The First Fully Planar C_5-Conformation of Homooligopeptides Prepared from a Chiral α-Ethylated α,α-Disubstituted Amino Acid: (*S*)-Butylethylglycine (= (2*S*)-2-Amino-2-ethylhexanoic Acid)

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An optically active α-ethylated α,α-disubstituted amino acid, (*S*)-butylethylglycine (= (2*S*)-2-amino-2-ethylhexanoic acid; (*S*)-Beg; (*S*)-**2**), was prepared starting from butyl ethyl ketone (**1**) by the *Strecker* method and enzymatic kinetic resolution of the racemic amino acid. Homooligopeptides containing (*S*)-Beg (up to hexapeptide) were synthesized by conventional solution methods. An ethyl ester was used for the protection at the C-terminus, and a trifluoroacetyl group was used for the N-terminus of the peptides. The structures of tri- and tetrapeptides **5** and **6** in the solid state were solved by X-ray crystallographic analysis, and were shown to have a bent planar C_5-conformation (tripeptide) and a fully planar C_5-conformation (tetrapeptide) (see *Figs. 1* and *2*, resp.). The IR and ^{1}H-NMR spectra of hexapeptide **8** revealed that the dominant conformation in $CDCl_3$ solution was also a fully planar C_5-conformation. These results show for the first time that the preferred conformation of homopeptides containing a chiral α-ethylated α,α-disubstituted amino acid is a planar C_5-conformation.

Introduction. – Introduction of non-proteinogenic amino acids into peptides severely changes the conformational freedom and stabilizes secondary structures [1] such as helix and β-turn conformations. The conformational studies of α,α-disubstituted amino acids were focused on α-aminoisobutyric acid (= α-methylalanine = dimethylglycine; Aib) [2][3] because Aib is an achiral amino acid and its structure is very simple, with only two Me substituents as side chains. It is well known among peptide chemists that Aib has the propensity to induce a 3_{10}-helical structure and, therefore, it is often used to construct the helical secondary structure in the *de novo* design of proteins [1][2]. Besides Aib, homopeptides containing achiral amino acids, such as diethylglycine (Deg) [3][4], dipropylglycine (Dpg) [5], and alicyclic glycines (Ac(*n*)c) [6], have been reported. The amino acids Deg and Dpg favor a planar C_5-conformation (*i.e.*, N–H and C=O are involved in a pentagonal ring, together with C(α)), and the alicyclic glycines Ac(*n*)c, such as 1-aminocyclopropanecarboxylic acid ($n = 3$) [6a], 1-aminocyclobutanecarboxylic acid ($n = 4$) [6b–d], 1-aminocyclopentanecarboxylic acid ($n = 5$) [6e], and 1-aminocyclohexanecarboxylic acid ($n = 6$) [6f] tend to induce 3_{10}-helical structure[1]). Recent developments in asymmetric synthesis[2]) enable peptide chemists to use chiral α-methylated α,α-disubstituted amino acids as a tool for the study of the conformation of various peptides. However, the conformational studies of peptides containing chiral α,α-disubstituted amino acids were restricted to α-methylated

[1]) The conformation of a homopeptide prepared from an α,α-disubstituted amino acid bearing an ether group at the side chain was recently reported [6g].

[2]) For reviews on the asymmetric syntheses of chiral α,α-disubstituted amino acids, see [7].

α,α-disubstituted amino acids [8][9] because only the α-methylated optically active α,α-disubstituted amino acids are easily prepared on the gram scale [7]. It is already known that the homooligopeptides containing chiral α-methylated α,α-disubstituted amino acids, such as isovaline (Iva), α-methylvaline (αMeVal), and α-methylleucine (αMeLeu) prefer the 3_{10}-helical structures (*Table 1*). Here, we wish to report the first preparation of homooligopeptides containing optically active (*S*)-butylethylglycine (=(2*S*)-2-amino-2-ethylhexanoic acid; (*S*)-Beg) as a chiral α-ethylated α,α-disubstituted amino acid[3]), and on their conformations in the solid state and in solution.

Table 1. *Homooligopeptides Containing α,α-Disubstituted Amino Acids*

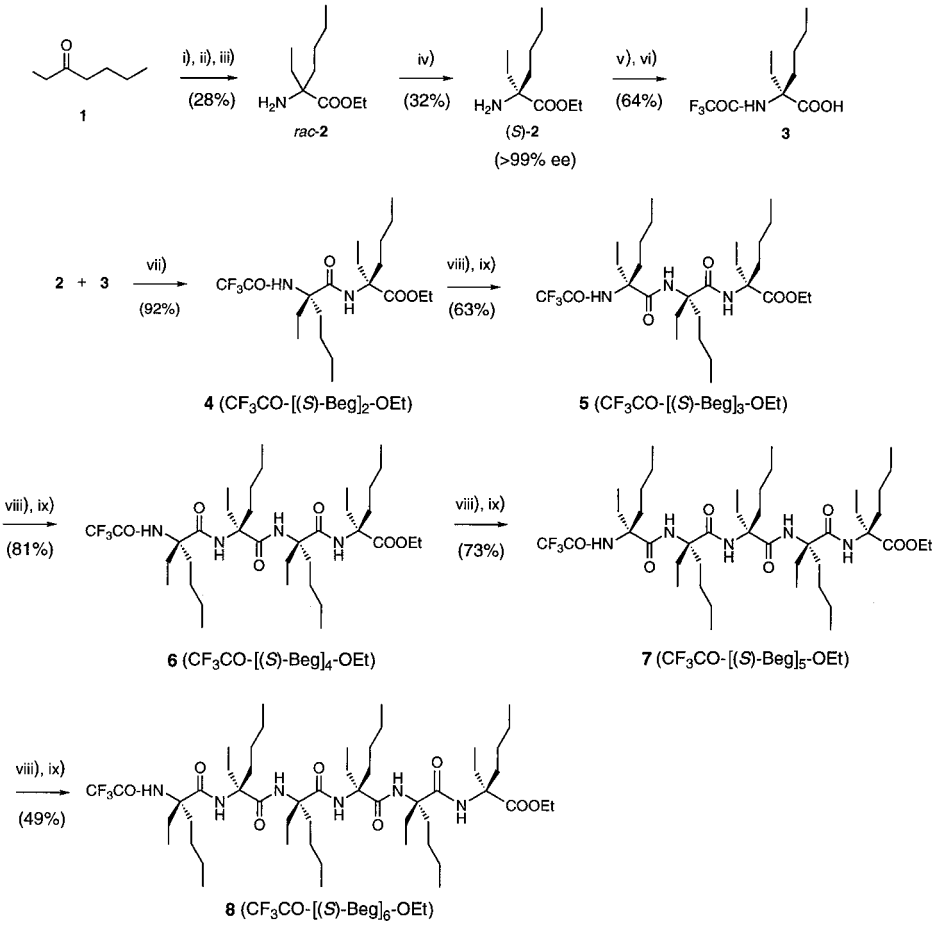
Amino acid	Peptide	Conformation in the solid state
Achiral α,α-disubstituted amino acid:		
α-Methylalanine (Aib) [2][3]	*p*BrBz-(Aib)$_8$-O-*t*-Bu	(*P*)- and (*M*)-3_{10}-helix [11]
Diethylglycine (Deg) [3][4]	CF_3CO-(Deg)$_5$-O-*t*-Bu	C_5-conformation
	CF_3CO-(Deg)$_6$-OEt	(*P*) and (*M*)-3_{10}-helix
Dipropylglycine (Dpg) [5]	Ac-(Dpg)$_2$-NHMe	C_5-conformation
Alicyclic glycine (Ac(*n*)c) [6]	Z-[Ac(*n*)c]$_m$-O-*t*-Bu[a])	(*P*)- and (*M*)-3_{10}-helix
Chiral α,α-disubstituted amino acid:		
Isovaline (Iva) [8a,b,e,f,i]	*p*BrBz-[(*R*)-Iva]$_5$-O-*t*-Bu	(*M*)-3_{10}-helix
	Boc-[(*S*)-Iva]$_6$-OMe	(*P*)- and (*M*)-3_{10}-helix
α-Methylvaline ((αMe)Val) [8a][9b,c]	Z-[(*S*)-(αMe)Val]$_8$-O-*t*-Bu	(*P*)-3_{10}-helix
α-Methylleucine ((αMe)Leu) [8b]	*p*BrBz-[(*R*)-(αMe)Leu]$_4$-OH	(*P*)-3_{10}-helix
α-Methylphenylalanine ((αMe)Phe) [8b–d]	*p*BrBz-[(*R*)-(αMe)Phe]$_4$-O-*t*-Bu	(*P*)-3_{10}-helix
α-Ethylphenylalanine ((αEt)Phe) [10b,c]	Z-(Aib)$_2$-[(*S*)-(αEt)Phe]-Aib-OH[b])	(*P*)-3_{10}-helix

[a]) Homopeptides prepared from alicyclic α,α-disubstituted amino acids: 1-aminocyclopropanecarboxylic acid ($n=3$), 1-aminocyclobutanecarboxylic acid ($n=4$), 1-aminocyclopentanecarboxylic acid ($n=5$), and 1-aminocyclohexanecarboxylic acid ($n=6$). [b]) This peptide is not a homopeptide, but a heteropeptide containing an α-ethylated amino acid. The 3_{10}-helical conformation may be formed by the introduction of Aib residues.

Results. – *Synthesis of (*S*)-Butylethylglycine and of Its Homopeptides.* Racemic butylethylglycine ethyl ester (*rac*-**2**) was prepared on a gram scale from butyl ethyl ketone (**1**) by treatment with KCN and NH_4Cl, hydrolysis of the nitrile, and subsequent esterification, according to the methods of *Pfister* and co-workers [12] (*Scheme*). The kinetic resolution of racemic **2** using porcine liver esterase (PLE) according to the method of *Liu* and co-workers [13] afforded the enantiomerically pure (*S*)-**2** as the recovered starting material. The α-ethylated α,α-disubstituted amino acids possess very hindered amino and carboxylic acid functions; therefore, severe reaction conditions were required for their coupling. We prepared homooligopeptides from the C-terminus, employing an ethyl ester as C-terminal and a trifluoroacetyl group as N-terminal protection of the peptide by conventional solution-phase methods [4f]. Saponification of the ester function in (*S*)-**2**, followed by trifluoroacetylation of the amino group afforded the *N*-(trifluoroacetyl)-protected amino acid **3** in 64% yield. Dipeptide **4** was synthesized in 92% yield by coupling of the amino ester (*S*)-**2** and acid **3** *via* the oxazol-5(4*H*)-one intermediate by treatment with 1-ethyl-3-[3-(dimethylamino)propyl]carbo-

[3]) For conformations of heteropeptides prepared from a chiral α-ethylated phenylalanine, see [10].

Scheme



i) KCN, NH_4Cl, 60°. *ii*) Conc. HCl, 80°. *iii*) H_2SO_4, EtOH, reflux. *iv*) PLE, phosphate buffer (pH 8.0). *v*) NaOH. *vi*) $(CF_3CO)_2O$. *vii*) 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide · HCl (EDC), MeCN, reflux. *viii*) $NaBH_4$, EtOH, reflux. *ix*) **3**, EDC, MeCN, reflux.

diimide hydrochloride (EDC) in refluxing MeCN. Tripeptide **5** was prepared in 63% yield by deprotection of the trifluoroacetyl function of **4** with $NaBH_4$ and subsequent coupling with acid **3** in the presence of EDC in refluxing MeCN. Tetra-, penta-, and hexapeptides **6**–**8** were synthesized in a manner similar to that described for **4**. The spectroscopic data of all compounds supported their structures.

Solid-State Conformational Analysis. We determined the molecular and crystal structures of the two terminally blocked tri- and tetrapeptides **5** and **6** by X-ray crystallographic analysis. Crystals of good-to-moderate quality for X-ray analysis were obtained by slow evaporation of an EtOH or MeOH solution, respectively, at room temperature. In the case of penta- and hexapeptides **7** and **8**, no good crystals for X-ray

analysis could be obtained. The molecular structures of **5** and **6** with atomic-numbering schemes are shown in *Figs. 1* and *2*. Relevant backbone and side-chain torsion angles are given in *Table 2*. The intra- and intermolecular H-bond parameters are listed in *Table 3*.

The structure of tripeptide **5** was solved in the space group $P2_12_12_1$. Two intramolecular H-bonds are observed in the residues Beg^1 and Beg^3. This means that an intramolecularly H-bonded C_5-conformation of Beg^1 and Beg^3 is present in the solid state. The set of ϕ, ψ angles for the residue are -170.3°, $+171.5^\circ$ for Beg^1 and -179.9°, $+174.9^\circ$ for Beg^3. The N(1)$\cdots$O(1) distance is 2.54 Å and the N(3)$\cdots$O(3) distance 2.59 Å. In the packing mode, one intermolecular H-bond is shown between H–N(2) peptide donor and the C(2)=O(2) carbonyl O-atom of the peptide of a symmetry-related molecule $(1/2+x, -y, 1/2+z)$, with a N(2)$\cdots$O(2) distance of 2.89 Å. The set of ϕ, ψ angles for Beg^2 are $+61.4^\circ$, -42.8°. The conformation observed in the solid state of **5** is very similar to that of tripeptide CF_3CO-$(Deg)_3$-OEt prepared from diethylglycine (Deg) [4f], except that the centers of symmetry are present in the crystal of the latter but not in the crystal of **5**.

Tetrapeptide **6** crystallizes in the space group $P2_1$. One molecule exists in the asymmetric unit. The set of ϕ, ψ angles of each amino acid residue is close to $180^\circ, 180^\circ$, which indicates that four consecutive C_5-conformations exist in the tetrapeptide, that is to say, the tetrapeptide **6** forms a fully planar C_5-conformation in the solid state. All NH groups are intramolecularly H-bonded to the carbonyl groups of the same amino-acid

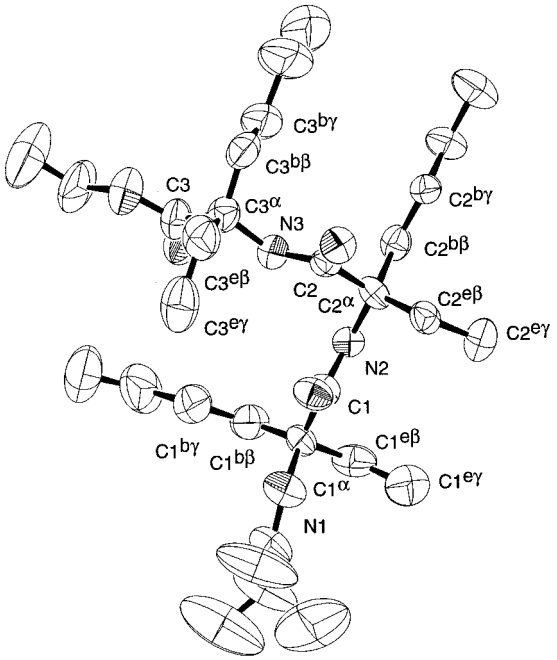


Fig. 1. *ORTEP Drawing of the crystal structure of tripeptide* **5** *with atom numbering* (ellipsoids at 50% probability)

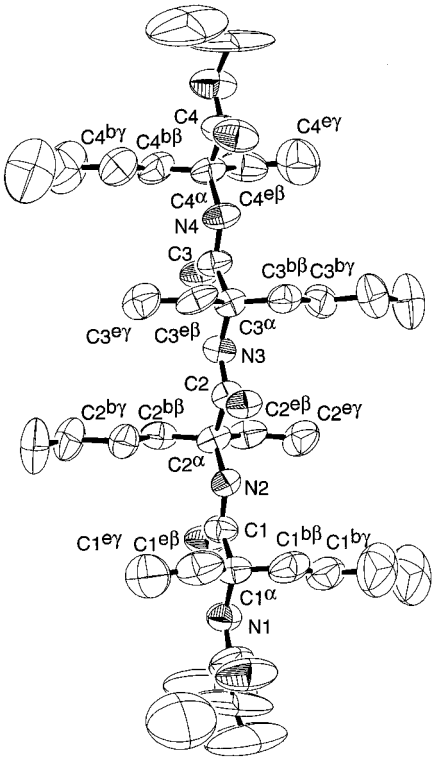


Fig. 2. *ORTEP Drawing of the crystal structure of tetrapeptide* **6** *with atom numbering* (ellipsoids at 50% probability)

residues in the C_5-conformation. The average distance of $N(i)\cdots O(i)$ is 2.56 Å. No intermolecular H-bonds exist in the solid state of tetrapeptide **6**. The butyl and ethyl side chains at each C(α) atom are extended in all amino-acid residues, with the χ^b and χ^e values for each residue close to $+60$ (g^+) and -60 (g^-), respectively. Unfavorable intramolecular interactions could be minimized in these side-chain angles [4b,c].

Solution Conformational Analysis. FT-IR Absorption spectra of homopeptides **4**–**8** were measured for the analysis of conformational preferences in $CDCl_3$ solution. In the concentration range examined (1.0–10 mM), the IR spectra of hexapeptide **8** remain essentially unchanged, meaning that the strength of the intermolecular H-bonds does not change with concentration. In the case of a 3_{10}-helical conformation, the IR spectra would vary with the concentration due to the intermolecular H-bonds. It was expected that all NH functional groups are intramolecularly H-bonded to the carbonyl groups of the same amino-acid residues in the case of a fully extended C_5-conformation. *Fig. 3* shows the IR absorption of the di- to hexapeptides **4**–**8** in the 3250–3500 cm^{-1} region. The band at 3380–3415 cm^{-1} is assigned to amide NH groups with a relatively strong $C-F\cdots H(N)\cdots O=C$ intramolecular H-bond, and that at 3335–3360 cm^{-1} to peptide NH groups with $N-H\cdots O=C$ intramolecular H-bonds of different strength. With increasing chain length, the strong absorption observed at 3335 cm^{-1} in the dipeptide

Table 2. *Torsion Angles* [°] *for Homopeptides* CF_3CO-*[(*S*)-Beg]$_3$-*OEt* (**5**) *and* CF_3CO-*[(*S*)-Beg]$_4$-*OEt* (**6**)

Torsion angle[a])	**5**	**6**
ω_0	171.0	162.5
ϕ_1	−170.3	−177.8
ψ_1	171.5	−177.7
ω_1	−176.0	177.7
ϕ_2	61.4	178.6
ψ_2	−42.8	179.9
ω_2	−167.9	178.3
ϕ_3	−179.9	−179.2
ψ_3	174.9	−179.6
ω_3	174.3	178.6
ϕ_4	–	−178.9
ψ_4	–	−179.8
ω_4	–	172.7
χ_1^e	−52.1	50.0
χ_1^b	55.5	−54.3
χ_2^e	66.5	52.2
χ_2^b	−178.3	−52.3
χ_3^e	−56.8	58.4
χ_3^b	61.7	−57.8
χ_4^e	–	59.9
χ_4^b	–	−61.6

[a]) The descriptors e and b refer to the side chains ethyl and butyl, respectively.

Table 3. *Intra- and Intermolecular Hydrogen Bonds for Homopeptides* CF_3CO-*[(*S*)-Beg]$_3$-*OEt* (**5**) *and* CF_3CO-*[(*S*)-Beg]$_4$-*OEt* (**6**)

	Donor H−D[a])	Acceptor A[a])	Distance [Å] D···A	Angle [°] D−H···A	Symmetry operation[b])
5	H−N(1)	O(1)	2.54	110	x,y,z
	H−N(3)	O(3)	2.59	108	x,y,z
	H−N(2)	O(2′)	2.89	168	$1/2+x,\ -y,\ 1/2+z$
6	H−N(1)	O(1)	2.55	108	x,y,z
	H−N(2)	O(2)	2.54	109	x,y,z
	H−N(3)	O(3)	2.56	110	x,y,z
	H−N(4)	O(4)	2.57	108	x,y,z

[a]) The peptide-backbone numbering begins at the N-terminus. [b]) x,y,z: intramolecular H-bond; $1/2+x,\ -y,\ 1/2+z$: intermolecular H-bond.

shifts to higher wave numbers (3360 cm^{-1}), and also the relative intensity of this absorption band increases gradually. These IR spectra are very similar to those of homopeptides prepared from Deg, which show fully extended C_5-conformations in solution [4b,c,f].

We measured the ^{1}H-NMR spectra of hexapeptide **8** under various conditions to obtain more detailed information. In $CDCl_3$ solution, the signal of the trifluoroacetamide NH at the N-terminus of **8** is unambiguously determined by its high-field position at δ 6.78 (br. *s*, 1 H), and that of the amide NH at the C-terminus is assigned to δ 8.03 (br. *s*, 1 H; *Fig. 4,b*), by analogy of the N-terminal and C-terminal NH signals of

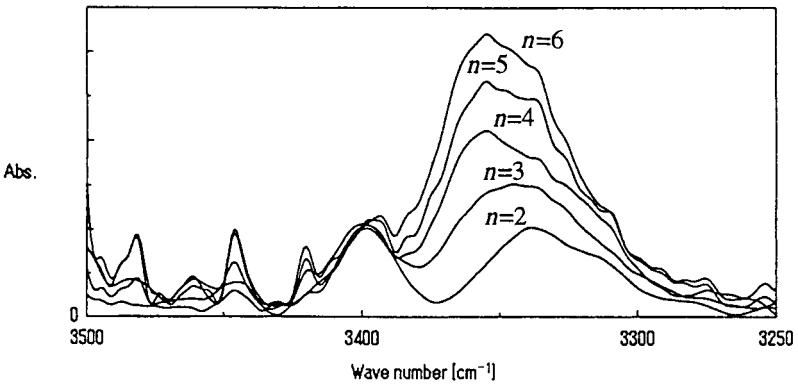


Fig. 3. *FT-IR Absorption spectra* (3500–3250 cm^{-1} region) *of* CF_3CO-*[(S)-Beg]*$_n$-*OEt* ($n = 2–6$) *homopeptides* **4**–**8** *in* $CDCl_3$ *solution*. Peptide concentration 1.0 mM.

dipeptide **4**. The internal four NH signals ($Beg^{2–5}$) appear in a narrow region of δ 7.37–7.46 and, therefore, these signals could not be assigned. The ^{1}H-chemical shifts of all NH of **8** are essentially independent of the concentration in the range 1.0–10 mM. The ^{1}H,^{1}H-NOESY NMR spectrum of **8** does not show any correlation among the amide NH signals; this correlation would be observed in the case of a 3_{10}-helical conformation [8i]. The additional effects of the strong H-bond-acceptor solvent DMSO (*Fig. 4*,*b*)) or the paramagnetic free radical 2,2,6,6-tetramethyl-1-piperidyloxyl (TEMPO) (*Fig. 4*,*d*)) on the NH signals of hexapeptide **8** were examined, with hexapeptide $CF_3CO–(Aib)_6–OEt$ as a reference standard for a 3_{10}-helical conformation (*Fig. 4*,*a* and *c*). The NH signals of **8** were almost insensitive to the addition of the two perturbing agents DMSO (0–10% (*v*/*v*) and TEMPO ($0–5 \cdot 10^{-2}$ % (*w*/*v*)). In contrast, two NH signals (Aib^1 and Aib^2) of the Aib hexapeptide were very sensitive (solvent-exposed NH groups), and this is consistent with disruption of the two intermolecular H-bonds of the 3_{10}-helical structure formed by this molecule (*Fig. 4*).

The CD spectra of the di- to hexapeptides **4**–**8** in 2,2,2-trifluoroethanol (CF_3CH_2OH) solution were also measured to obtain global secondary-structure information. *Toniolo* and co-workers recently mentioned that the helical structures (including the screw sense of the helix and discrimination between a 3_{10}- and an α-helix) could be assigned by the negative or positive maximum and intensity of two bands at 222 and 208 nm in the CD spectra of a peptide constituted of chiral α-methylated α,α-disubstituted amino acids [9]. However, the CD spectra of homopeptides containing (*S*)-Beg did not show the characteristic bands for helix, as shown in *Fig. 5*.

Discussion. – The conformation in the solid state of tetrapeptide **6** containing the chiral (*S*)-butylethylglycine is not a 3_{10}-helical structure but a fully planar C_5-conformation. Good crystals for X-ray analysis have not yet been obtained for the penta- and hexapeptides **7** and **8**, respectively. In the tetrapeptide **6**, four consecutive C_5-conformations are present, and the arrangement of the butyl and ethyl side chains at the C(α)s alternates with respect to the plane of the peptide backbone. In the C_5-

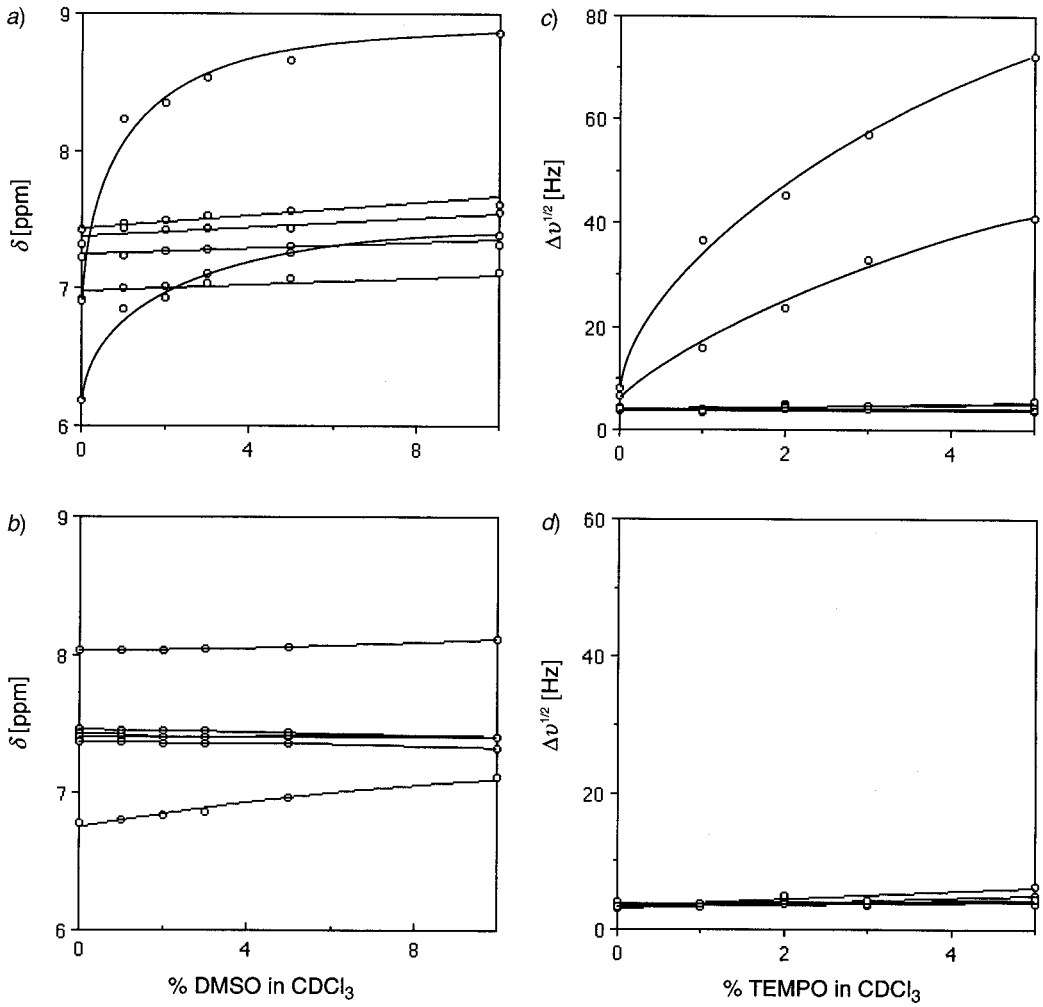


Fig. 4. a) *Plots of NH chemical shifts in the* ^{1}*H-NMR spectra of* CF_3CO-$(Aib)_6$-*OEt* (peptide concentration 0.5 mM) *and* b) *of* CF_3CO-$[(S)$-*Beg*$]_6$-*OEt* (**8**; peptide concentration 1.0 mM) *as a function of increasing percentages of DMSO* (*v*/*v*) *added to the* $CDCl_3$ *solution.* c) *Plots of the bandwidth of the NH protons of* CF_3CO-$(Aib)_6$-*OEt* (peptide concentration 0.9 mM) *and* d) *of* CF_3CO-$[(S)$-*Beg*$]_6$-*OEt* (**8**; peptide concentration 1.0 mM) *as a function of increasing percentages of TEMPO* (*w*/*v*) *added to the* $CDCl_3$ *solution.*

conformation of **6**, the angles internal to the pentagonal C_5 ring (the average $N(i)-C(\alpha)(i)-C(i)$ angle is 103.5°) are smaller than 107°; the latter angle was estimated to be the border angle for an amino acid in a 3_{10}-helix *vs.* a planar C_5-conformation. On the other hand, the angles external to the pentagonal ring tend to be larger than the regular tetrahedral value. These results also support the existence of the intramolecular H-bond in the C_5-conformation.

The IR and ^{1}H-NMR spectra of the homopeptides containing (*S*)-Beg resemble those of the homopeptides containing Deg [4b,c,f]. Especially, the effects on the NH

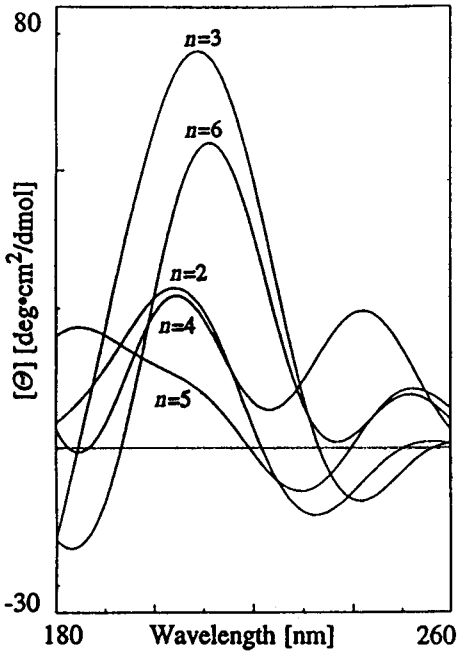


Fig. 5. *CD Spectra of homopeptides CF_3CO-[(S)-Beg]$_n$-OEt* **4**–**8** ($n = 2-6$) *in CF_3CH_2OH solution.* Peptide concentration 1.0 mM.

^{1}H-NMR signals of hexapeptide **8** observed on addition of DMSO and/or TEMPO are very similar to those observed in the case of $CF_3CO-(Deg)_6-OEt$, which showed the planar C_5-conformation in solution; on the contrary, they are very different from those observed in the case of $CF_3CO-(Aib)_6-OEt$, which was used as a standard for the 3_{10}-helical conformation. Furthermore, the characteristic bands for 3_{10}- and/or α-helical structures could not be observed in the CD spectra of **4**–**8**. On the basis of these results, and the fact that the dominant conformation of the homopeptides prepared from Deg was a fully planar C_5-conformation in solution, we judge that the largely populated structure of the (*S*)-Beg homopeptides is also a fully planar C_5-conformation in solution.

Conclusion. – The preferred conformation of the homopeptides prepared from the α-ethylated α,α-disubstituted amino acid (*S*)-**2** is not a 3_{10}-helical structure but a fully extended planar C_5-conformation, both in the solid state and in solution, while the preferred conformation of the homopeptides prepared from the chiral α-methylated α,α-disubstituted amino acids is the 3_{10}-helical structure, and the absolute configuration of a chiral quaternary C-atom would control the screw sense of the helix [8b]. The C(γ) atom of the ethyl side chain would strongly affect the propensity of the α,α-disubstituted amino acids. Although it has already been reported that the homopeptides prepared from the achiral Deg preferred the fully planar C_5-conformations in solution, the results described here show for the first time that also a chiral α-ethylated

α,α-disubstituted amino acid prefers the fully planar C_5-conformation. We have already reported that the employment of an ethyl ester as the C-terminal protecting group of the Deg homopeptides leads preferentially to 3_{10}-helical structures rather than to the planar C_5-structures in the solid state [4f]. This result suggests that the propensity for the planar C_5-conformation in homopeptides built from (*S*)-Beg is stronger than in those built from Deg. The availability of chiral α-ethylated α,α-disubstituted amino acids opens the way to a new method to construct rigid peptide conformations, which would be different from those obtained from α-methylated α,α-disubstituted amino acids, and could introduce chirality in planar extended peptide conformations.

Experimental Part

General. General procedures used for syntheses were followed as described in previous reports [4f][8i]. CC = column chromatography. $[\alpha]_D$: *Jasco DIP-316* polarimeter, 1.0-dm cell. CD Spectra: *Jasco J-720W* spectropolarimeter, 10.0-mm path length cell. IR Spectra: *Jasco A-100* spectrometer for conventional measurements (KBr and neat) and *Jasco FT-IR 420* spectrophotometer for $CDCl_3$ solns. (0.1-mm path length, NaCl cell); in cm^{-1}. ^{1}H-NMR Spectra: at 270 (*Jeol GX-270*) or 500 MHz (*Varian Unity-500P*); δ in ppm, *J* in Hz. EI- and FAB-MS: *Jeol JMS-610 H* or *Jeol JMS-SX-102* spectrometer. Elemental analyses were performed in the Analytical Center of the Faculty of Science at Kyushu University.

Ethyl rac-*2-Butyl-2-ethylglycinate* (= *Ethyl* rac-*2-Amino-2-ethylhexanoate*; Beg-OEt; *rac*-**2**). A mixture of heptan-3-one (10 g, 87.5 mmol), KCN (5.7 g, 86.5 mmol), and NH_4Cl (9.36 g, 87.5 mmol) in H_2O (25 ml) and EtOH (3 ml) was heated at 55–60° for 2 days and then cooled to r.t. The mixture was extracted with Et_2O, the extract dried ($MgSO_4$) and evaporated; the residue dissolved in conc. HCl (30 ml), and the mixture refluxed for 24 h. After evaporation, the mixture of the residue and conc. H_2SO_4 soln. (3 ml) in EtOH (50 ml) was refluxed overnight and then diluted with 5% aq. $NaHCO_3$ soln. The EtOH was evaporated, the aq. phase extracted with $CHCl_3$, the extract dried ($MgSO_4$) and evaporated, and the colorless oil purified by distillation at 95°/15 Torr: *rac*-**2** (4.63 g, 28%). Colorless oil. IR (neat): 3390 (br.), 1730. ^{1}H-NMR (270 MHz, $CDCl_3$): 4.17 (*q*, *J* = 7.1, 2 H); 1.71 (br. *s*, 2 H); 1.70–1.86 (*m*, 2 H); 1.46–1.62 (*m*, 2 H); 1.04–1.42 (*m*, 4 H); 1.27 (*t*, *J* = 7.1, 3 H); 0.89 (*t*, *J* = 7.1, 3 H); 0.85 (*t*, *J* = 7.4, 3 H). FAB-MS: 188.3 ($[M+H]^+$).

*Ethyl (*S*)-2-Butyl-2-ethylglycinate* ((*S*)-Beg-OEt; (*S*)-**2**). A suspension of *rac*-**2** (26.4 g, 141 mmol) and porcine liver esterase (PLE; 6.5 ml, 21 mg prot./ml) in phosphate buffer (pH 8.0, 2.50 l) was stirred at 30° for 7.5 h. The soln. was extracted with Et_2O and the extract dried ($MgSO_4$) and evaporated: (*S*)-**2** (8.16 g, 31%). Colorless oil. $[\alpha]_D^{26} = +6.41$ (*c* = 2.24, $CHCl_3$); >99% ee by HPLC (*Chiralpak AD*, hexane/^{i}PrOH 99:1, flow rate 0.5 ml/min, RI detection), with *rac*-**2** as a reference standard.

*(*S*)-2-Butyl-2-ethyl-*N*-(trifluoroacetyl)glycine* (=*(2*S*)-2-Ethyl-2-[(trifluoroacetyl)amino]hexanoic Acid*; CF_3CO-(*S*)-Beg; **3**). A suspension of (*S*)-**2** (1.0 g, 5.35 mmol) and NaOH (500 mg, 12.5 mmol) in H_2O (10 ml) was stirred at r.t. for 16 h and then at 60° for 5 h. The soln. was neutralized with 10% HCl soln. and then evaporated. The residue was dissolved in $(CF_3CO)_2O$ (5 ml) and left standing for 5 days. The soln. was neutralized with 5% aq. $NaHCO_3$ soln. and washed with Et_2O. The aq. soln. was acidified with citric acid and extracted with $CHCl_3$ and the extract dried ($MgSO_4$) and evaporated: crude **3** (970 mg, 71%), which was used in the next step without purification. Colorless solid. M.p. 48–49°. IR (KBr): 3350, 3100 (br.), 1710. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.23 (br. *s*, 1 H); 2.44–2.59 (*m*, 2 H); 1.81–2.00 (*m*, 2 H); 0.99–1.40 (*m*, 4 H); 0.89 (*t*, *J* = 7.1, 3 H); 0.83 (*t*, *J* = 7.6, 3 H). FAB-MS: 256.2 ($[M+H]^+$). $[\alpha]_D^{25} = +24.1$ (*c* = 1.01, $CHCl_3$). Anal. calc. for $C_{10}H_{16}F_3NO_3$: C 47.06, H 6.32, N 5.49; found: C 47.37, H 6.34, N 5.48.

*Ethyl Trifluoroacetyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycinate* (CF_3CO-[(*S*)-Beg]$_2$-OEt; **4**). A mixture of **3** (300 mg, 1.18 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 271 mg, 1.42 mmol) in MeCN (10 ml) was stirred at r.t. for 2 h. Amino ester (*S*)-**2** (262 mg, 1.42 mmol) was added to the soln., and the mixture was refluxed for 16 h. After evaporation, the residue was diluted with $CHCl_3$, the soln. washed with 3% HCl soln., 5% aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and evaporated, and the residue purified by CC (silica gel, 4% AcOEt/hexane): **4** (460 mg, 92%). Colorless crystals. M.p. 87–88° (from MeOH). $[\alpha]_D^{21} = +18.6$ (*c* = 1.05, $CHCl_3$). IR ($CHCl_3$): 3400, 3340, 1730, 1670. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.97 (br. *s*, 1 H); 6.81 (br. *s*, , 1 H); 4.28 (*q*, *J* = 7.1, 2 H); 2.59–2.72 (*m*, 2 H); 2.36–2.54 (*m*, 2 H); 1.32 (*t*, *J* = 7.1, 3 H); 1.54–1.89 (*m*, 4 H); 0.71–1.38 (*m*, 20 H). FAB-MS: 425.0 ($[M+H]^+$). Anal. calc. for $C_{20}H_{35}F_3N_2O_4$: C 56.59, H 8.31, N 6.60; found: C 56.61, H 8.32, N 6.58.

*Ethyl Trifluoroacetyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycinate* (CF_3CO-[(*S*)-Beg]$_3$-OEt; **5**). $NaBH_4$ (600 mg, 15.9 mmol) was added to the stirred soln. of **4** (1.00 g, 2.36 mmol) in EtOH (30 ml), and the mixture was refluxed for 40 h. After dilution with H_2O (50 ml), the EtOH was evaporated. The aq. soln. was acidified with 5% HCl soln. to destroy the excess of reagent. Then the soln. was neutralized with 5% aq. $NaHCO_3$ soln. and extracted with $CHCl_3$, the extract dried ($MgSO_4$) and evaporated, and the residue purified by CC (silica gel): amino ester (317 mg, 89% based on 54% recovery of **4**). A mixture of this amino ester (317 mg, 966 μmol), acid **3** (370 mg, 1.45 mmol), and EDC (370 mg, 1.93 mmol) in MeCN (15 ml) was refluxed for 36 h. After evaporation, the residue was diluted with $CHCl_3$, the soln. washed with 3% HCl soln., 5% aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and evaporated, and the residue purified by CC (silica gel, 5% AcOEt/hexane): **5** (387 mg, 71%). Colorless crystals. M.p. 98–99° (from EtOH). $[\alpha]_D^{21} = +21.0$, ($c = 1.02$, $CHCl_3$). IR ($CHCl_3$): 3680, 3620, 3400, 3340, 1720, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.01 (br. *s*, 1 H); 7.40 (br. *s*, 1 H); 6.78 (br. *s*, 1 H); 4.27 (*q*, $J = 7.1$, 2 H); 2.56–2.70 (*m*, 4 H); 2.34–2.49 (*m*, 2 H); 1.50–1.87 (*m*, 6 H); 1.32 (*t*, $J = 7.1$, 3 H); 0.72–1.34 (*m*, 30 H). FAB-MS: 567.6 ($[M+H]^+$). Anal. calc. for $C_{28}H_{50}F_3N_3O_5$: C 59.45, H 8.91, N 7.43; found: C 59.58, H 8.90, N 7.23.

*Ethyl Trifluoroacetyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycinate* (CF_3CO-[(*S*)-Beg]$_4$-OEt; **6**). As described for **5**, from **3** and **5**. Purification by CC (silica gel, 10% AcOEt/hexane) afforded **6** (81%). Colorless crystals. M.p. 182–183° (from MeOH). $[\alpha]_D^{23} = +25.8$ ($c = 1.15$, $CHCl_3$). IR ($CHCl_3$): 3670, 3610, 3320, 1715, 1660, 1640. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.03 (br. *s*, 1 H); 7.44 (br. *s*, 1 H); 7.37 (br. *s*, 1 H); 6.78 (br. *s*, 1 H); 4.27 (*q*, $J = 7.1$, 2 H); 2.55–2.70 (*m*, 6 H); 2.35–2.49 (*m*, 2 H); 1.54–1.86 (*m*, 8 H); 1.32 (*t*, $J = 7.1$, 3 H); 0.72–1.27 (*m*, 40 H). FAB-MS: 707.8 ($[M+H]^+$). Anal. calc. for $C_{36}H_{65}F_3N_4O_6$: C 61.17, H 9.27, N 7.93; found: C 61.11, H 9.27, N 7.86.

*Ethyl Trifluoroacetyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycinate* (CF_3CO-[(*S*)-Beg]$_5$-OEt; **7**). As described for **5**, from **3** and **6**. Purification by CC (silica gel, 15% AcOEt/hexane) afforded **7** (71%). Colorless crystals. M.p. 226–227° (from MeOH). $[\alpha]_D^{22} = +24.3$ ($c = 1.03$, $CHCl_3$). IR ($CHCl_3$): 3400, 3350, 1720, 1670, 1650. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.04 (br. *s*, 1 H); 7.46 (br. *s*, 1 H); 7.41 (br. *s*, 1 H); 7.37 (br. *s*, 1 H); 6.78 (br. *s*, 1 H); 4.27 (*q*, $J = 7.1$, 2 H); 2.35–2.68 (*m*, 10 H); 1.53–1.87 (*m*, 10 H); 0.91–1.37 (*m*, 20 H); 1.32 (*t*, $J = 7.1$, 3 H); 0.72–0.88 (*m*, 30 H). FAB-MS: 848.9 ($[M+H]^+$). Anal. calc. for $C_{44}H_{80}F_3N_5O_7$: C 62.31, H 9.51, N 8.26; found: C 62.35, H 9.53, N 8.21.

*Ethyl Trifluoroacetyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycyl-(*S*)-2-butyl-2-ethylglycinate* (CF_3CO-[(*S*)-Beg]$_6$-OEt; **8**). As described for **5**, from **3** and **7**. Purification by CC (silica gel, 30% AcOEt/hexane) afforded **8** (52%). Colorless crystals. M.p. 252–253° (from MeOH). $[\alpha]_D^{22} = +23.7$ ($c = 1.21$, $CHCl_3$). IR ($CHCl_3$): 3690, 3630, 3350, 1720, 1650. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.03 (br. *s*, 1 H); 7.46 (br. *s*, 1 H); 7.43 (br. *s*, 1 H); 7.41 (br. *s*, 1 H); 7.37 (br. *s*, 1 H); 6.78 (br. *s*, 1 H); 4.27 (*q*, $J = 7.1$, 2 H); 2.36–2.69 (*m*, 12 H); 1.52–1.86 (*m*, 12 H); 1.32 (*t*, $J = 7.1$, 3 H); 0.72–1.39 (*m*, 60 H). FAB-MS: 990.3 ($[M+H]^+$). Anal. calc. for $C_{52}H_{95}F_3N_6O_8$: C 63.13, H 9.68, N 8.49; found: C 63.08, H 9.60, N 8.37.

X-Ray Diffraction. Crystals were grown from EtOH in the case of tripeptide **5** and from MeOH in the case of tetrapeptide **6**. Data collection was performed on a *Rigaku-AFC5R* diffractometer, with Ni-foil-filtered CuK_α radiation. Crystal and collection parameters are listed in *Table 4*. The two crystals remained stable at r.t. during the data collection. The structures were solved by direct methods using SIR92 [14] and expanded by *Fourier* techniques [15]. All non-H-atoms were given anisotropic thermal parameters, and H-atoms included in calculated positions were given isotropic thermal parameters. The final cycle of full-matrix least-squares refinement of tripeptide **5** gave a conventional *R* factor of 0.064 ($R_w = 0.060$) based on 1444 ($I > 3.0\ \sigma(I)$) reflections, and the largest peak and hole in the final difference *Fourier* map were 0.15 and -0.22 eÅ^{-3}. The *R* factor of tetrapeptide **6** was 0.0645 ($R_w = 0.0447$) for 1739 data ($I > 2.0\ \sigma(I)$), and the largest peak and hole in the final difference *Fourier* map were 0.13 and -0.17 eÅ^{-3}. All calculations were performed using the teXsan [16] crystallographic package of *Molecular Structure Corporation*.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-139659 and -139660. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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Table 4. *Crystallographic Data of Homopeptides CF_3CO-[(S)-Beg]$_3$-OEt* (**5**) *and CF_3CO-[(S)-Beg]$_4$-OEt* (**6**)

	5	**6**
Solvent of crystallization	EtOH	MeOH
Empirical formula	$C_{28}H_{50}O_5N_3F_3$	$C_{36}H_{65}O_6N_4F_3$
M_r	565.72	706.93
Crystal dimensions [mm]	$0.30 \times 0.10 \times 0.10$	$0.30 \times 0.20 \times 0.10$
Crystal system	orthorhombic	monoclinic
Lattice parameters:		
a, b, c [Å]	13.453, 23.417, 11.011	6.872, 36.822, 8.549
α, β, γ [°]	90, 90, 90	90, 97.91, 90
V [Å^3]	3468.8	2142
Space group	$P2_12_12_1$	$P2_1$
Z value	4	2
D_{calc} [g/cm^3]	1.083	1.096
$\mu(CuK_\alpha)$ [cm^{-1}]	7.03	6.82
No. of observations	1444 ($I > 3.0\sigma(I)$)	1739 ($I > 2.0\ \sigma(I)$)
No. of variables	359	443
R, R_w	0.064, 0.060	0.065, 0.045

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