogen bonded) NH groups by ^1H NMR was performed by using (*i*) solvent dependence of NH chemical shifts by adding increasing amounts of the hydrogen bonding acceptor DMSO[54,55] to the $CDCl_3$ solution and (*ii*) free-radical (TEMPO)-induced line broadening of NH resonances.[56]

With regard to the Iva peptides, a partial tentative assignment has been performed for the two upfield resonances, to the N(1)H and N(2)H protons, by analogy with the chemical shifts in chloroform of other N^{α}-*p*-bromobenzoylated peptides from different types of $C^{\alpha,\alpha}$-disubstituted glycine.[57,58] In contrast, complete assignment of the NH protons of the (αMe)Val peptides has been achieved by comparison with the corresponding protons of the isomeric isotactic peptides, which were assigned by analysis of their COSY and ROESY spectra.[27]

From an analysis of the spectra as a function of concentration (10^{-2}–10^{-3} mol dm^{-3}) in $CDCl_3$ solution (results not shown), we have been able to conclude that dilution induces a negligible (< 0.02 ppm) shift to higher fields of the NH resonances of the Iva di-, tri-, and tetra-peptides and all (αMe)Val peptide amides investigated in this work. However, this effect becomes somewhat significant for the Iva penta- and hexa-peptides. In particular, their N(2)H protons shift by 0.12 and 0.40 ppm, respectively.

In the Iva and (αMe)Val peptides examined in the $CDCl_3$–DMSO solvent mixtures and in the presence of the paramagnetic perturbing agent, TEMPO, at 2×10^{-3} mol dm^{-3} peptide concentration (for two representative examples see Fig. 6), two classes of NH protons were observed. Class (*i*) [N(1)H and N(2)H protons] includes protons whose chemical shifts are sensitive to the addition of DMSO and whose resonances broaden significantly upon addition of TEMPO. Interestingly, the sensitivity of the N(1)H proton is higher than that of the N(2)H proton; in addition, the extent of the perturbation on the N(2)H proton appears to decrease progressively as main-chain length is reduced. Class (*ii*) [N(3)H to N(6)H protons] includes those displaying a behaviour characteristic of shielded protons (relative insensitivity of chemical shifts to solvent composition, and of linewidths to the presence of TEMPO).

In summary, these ^1H NMR results allow us to conclude that, in $CDCl_3$ solution at 10^{-2} mol dm^{-3} concentration, only the penta- and hexa-peptides have a tendency (although modest) to self-associate and that in this process, the amide N(2)H proton plays a major role as hydrogen bonding donor. At lower concentrations, the N(3)H to N(6)H protons of the tri-, tetra-,

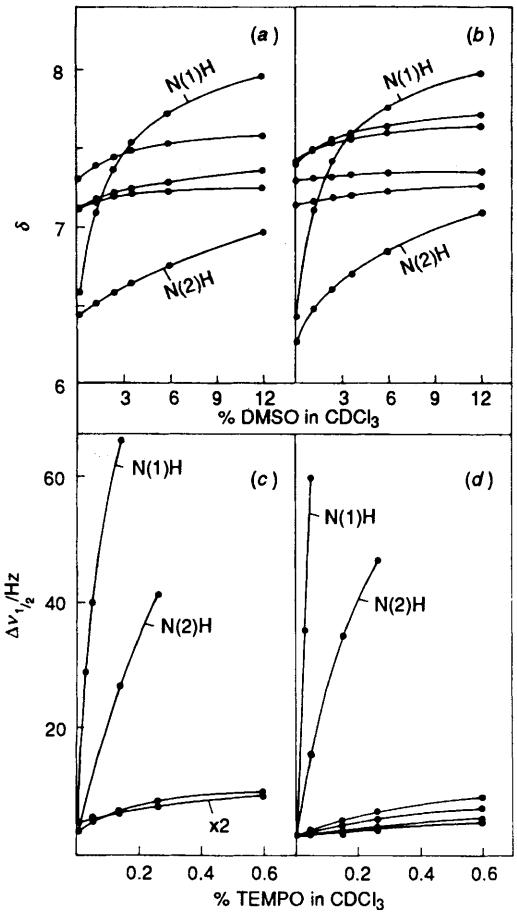

Fig. 6 Plot of NH chemical shifts in the ^{1}H NMR spectra of (*a*) *p*BrBz-(D-Iva-L-Iva)$_2$-D-Iva-OBu^t and (*b*) *p*BrBz-(D-Iva-L-Iva)$_3$-OBu^t as a function of increasing percentages of DMSO (*v*/*v*) added to the $CDCl_3$ solution. Plot of the bandwidth of the NH protons of same peptides [(*c*) and (*d*), respectively] as a function of increasing percentages of TEMPO (*w*/*v*) added to the $CDCl_3$ solution. Peptide concentration = 2×10^{-3} mol dm^{-3}.

penta-, and hexa-peptides are almost inaccessible to perturbing agents and are, therefore, most probably intramolecularly hydrogen bonded. In view of these observations, it is reasonable to conclude that the most populated structures adopted in $CDCl_3$ solution by the terminally blocked Iva and (αMe)Val syndiotactic tri-, tetra-, penta- and hexa-peptides are the β-turn, two consecutive β-turns and the 3_{10}-helix, respectively. These conclusions are in agreement with those extracted from the FTIR absorption study discussion above.

Conclusions

In this first detailed investigation of the conformational preferences of syndiotactic homo-peptides (with a D-amino acid as the *N*-terminal residue) from the sterically hindered $C^{\alpha,\alpha}$-disubstituted glycines Iva and (αMe)Val, we have been able to show that these compounds may fold either into a type-II′ β-bend followed by an incipient right-handed 3_{10}-helix or into a left-handed 3_{10}-helix. No experimental evidence has been found supporting the onset of either the polar 3_{10}-pleated sheet or the (LD) β-bend ribbon structure. In view of the absence of the polar 3_{10}-pleated sheet, we are inclined to conclude that intramolecular hydrogen-bonding stabilization would more than compensate for the energy loss due to the unfavourable (*semi*-extended or 'inverse' helical) conformations which part of the residues are forced to adopt in either 3_{10}-helical structure. In addition, in the homo-oligopeptide amides with an odd number of residues, the numerically prevailing D-amino acids are in their most stable conformation if the peptide is left-handed 3_{10}-helical but not if it is type-II′ β-bend/right-handed 3_{10}-helical. Therefore, it is not surprising that the (αMe)Val tripeptide amide should prefer the left-handed 3_{10}-helix, as found in this work. Finally, it is noteworthy that in the crystal state, the isomeric, isotactic *p*BrBz-(D-Iva)$_5$-OBu^t [59] and Z-[D-(αMe)-Val]$_3$-NHPr^i [27] homo-oligomers have also been shown to adopt the left-handed 3_{10}-helical structure.

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Paper 4/02414A
Received 25*th April* 1994
Accepted 6*th May* 1994