# Structural Versatility of Peptides from $C^{\alpha,\alpha}$-Disubstituted Glycines. Synthesis, Characterization, and Solution and Crystal-State Conformational Analysis of Homopeptides from $C^{\alpha}$-Methyl-$C^{\alpha}$-isopropylglycine, [(αMe)Val][1]

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ABSTRACT: Terminally blocked homodi- and homotripeptides from (αMe)Val, a $C^{\alpha,\alpha}$-disubstituted glycine, were prepared by solution methods and fully characterized. The preferred conformation in chloroform solution was assessed by FT-IR and $^1$H NMR as a function of concentration and addition of perturbing agents. The molecular and crystal structures of the dipeptide and tripeptide amides, Z—[D-(αMe)Val]$_n$—NH*i*Pr ($n$ = 2, 3) were also determined by X-ray diffraction. While the dipeptide amide adopts a type-III′ β-turn conformation stabilized by a 1←4 C=O···H—N intramolecular H bond, the tripeptide amide is folded in an incipient left-handed $3_{10}$-helix. These results confirm that (i) the (αMe)Val residue is an effective β-turn and helix promoter and (ii) the relationship between (αMe)Val chirality and helix screw sense is the same as that exhibited by protein amino acids. A comparison is made with the conclusions obtained from published work on homopeptides from other $C^{\alpha}$-methylated α-amino acids.

## Introduction

The stabilization of specific peptide secondary structures has recently become a major issue in biopolymer science, particularly in conjunction with the de novo design of proteins and enzyme mimetics.[2-4] In connection with this one of the most effective strategies pursued for the stabilization of helical conformations is $C^{\alpha}$-methylation of the peptide chain.[4-7]

Among the homooligomers from $C^{\alpha}$-methylated α-amino acids, the structural preferences of those derived from Aib (α-aminoisobutyric acid, also called $C^{\alpha}$-methylalanine),[5-7], Iva (isovaline or $C^{\alpha}$-methyl-α-aminobutyric acid),[8] (αMe)Leu ($C^{\alpha}$-methylleucine),[8] and (αMe)Phe ($C^{\alpha}$-methylphenylalanine)[8-10] have already been described.

To gain a better understanding of the preferred conformation of this family of $C^{\alpha,\alpha}$-disubstituted glycines, we embarked on a program directed toward the first preparation and structural characterization of homooligomers from a $C^{\alpha}$-methylated *β-branched* residue, namely (αMe)-Val ($C^{\alpha}$-methylvaline). In particular, in this paper we describe the solution synthesis and a detailed conformational analysis (using FT-IR absorption, $^1$H NMR, and X-ray diffraction) of the terminally blocked Z-[D-(αMe)-Val]$_n$-NH*i*Pr ($n$ = 1-3; Z, benzyloxycarbonyl; -NH*i*Pr, isopropylamino) series. Results of a solution and crystal-state conformational investigation of Gly, L-Ala, and Aib host peptides containing a single (αMe)Val guest residue have already been reported.[11-13]

## Experimental Section

**Synthesis of Peptides.** The synthesis and characterization of the intermediates Z-L-(αMe)Val-OH monohydrate, [Z-L-(αMe)Val]$_2$O, 5(4*H*)-oxazolone from *p*BrBz-L-(αMe)Val-OH (*p*BrBz, *p*-bromobenzoyl), and Z-L-(αMe)Val-O*t*Bu (O*t*Bu, *tert*-butoxy) have been described.[12] Newly synthesized (αMe)-Val derivatives and homopeptides are as follows.

**Z-L-(αMe)Val-NH*i*Pr.** This compound was synthesized from Z-L-(αMe)Val-OH monohydrate and isopropylamine in anhydrous acetonitrile in the presence of EDC·HCl [*N*-ethyl-*N*′-(3-(dimethylamino)propyl)carbodiimide hydrochloride] at room temperature for 48 h: yield 91%; mp 94-96 °C (from ethyl acetate-petroleum ether); tlc (silica gel plates 60F-254 Merck) $R_{f1}$ ($CHCl_3$-ethanol 9:1) 0.95, $R_{f2}$ (1-butanol-acetic acid-water 3:1:1) 0.95, $R_{f3}$ (toluene-ethanol 7:1) 0.60; $[\alpha]^{20}_D$ 0.4° (*c* 0.5, methanol); $[\alpha]^{20}_{436}$ -1.7° (*c* 0.5, methanol). IR absorption (KBr): $\nu_{max}$ 3383, 3328, 3297, 1729, 1710, 1694, 1662, 1647, 1586, 1542, 1524 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 10 mM): δ 7.37 (m, 5H, Z phenyl), 6.21 (d, 1H, *i*Pr NH), 5.15 (s, 1H, NH), 5.08 (m, 2H, Z-$CH_2$), 4.04 (m, 1H, *i*Pr α-CH), 2.30 (m, 1H, β-CH), 1.46 (s, 3H, β-$CH_3$), 1.11 (m, 6H, *i*Pr β-$CH_3$), 0.92 (m, 6H, γ-$CH_3$).

**Z-[D-(αMe)Val]$_2$-NH*i*Pr.** This compound was prepared from Z-[D-(αMe)Val]$_2$-OH (see below) and EDC·HCl in an acetonitrile-chloroform 8:1 mixture at room temperature for 3 h. The resulting oily product was treated with isopropylamine in anhydrous acetonitrile at room temperature for 15 h: yield 74%; mp 141-143 °C (from ethyl acetate-petroleum ether); $R_{f1}$ 0.95, $R_{f2}$ 0.95, $R_{f3}$ 0.55; $[\alpha]^{20}_D$ -20.6° (*c* 0.5, methanol). IR absorption (KBr): $\nu_{max}$ 3441, 3356, 3275, 1709, 1687, 1652, 1524 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 10 mM): δ 7.36 (m, 5H, Z phenyl), 7.03 (d, 1H, *i*Pr NH), 6.23 (s, 1H, NH), 5.21 and 5.00 (m, 2H, Z-$CH_2$), 5.07 (s, 1H, NH), 4.07 (m, 1H, *i*Pr α-CH), 1.95 (m, 2H, 2β-CH), 1.50 (s, 3H, β-$CH_3$), 1.45 (s, 3H, β-$CH_3$), 1.17 (m, 6H, *i*Pr β-$CH_3$), 0.98-0.72 (m, 12H, γ-$CH_3$).

**Z-[D-(αMe)Val]$_3$-NH*i*Pr.** This compound was synthesized from [Z-D-(αMe)Val]$_2$O and H-[D-(αMe)Val]$_2$-NH*i*Pr (obtained, in turn, by catalytic hydrogenation of the corresponding Z-derivative) in anhydrous acetonitrile under reflux for 24 h and purified by flash-chromatography[14] by eluting the column with a step gradient of ethyl acetate in petroleum ether followed by an isocratic mixture of 9:1 chloroform-ethanol: yield 35%; mp 196-197 °C (from ethyl acetate); $R_{f1}$ 0.95, $R_{f2}$ 0.95, $R_{f3}$ 0.50; $[\alpha]^{20}_D$ -20.6° (*c* 0.5, methanol). IR absorption (KBr): $\nu_{max}$ 3445, 3349, 3318, 3256, 1704, 1673, 1650, 1520 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 10 mM): δ 7.37 (m, 5H, Z phenyl), 7.25 (d, 1H, *i*Pr NH), 6.75 (s, 1H, NH), 6.51 (s, 1H, NH), 5.11 (m, 2H, Z-$CH_2$), 5.02 (s, 1H, NH), 4.08 (m, 1H, *i*Pr α-CH), 1.98 (m, 2H, 2β-CH), 1.74 (m, 1H, β-CH),

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**Table I**
**Crystallographic Data for the (αMe)Val Homopeptides**

| parameter | Z-[D-(αMe)Val]$_2$-NH*i*Pr | Z-[D-(αMe)Val]$_3$-NH*i*Pr |
|---|---|---|
| mol formula | $C_{23}H_{37}N_3O_4$ | $C_{29}H_{48}N_4O_5$ |
| mol wt | 419.6 | 532.7 |
| cryst dimens, mm | 0.4 × 0.4 × 0.6 | 0.16 × 0.4 × 0.4 |
| cryst syst | orthorhombic | monoclinic |
| space group | $P2_12_12_1$ | $P2_1$ |
| $Z$, molecules/unit cell | 4 | 2 |
| $a$, Å | 16.155(2) | 15.471(2) |
| $b$, Å | 14.514(2) | 9.908(2) |
| $c$, Å | 10.555(2) | 10.423(2) |
| $\alpha$, deg | 90.0 | 90.0 |
| $\beta$, deg | 90.0 | 101.2(1) |
| $\gamma$, deg | 90.0 | 90.0 |
| $V$, Å$^3$ | 2474.9(7) | 1567.3(7) |
| $d$(calcd), g/cm$^3$ | 1.13 | 1.13 |
| diffractometer | Philips PW 1100 | Philips PW 1100 |
| radiation; λ, Å | Mo K$\alpha$; 0.7107 | Mo K$\alpha$; 0.7107 |
| no. of unique refls | 3342 | 4002 |
| no. of refls considered obsd | 1022 [$F \geq 7\sigma(F)$] | 1091 [$F \geq 6\sigma(F)$] |
| scan mode; $\theta_{max}$, deg | $\theta$–$2\theta$; 28 | $\theta$–$2\theta$; 28 |
| solved by | SHELXS 86[20] | SHELXS 86[20] |
| refined by | full-matrix least squares | full-matrix least squares |
| final $R$ value | 0.046 | 0.076 |
| $w$ | $1/[\sigma^2(F) + 0.0027F^2]$ | $1/[\sigma^2(F) + 0.009F^2]$ |
| final $R_w$ value | 0.048 | 0.081 |
| temp, K | 293 | 293 |
| crystallization solvent | ethyl acetate | acetone |
| H atoms | in part located on a $\Delta F$ map, all isotropically refined | in part located on a $\Delta F$ map, not refined |
| $(\Delta/\sigma)_{max}$ | 0.73 | 0.64 |
| $\mu$, cm$^{-1}$ | 0.45 | 0.45 |
| $S$ | 0.98 | 1.01 |
| highest map residual, e Å$^{-3}$ | ±0.16 | ±0.25 |

1.50 (s, 3H, β-$CH_3$), 1.46 (s, 3H, β-$CH_3$), 1.43 (s, 3H, β-$CH_3$), 1.17 (m, 6H, *i*Pr β-$CH_3$), 1.01–0.80 (m, 18H, γ-$CH_3$).

**Z-[D-(αMe)Val]$_2$-O*t*Bu.** This compound was prepared from [Z-D-(αMe)Val]$_2$O and H-D-(αMe)Val-O*t*Bu (obtained, in turn, by catalytic hydrogenation of the corresponding Z-derivative) in anhydrous acetonitrile under reflux for 30 h and purified by flash-chromatography by eluting the column with an isocratic mixture of 4:1 petroleum ether–ethyl acetate: yield 47%; mp 85–87 °C (from ethyl acetate); $R_{f1}$ 0.95, $R_{f2}$ 0.95, $R_{f3}$ 0.75; $[\alpha]^{20}_D$ −13.0° (*c* 0.5, methanol). IR absorption (KBr): $\nu_{max}$ 3392, 3306, 1719, 1659, 1533 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 10 mM): δ 7.35 (m, 5H, Z phenyl), 7.24 (s, 1H, NH), 5.28 (s, 1H, NH), 5.08 (m, 2H, Z-$CH_2$), 2.40 (m, 1H, β-CH), 2.19 (m, 1H, β-CH), 1.51 (s, 3H, β-$CH_3$), 1.47 (s, 3H, β-$CH_3$), 1.46 (s, 9H, O*t*Bu), 0.92 (m, 12H, γ-$CH_3$).

**Z-[D-(αMe)Val]$_2$-OH.** This compound was synthesized by treatment of Z-[D-(αMe)Val]$_2$-O*t*Bu with a 1:1 mixture of trifluoroacetic acid–methylene chloride: yield 90%; mp 162–163 °C (from diethyl ether); $R_{f1}$ 0.65, $R_{f2}$ 0.95, $R_{f3}$ 0.45; $[\alpha]^{20}_D$ −20.4° (*c* 0.5, methanol). IR absorption (KBr): $\nu_{max}$ 3327, 1723, 1655, 1521 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 10 mM): δ 7.36 (m, 5H, Z phenyl), 7.19 (s, 1H, NH), 5.10 (m, 2H, Z-$CH_2$), 5.06 (s, 1H, NH), 2.34 (m, 2H, 2β-CH), 1.40 (s, 3H, β-$CH_3$), 1.39 (s, 3H, β-$CH_3$), 0.88 (m, 12H, γ-$CH_3$).

***p*BrBz-[L-(αMe)Val]$_2$-O*t*Bu.** This compound was prepared from 5(4*H*)-oxazolone from *p*BrBz-L-(αMe)Val-OH and H-L-(αMe)Val-O*t*Bu in anhydrous acetonitrile under reflux for 50 h and purified by flash-chromatography by eluting the column with a step gradient of ethyl acetate in petroleum ether: yield 8%; mp 113–115 °C (from ethyl acetate–petroleum ether); $R_{f1}$ 0.95, $R_{f2}$ 0.95, $R_{f3}$ 0.70; $[\alpha]^{20}_D$ 44.2° (*c* 0.5, methanol). IR absorption (KBr): $\nu_{max}$ 3415, 3345, 1717, 1662, 1587, 1570 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 10 mM): δ 7.61 (m, 4H, *p*BrBz phenyl), 7.23 (s, 1H, NH), 7.11 (s, 1H, NH), 2.76 (m, 1H, β-CH), 2.30 (m, 1H, β-CH), 1.70 (s, 3H, β-$CH_3$), 1.57 (s, 3H, β-$CH_3$), 1.46 (s, 9H, O*t*Bu), 1.06 and 0.96 (2d, 6H, γ-$CH_3$), 1.02 and 0.92 (2d, 6H, γ-$CH_3$). From the above reaction mixture we were able to isolate a second product, identified as *p*BrBz-L-(αMe)Val-O*t*Bu: yield 10%; mp 105–107 °C (from ethyl acetate–petroleum ether); $R_{f1}$ 0.95, $R_{f2}$ 0.95, $R_{f3}$ 0.80; $[\alpha]^{20}_D$ 16.5 (*c* 0.5, methanol). IR absorption (KBr): $\nu_{max}$ 3291, 1731, 1643, 1591, 1537 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 10 mM): δ 7.61 (m, 4H, *p*BrBz phenyl), 7.01 (s, 1H, NH), 2.51 (m, 1H, β-CH), 1.72 (s, 3H, β-$CH_3$), 1.50 (s, 9H, O*t*Bu), 1.06 and 0.95 (2m, 6H, γ-$CH_3$).

**Infrared Absorption.** Infrared absorption spectra were recorded with a Perkin-Elmer Model 1720X FT-IR spectrometer, nitrogen flushed, at 2-cm$^{-1}$ nominal resolution, averaging 16 scans for 10 and 1.0 mM sample concentrations, or 64 scans for 0.1 mM sample concentration. Solvent (base-line) 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 deuteriochloroform (99.8% *d*) was purchased from Merck. For the solid-state measurements the KBr disk technique was used.

**$^1$H Nuclear Magnetic Resonance.** The $^1$H NMR nuclear magnetic resonance spectra were recorded at 298 K either with a Bruker Model WP 200 SY or with a Bruker Model AM 400 spectrometer (processed on a Bruker X-32 computer). Measurements were carried out in deuteriochloroform (99.96% *d*; Merck) and dimethyl-$d_6$ sulfoxide ($Me_2SO$) (99.96% $d_6$; Stohler) with tetramethylsilane as the internal standard. The free radical 2,2,6,6-tetramethylpiperidinyl-1-oxy was purchased from Sigma. The DQF-COSY (double quantum filtered correlation spectroscopy)[15] spectrum was obtained with a phase cycle modified in order to eliminate rapid-pulsing artifacts.[16] The two-dimensional ROESY (rotating frame Overhauser effect spectroscopy)[17] spectrum was recorded with a continuous-wave spin-locking pulse of 200 ms delivered with a power of $\gamma B_2/2\pi$ = 8.6 kHz. Pure absorption spectra were obtained according to the TPPI (time proportional phase incrementation) method.[18,19] Final spectra of 2K × 2K real points were obtained from data matrices acquired as 400 experiments of 2K complex points. Shifted sine bell functions were applied in the $t_2$ dimension and square cosine functions were applied in the $t_1$ dimension prior to Fourier transformation.

**X-ray Diffraction.** Crystallographic data for Z-[D-(αMe)-Val]$_n$-NH*i*Pr ($n$ = 2, 3) are reported in Table I. Complete lists of bond lengths, bond angles, and torsion angles and tables of final atomic parameters with equivalent and anisotropic thermal factors for all non-hydrogen atoms of the two structures have been deposited and are available from the Cambridge Crystallographic Data Center.

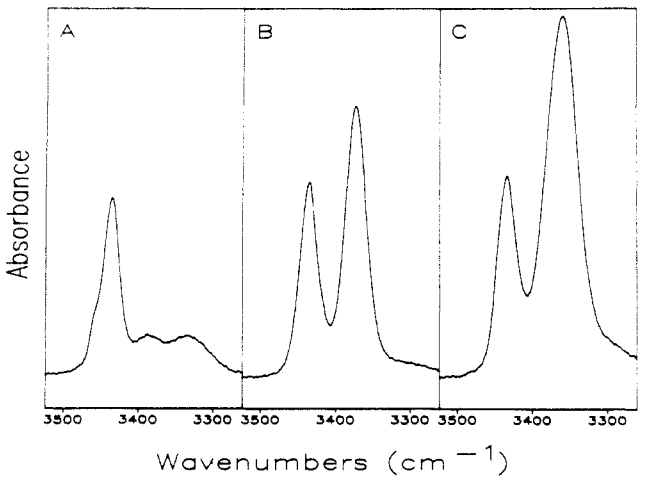


**Figure 1.** FT-IR absorption spectra in the N–H stretching region of the Z-[D-(αMe)Val]$_n$-NH*i*Pr (A, $n$ = 1; B, $n$ = 2; C, $n$ = 3) homopeptides in $CDCl_3$ solution (concentration 1 mM).

## Results and Discussion

**Peptide Synthesis.** For the large-scale production of the optically pure (αMe)Val enantiomers, we exploited an economically attractive, chemoenzymatic synthesis recently described by some of us.[21] The preparation and characterization of five terminally blocked homopeptides (to the trimer level) from this sterically hindered residue were performed. During the coupling reactions (in anhydrous acetonitrile under reflux for 3–50 h) the carboxyl group of the N$^{\alpha}$-blocked amino acid or peptide was activated using either the symmetrical anhydride or the 5(4*H*)-oxazolone method. The N$^{\alpha}$-blocked peptide free acid was obtained by treatment of the corresponding *tert*-butyl ester with diluted trifluoroacetic acid. Removal of the benzyloxycarbonyl N$^{\alpha}$-protecting group was achieved by catalytic hydrogenation.

**Solution Conformation.** The conformational preferences of the terminally blocked (αMe)Val homooligomers Z-[D-(αMe)Val]$_n$-NH*i*Pr ($n$ = 1–3) were investigated in a structure-supporting solvent ($CDCl_3$) by FT–IR absorption and $^1$H NMR at various concentrations (over the range 10–0.1 mM). The FT-IR absorption spectra in the most informative N–H stretching region (amide A) (concentration 1 mM) are illustrated in Figure 1. The curves are characterized by bands at 3455–3434 cm$^{-1}$ (free, solvated NH groups), 3385 cm$^{-1}$ (weakly H-bonded NH groups), and 3373–3359 cm$^{-1}$ (strongly H-bonded NH groups).[22-24] The intensity of the low-frequency band relative to the high-frequency band(s) increases significantly with increasing main-chain length; in parallel, the absorption maximum shifts to lower wavenumbers.

Using Mizushima's dilution method,[22] we have been able to show that even at 10 mM concentration self-association via N—H···O=C intermolecular H-bonding is negligible (less than 5%) for all oligomers (results not shown). Therefore, the observed H-bonding should be interpreted as arising almost exclusively from intramolecular N—H···O=C interactions.

The present FT-IR absorption analysis has provided evidence that main-chain length dependent intramolecular H-bonding is the predominant factor for the terminally blocked (αMe)Val homopeptides in $CDCl_3$ solution. To get additional information on the preferred conformation in $CDCl_3$ solution, we carried out a detailed 400-MHz $^1$H NMR investigation.

The analysis of the DQF-COSY spectrum of the homotrimer allowed the assignment of the C-terminal isopropyl group as well as the identification of the side chains of the three (αMe)Val residues. All possible intraresidue ROESY cross-peaks among the β-methyl, the amide NH, and the side-chain β-methine and γ-methyl protons were detected for all residues. The remaining ROESY cross-peaks could be rationalized in terms of sequential connectivities only. These peaks are summarized in Table II. The observation of strong $NH_i$–$NH_{i+1}$ connectivities allowed the unambiguous sequential assignment of all the resonances (Table III).

An analysis of the spectra of the homooligomers as a function of peptide concentration (26–1.2 mM)[25] in $CDCl_3$ solution (results not shown) indicates that dilution produces an extremely modest ($0.01 \leq$ ppm $\leq 0.08$) shift of all NH resonances.

The delineation of inaccessible NH groups was performed with the use of solvent dependencies of NH chemical shifts[26] and free-radical (TEMPO) induced line broadening of NH resonances.[27] Figure 2 clearly shows two classes of NH protons in the $Me_2SO/CDCl_3$ experiments: (1) The first class [N(1)H proton] includes a proton whose chemical shift is dramatically sensitive to the

**Table II**
**Interresidue Connectivities Derived from the ROESY Spectrum of Z-[D-(αMe)Val]$_3$-NH*i*Pr (Concentration 1.2 mM in $CDCl_3$)**

| | Z | Res. 1 | Res. 2 | Res. 3 | NH*i*Pr |
|---|---|---|---|---|---|
| $NH_i$-$NH_{i+1}$ | | \|——— | \|——— | \|——— | \| |
| $(\gamma CH_3)_i$-$NH_{i+1}$ | | \|——— | \|——— | \|——— | \| |
| $(\gamma CH_3)_i$-$(\beta CH_3)_{i+1}$ | | \|——— | \|——— | \| | |
| $(\beta CH)_i$-$NH_{i+1}$ | | \|——— | \| | | |
| $(CH_2)_i$-$(\gamma CH_3)_{i+1}$ | \|——— | \| | | | |

**Table III**
**Resonance Assignments of the Protons of Z-[D-(αMe)Val]$_3$-NH*i*Pr (Concentration 1.2 mM in $CDCl_3$)**

| | NH | β-$CH_3$ | $CH_2$ | β-CH | γ-$CH_3$ | aromatic |
|---|---|---|---|---|---|---|
| *Z* | | | 5.11 | | | 7.36 |
| 1 | 5.00 | 1.46 | | 1.98 | 0.97 | |
| 2 | 6.52 | 1.44 | | 1.74 | 0.82, 0.86 | |
| 3 | 6.73 | 1.50 | | 2.02 | 0.95, 0.99 | |
| NH*i*Pr | 7.22 | 1.15, 1.18 | | 4.06 | | |

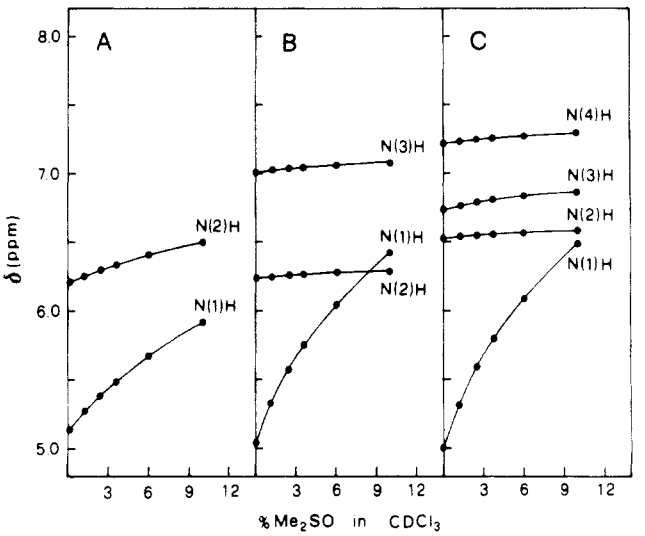


**Figure 2.** Plot of NH chemical shifts in the $^1$H NMR spectra of Z-[D-(αMe)Val]$_n$-NH*i*Pr (A, $n$ = 1; B, $n$ = 2; C, $n$ = 3) as a function of increasing percentages of $Me_2SO$ (v/v). Peptide concentration: 1.2 mM.

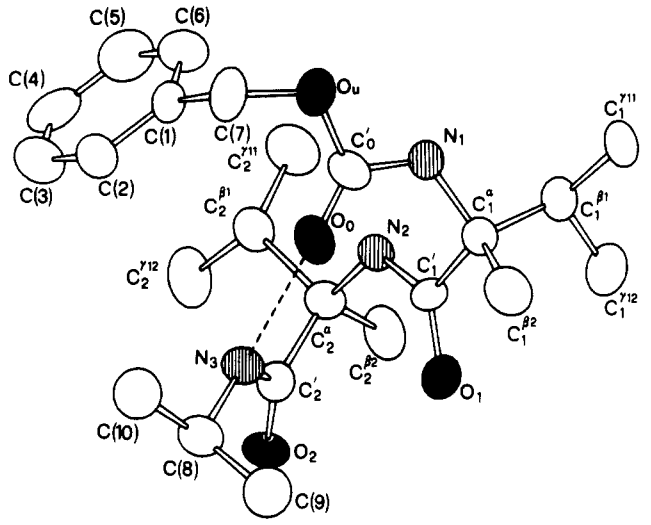


**Figure 3.** Molecular structure of Z-[D-(αMe)Val]$_2$-NH*i*Pr with numbering of the atoms. The intramolecular H bond is represented as a dashed line.

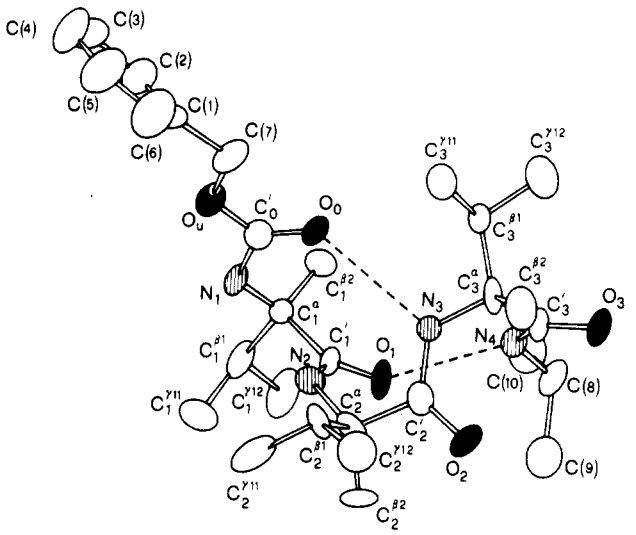


**Figure 4.** Molecular structure of Z-[D-(αMe)Val]$_3$-NH*i*Pr with numbering of the atoms. The two intramolecular H bonds are represented as dashed lines.

**Table IV**
**Relevant Torsion Angles (Degrees) with Esd's for the (αMe)Val Homopeptides**

| angle | Z-[D-(αMe)Val]$_2$-NH*i*Pr | Z-[D-(αMe)Val]$_3$-NH*i*Pr |
|---|---|---|
| $\theta^3$ | -45.6(9) | -58.4(18) |
| $\theta^2$ | -75.2(8) | 175.1(12) |
| $\theta^1$ | 169.1(6) | 175.5(11) |
| $\omega_0$ | 177.4(5) | 166.2(11) |
| $\phi_1$ | 57.1(8) | 63.6(15) |
| $\psi_1$ | 33.2(7) | 18.8(16) |
| $\omega_1$ | 178.2(5) | 177.8(11) |
| $\phi_2$ | 50.9(7) | 55.3(16) |
| $\psi_2$ | 41.4(7) | 29.7(17) |
| $\omega_2$ | -176.2(6) | -177.6(11) |
| $\phi_3$ | | 53.6(16) |
| $\psi_3$ | | 36.7(16) |
| $\omega_3$ | | -174.6(12) |
| $\chi_1^{1,1}$ | -166.3(6) | -57.1(16) |
| $\chi_1^{1,2}$ | 65.1(7) | 176.4(13) |
| $\chi_2^{1,1}$ | 62.7(7) | 70.4(24) |
| $\chi_2^{1,2}$ | -171.2(6) | -169.9(29) |
| $\chi_3^{1,1}$ | | -162.9(12) |
| $\chi_3^{1,2}$ | | 70.4(13) |
| $\pi^{1,1}$ | 79.9(9) | 95.0(16) |
| $\pi^{1,2}$ | -156.7(7) | -146.3(13) |

addition of the strong H-bonding acceptor solvent $Me_2SO$.[28] (2) The second class (all other NH protons) includes those displaying a behavior characteristic of shielded protons (very modest sensitivity of chemical shifts to solvent composition). Strictly comparable results were obtained in the experiments with the paramagnetic agent TEMPO. The present $^1$H NMR results support the view that in $CDCl_3$ solution the N(2)H and the following protons in the peptide chain of the (αMe)Val homooligomers are not freely accessible to the perturbing agents.

In summary, the absence of an intense absorption related to a strongly H-bonded NH group in the FT-IR spectrum of the (αMe)Val monomer together with the presence of such a band (of different intensity) in the dimer and trimer point to the onset of an intramolecularly H-bonded β-turn conformation and of two consecutive β-turn conformations (incipient $3_{10}$-helix) in the dimer and trimer, respectively, in $CDCl_3$ solution. This conclusion might be corroborated by the $^1$H NMR results, if the modest accessibility to perturbing agents exhibited by the N(2)H proton would not be related to intramolecular H-bond formation, but rather to a shielding effect produced by the bulky, β-branched side chain.

**Crystal-State Conformation.** We determined by X-ray diffraction the molecular and crystal structures of two terminally blocked (αMe)Val homopeptides, namely Z-[D-(αMe)Val]$_n$-NH*i*Pr ($n$ = 2, 3). The molecular structures with the atomic numbering schemes are illustrated in Figures 3 and 4, respectively. Relevant backbone and side-chain torsion angles[29] are given in Table IV. In Table V the intra- and intermolecular H-bond parameters are listed.

Bond lengths and bond angles (deposited) are in general agreement with previously reported values for the geometry of the (benzyloxycarbonyl)amino[30] and isopropylamido[31,32] moieties, the (αMe)Val residue,[11-13] and the peptide unit.[33]

All five D-(αMe)Val residues are found in the left-handed helical region A* of the conformational map.[34] The average φ and ψ values are 56 and 32°, close to those expected for a $3_{10}$-helix (57, 30°).[35,36] The N$^\alpha$-protected dipeptide amide adopts a type-III′ β-turn conformation[37-39] stabilized by a 1←4 C=O···H—N intramolecular H bond. The $N_3\cdots O_0$ separation is 3.101(7) Å, within the range expected for such H bonds.[40-42] The N$^\alpha$-protected tripeptide amide is folded in two consecutive type-III′ β-turns (incipient left-handed $3_{10}$-helix), characterized by two 1←4 C=O···H—N intramolecular H bonds. The $N_3\cdots O_0$ and $N_4\cdots O_1$ distances are 3.148(13) and 2.899(12) Å, respectively.

The distribution of the side-chain conformations for the D-(αMe)Val residues ($\chi^1$ torsion angle) is $4g^+$, 5t, $1g^-$,

**Table V**
**Intra- and Intermolecular H-Bond Parameters for the (αMe)Val Homopeptides**

| compd | donor D-H | acceptor A | symmetry equiv of A | distance (Å) D···A | distance (Å) H···A | angle (deg) D-H···A |
|---|---|---|---|---|---|---|
| Z-[D-(αMe)Val]$_2$-NH*i*Pr | $N_3$-$H_3$ | $O_0$ | $x, y, z$ | 3.101(7) | 2.40(6) | 158(6) |
| | $N_1$-$H_1$ | $O_2$ | $-1-x, {}^1/_2+y, {}^{-1}/_2-z$ | 2.973(7) | 2.21(8) | 174(8) |
| Z-[D-(αMe)Val]$_3$-NH*i*Pr | $N_3$-$H_3$ | $O_0$ | $x, y, z$ | 3.148(13) | 2.068(9) | 165.8(7) |
| | $N_4$-$H_4$ | $O_1$ | $x, y, z$ | 2.889(12) | 1.968(8) | 139.6(7) |
| | $N_1$-$H_1$ | $O_3$ | $x, y, z-1$ | 2.929(13) | 2.117(9) | 129.9(7) |

in agreement with previous data on (αMe)Val peptides[11-13] and with results of statistical analyses of the Val residue in peptides and proteins.[43-46]

All the urethane, amide, and peptide groups (ω torsion angles) are trans, as expected,[30-33] with only the urethane -CONH- group of the trimer, $\omega_0 = 166.2(11)°$, deviating substantially from planarity. The conformation of the two Z-urethane groups ($\theta^1$ and $\omega_0$ torsion angles) is the usual trans,trans or type-b conformation.[30] Also the values of $\theta^2$ and $\theta^3$ torsion angles are typical for the Z-urethane group.[30] The conformation of the two isopropylamido groups ($\pi$ torsion angle) 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.[31-32]

In the crystals of Z—[D-(αMe)Val]$_2$—NH*i*Pr rows of molecules are generated in the *y*-direction through (urethane) $N_1—H_1\cdots O_2=C_2'$ (amide) intermolecular H bonds. The N···O separation is 2.973(7) Å. In the packing mode of Z—[D-(αMe)Val]$_3$—NH*i*Pr we find a linear array of molecules in the *z*-direction linked together by (urethane) $N_1—H_1\cdots O_3=C_3'$ (amide) intermolecular H bonds. The N···O distance is 2.929(13) Å. In neither oligomer is the (peptide) N—H function of residue 2 found to participate in a H bond.

## Conclusions

We have been able to show that monodispersed homooligomers from the severely sterically hindered (αMe)-Val residue may be synthesized step-by-step by solution methods. The present detailed conformational analysis confirms that this β-branched residue is a strong β-turn and helix former and that the relationship between (αMe)-Val chirality and helix handedness is the same as that exhibited by protein amino acids, including Val, its unmethylated counterpart.[11-13] A comparison with the results of homooligomers from the other $C^\alpha$-methylated amino acids investigated to date[5-10] favors the conclusion that this backbone modification tends to strongly promote folding in the resulting peptides.

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## References and Notes


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