Helical *versus* Planar Conformation of Homooligopeptides Prepared from Diethylglycine (= 2-Amino-2-ethylbutanoic Acid)

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Homooligopeptides containing α,α-diethylgycine (= 2-amino-2-ethylbutanoic acid), were synthesized by conventional solution methods. An ethyl or methyl ester was used as protecting group at the C-terminus and a trifluoroacetyl group as protecting group at the N-terminus of the peptides. The conformations of such tri-, penta-, and hexapeptides in the solid state were studied using X-ray crystallographic analysis, and were shown to be a bent planar *C*5-conformation in the case of tripeptide **8a**, and a 3_{10}-helical structure in the case of pentapeptide **10** and hexapeptide **11**. IR and ^{1}H-NMR spectra revealed that the dominant conformation of hexapeptide **11** in $CDCl_3$ solution was not the 3_{10}-helical structure shown in the solid state, but a fully planar *C*5 structure.

Introduction. – Non-proteinogenic modified amino acids and their peptides have become some of the most important areas of research in the fields of organic chemistry, medicinal chemistry, and protein engineering [1]. The introduction of alkyl substituents into the α-position of an α-amino acid (α,α-disubstituted amino acids) is a popular modification method of α-amino acids. The α-alkyl substituents in α,α-disubstituted amino acids severely restrict the conformational freedom of peptides containing such residues. Therefore, these peptides offer a means to investigate the factors which determine the flexibility of a peptide and to construct a stable secondary structure. The introduction of α,α-disubstituted amino acids may also provide a way of probing the bioactive conformation of bioactive peptides. The findings that α-aminoisobutyric acid (= α-methylalanine = dimethylglycine; Aib) and isovaline have been isolated from microorganisms as the peptaibol antibiotics [2] have stimulated peptide chemists to synthesize new peptides containing α,α-disubstituted amino acids and to analyze the conformation of the peptides. The conformational studies of α,α-disubstituted amino acids and their peptides concentrated on the peptide-bearing Aib because of its simple molecular structure [3][4]. It is already known that Aib strongly stabilizes conformation near the $3_{10}/\alpha$-helical region ($\varphi \pm 60°$, $\psi \pm 30°$). The propensity for helical conformation has made achiral Aib a tool for the construction of a helical secondary structure in the *de novo* design of proteins. Besides Aib, few properties of other achiral α,α-disubstituted amino acids are known. Homopeptides constructed from diethylglycine (= 2-amino-2-ethylbutanoic acid; Deg) [4][5] or dipropylglycine [4][5][6] adopt a planar, fully extended *C*5 conformation (*i.e.*, N(i)–H and C(i)=O are involved in a pentagonal ring, together with Cα(i)) [5], and homopeptides prepared from cyclic α,α-disubstituted amino acids adopt regular 3_{10}-helical (1-aminocyclobutanecarboxylic acid [7], 1-aminocyclopentanecarboxylic acid [8], and 1-aminocyclohexanecarboxylic acid [9]) and distorted 3_{10}-helical structures (1-aminocyclopropanecarboxylic acid [10])

(*Fig. 1*). Very recently, *Seebach* and co-workers (including one of us) [11] found that the C-terminal and N-terminal protecting groups of homopeptides constructed from isovaline strongly affect their conformations in the solid state [11]. This finding prompted us to study the conformation of the homopeptides prepared from Deg because the computer analysis of their conformation showed almost equal energy difference between the 3_{10}-helical and planar (*C*5) conformations [5]. The 3_{10}-helical conformation of heteropeptides containing dipropylglycine and dibutylglycine were described [6], but only the planar conformation of the homopeptides prepared from Deg was reported [5][12].

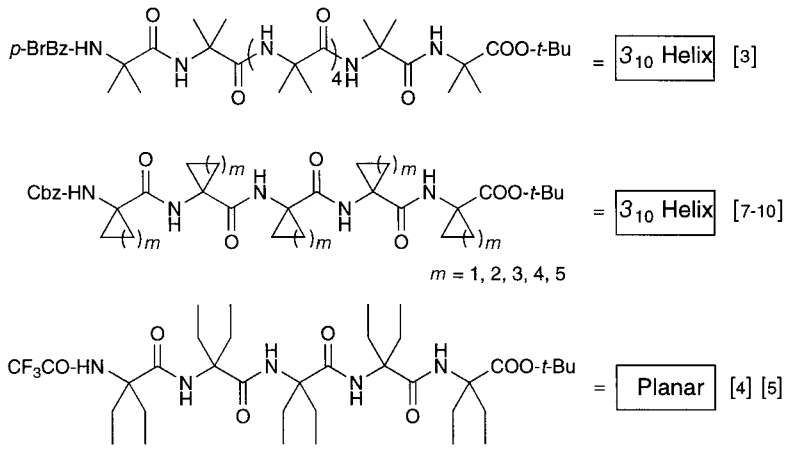
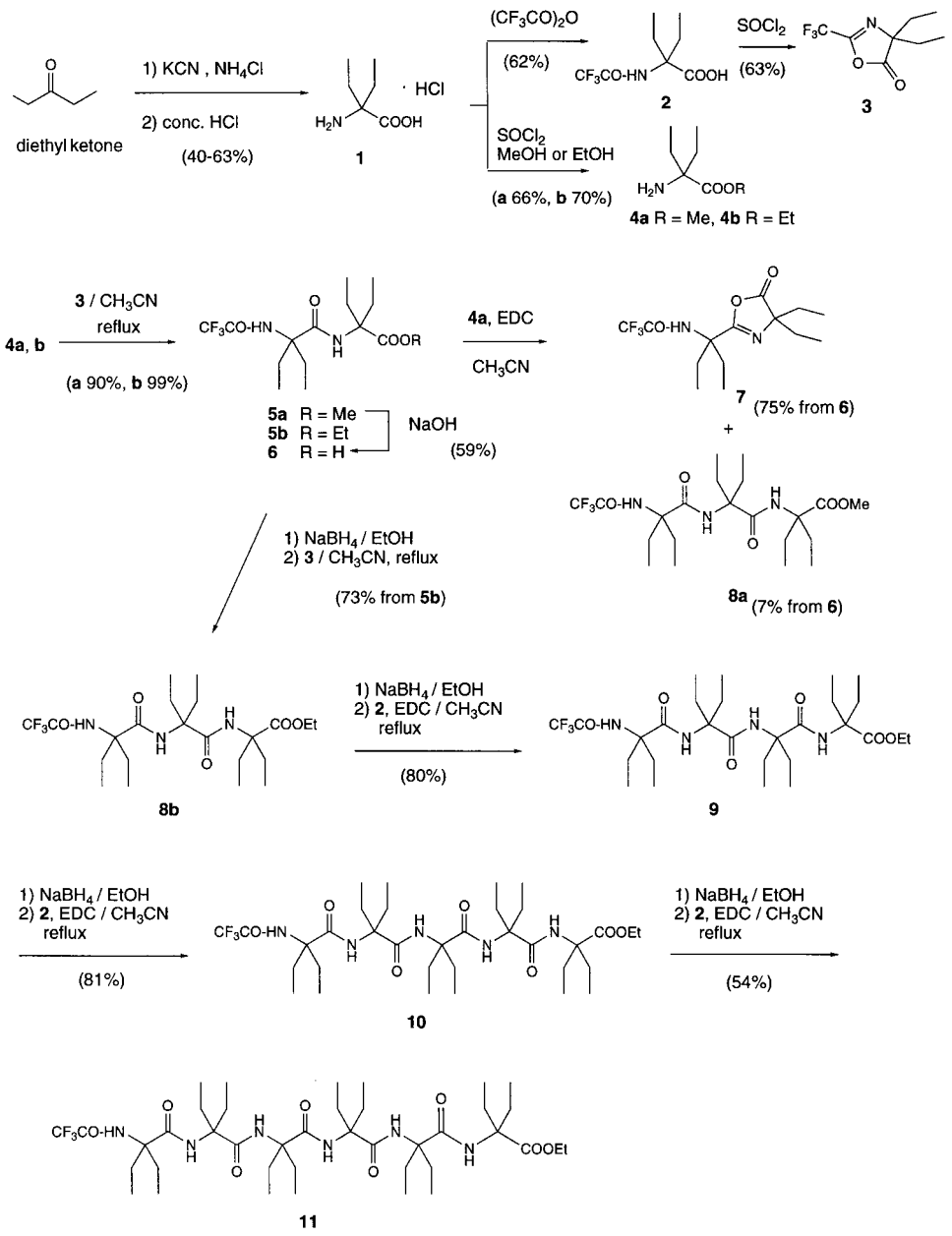


Fig. 1. *Crystal-state conformations of homopeptides prepared from α,α-disubstituted amino acids*

Results. – *Synthesis of Diethylglycine and of Its Homopeptides.* Diethylglycine hydrochloride was prepared from diethyl ketone on the gram scale by treatment with KCN and NH_4Cl and subsequent hydrolysis of the nitrile by using concentrated aqueous HCl solution, according to *Pfister*'s methods [13] (*Scheme*).

At first, the trifluoroacetyl group was employed for N-terminal and the methyl ester for C-terminal protection, and the preparation of the homopeptide was attempted from the N-terminus of peptide by solution-phase methods. Thus, dipeptide **5a** was synthesized by the coupling of oxazol-5(4*H*)-one **3** and amine **4a** in 90% yield (*Scheme*). After saponification of the methyl ester of **5a** by NaOH, acid **6** was coupled with amine **4a** using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) *via* an oxazol-5(4*H*)-one intermediate **7**; unfortunately, the isolated yield of tripeptide **8a** was very low (7%). Therefore, we decided to prepare the homopeptide from the C-terminus, employing an ethyl ester as the C-terminal protection, and achieving the deprotection of the trifluoroacetyl group by $NaBH_4$ reduction in refluxing EtOH. Thus, dipeptide **5b** was prepared in 99% yield by coupling oxazol-5(4*H*)-one **3** and amine **4b**. Subsequent deprotection of the trifluoroacetyl function with $NaBH_4$, followed by coupling with oxazol-5(4*H*)-one **3**, yielded tripeptide **8b** in 73% yield. The tetra-, penta-, and hexapeptides **9**–**11** were synthesized similarly to **8b**, except that **3** was prepared *in situ* from EDC and the acid **2** (*Scheme*).

Scheme



Solid-State Conformational Analysis. We determined the molecular and crystal structures of the three terminally blocked homopeptides **8a**, **10**, and **11** by X-ray diffraction. Good crystals for X-ray analysis were obtained by slow evaporation of MeOH at room temperature, except for tetrapeptide **9**. The molecular structures with

atomic numbering schemes are shown in *Figs. 2–6*. Relevant backbone and side-chain torsion angles are given in *Table 1*. The intra- and intermolecular H-bond parameters are listed in *Table 2*. Each molecule bearing no chiral centers crystallizes in space groups where centers of symmetry are present.

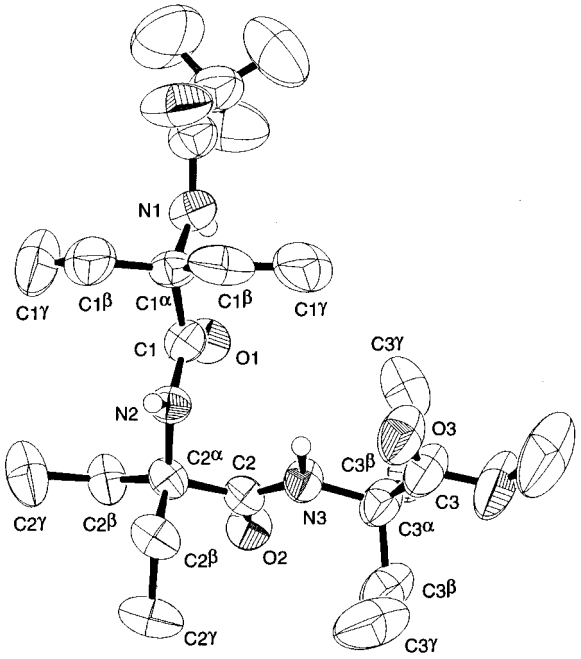


Fig. 2. *ORTEP Drawing of the crystal structure of tripeptide* **8a** *with atom numbering* (ellipsoids at 50% probalility)

In the case of tripeptide **8a**, two intramolecular H-bonds are observed in the residue Deg-1 and Deg-3. This indicates that intramolecularly H-bonded C_5 conformations of Deg-1 and Deg-3 are formed in the solid state. The set of ϕ/ψ angles for the amino-acid residues are $-178.1/+180.0°$ for Deg-1 and $+178.4/-178.5°$ for Deg-3. In the packing mode, one intermolecular H-bond is seen between the H–N(2) peptide donor and the C(2)=O(2) carbonyl O-atom of the peptide of a symmetry-related molecule $(-x+3/2, y+1/2, -z+1/2)$, with a N(2)···O(2) distance of 2.97 Å. The set of ϕ/ψ angles for Deg-2 is $+59.6/+44.5°$. The molecules of both handedness simultaneously occur in the centrosymmetric space group $P2_1/n$ (No. 14). The chains of H-bonded peptide molecules are formed along the *b* direction in the crystal.

The structure of pentapeptide **10** was solved in the $P\bar{1}$ (No. 2) space group. Two independent molecules occur in the asymmetric unit of the pentapeptide. Both molecules *A* and *B* are folded in the 3_{10}-helical structure. The molecules have almost the same structures, but they are crystallographically independent molecules, and small differences in the conformations are observed, as shown in *Table 1*. The enantiomers of the molecules also exist in the crystal because the centers of symmetry are present in the space group of $P\bar{1}$ (No. 2). In molecule *A*, three intramolecular H-bonds are seen,

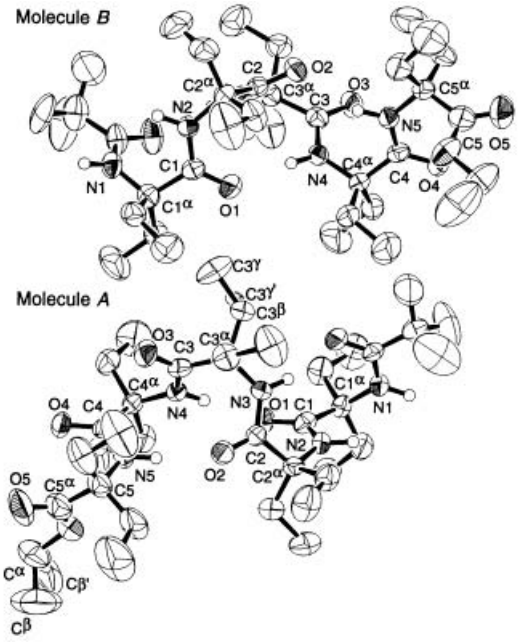


Fig. 3. *ORTEP Drawing of the two independent molecules* **A** *and* **B** *in the asymmetric unit of pentapeptide* **10** *with atom numbering, as viewed perpendicularly to the helix axis* (ellipsoids at 50% probability). Only one conformation for the CF_3 functions in the molecule **A** and **B** is displayed. The disorders of C-atoms C(β) and C(β'), and C(3γ) and C($3\gamma'$) in the molecule **A** are shown.

between H–N(3) and the C(0)=O(0) carbonyl O-atom of the trifluoroacetyl group with a N(3)···O(0) distance of 3.05 Å, between H–N(4) and C(1)=O(1) with a N(4)···O(1) distance of 3.15 Å, and between H–N(5) and C(2)=O(2) with the N(5)···O(2) distance of 2.97 Å. Similarly, three intramolecular H-bonds are also observed in molecule *B*, between H–N(3) and C(0)=O(0) with N(3)···O(0) distance of 3.02 Å, between H–N(4) and C(1)=O(1) with a N(4)···O(1) distance of 3.11 Å, and between H–N(5) and C(2)=O(2) with a N(5)···O(2) distance of 3.07 Å. The mean values of torsion angles ϕ and ψ for the sequence Deg-1 to Deg-4 in molecule *A* are -53.5 and $-31.0°$, respectively. The signs of the ϕ and ψ torsion angles ($+43.2$ and $+52.8°$ resp.) of the Deg-5 residue at the C-terminus are opposite to those of the preceding residues Deg-1 to Deg-4. This structure is widely observed in the structure of the homopeptide prepared from Aib, and is known as the 3_{10}-helix-terminating structure. The mean ϕ and ψ values for the sequence Deg-1 to Deg-4 in molecule *B* are -53.3 and $-31.2°$, respectively. The signs of the ϕ and ψ angles ($+42.0$ and $+52.0°$, resp.) at the C-terminus in the molecule *B* are also opposite to those of the preceding residues. In the packing mode of pentapeptide **10**, the intermolecular H-bond is observed in molecule *A* between the H–N(1) peptide donor and the C(4)=O(4) carbonyl O-atom of a symmetry-related molecule (x, y, $z+1$) with a N(1)···O(4) distance of 2.77 Å along the *c* direction. An intermolecular H-bond is also observed in molecule *B* between the H–N(1) donor and the C(4)=O(4) acceptor of a symmetry-related molecule (x, y, $z-1$) with a N(1)···O(4) distance of 2.82 Å. The chains of

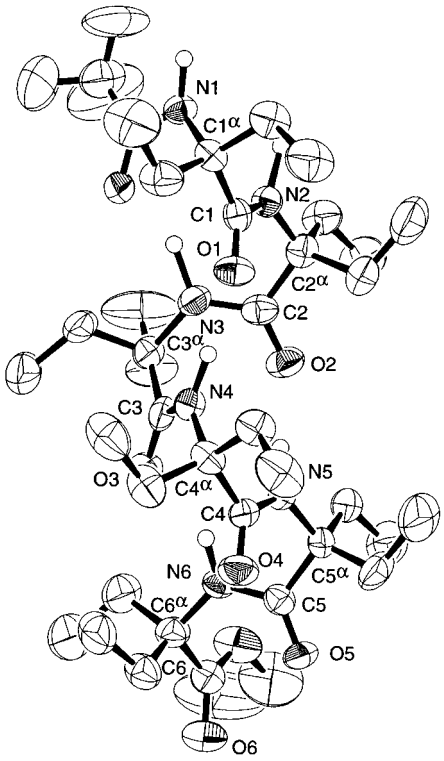


Fig. 4. *ORTEP Drawing of the crystal structure of hexapeptide* **11** *with atom numbering, as viewed perpendicularly to the helix axis* (ellipsoids at 50% proability).

intermolecularly H-bonded molecules are formed in a head-to-tail alignment of right-handed (*P*) 3_{10}-helical molecule *A* and left-handed (*M*) 3_{10}-helical molecule *A*, that is (...*P*...*P*...*P*... and ...*M*...*M*...*M*...) chains of the molecule *A* [14]. Also, the chains of right-handed (*P*) 3_{10}-helical molecule *B* and left-handed (*M*) 3_{10}-helical molecule *B* are in a head-to-tail alignment, that is (...*P*...*P*...*P*... and ...*M* ...*M*...*M*...) chains of the molecule *B*, are formed. The N⋯O distances observed for intermolecular H-bonds are shorter than those of intramolecular ones.

Hexapeptide **11** crystallizes in the $P2_1/n$ (No. 14) space group. Only one molecule exists in the asymmetric unit of the hexapeptide. The center of symmetry exists in this space group; therefore, both the right-handed (*P*) and the left-handed (*M*) 3_{10}-helical structures occur simultaneously in the crystal. Four intramolecular H-bonds are observed, between H−N(3) peptide donor and the C(0)=O(0) carbonyl O-atom of the trifluoroacetyl group at the N-terminus with a N(3)⋯O(0) distance of 2.94 Å, between H−N(4) and C(1)=O(1) with a N(4)⋯O(1) distance of 3.07 Å, between H−N(5) and C(2)=O(2) with a N(5)⋯O(2) distance of 2.96 Å, and between H−N(6) and C(3)=O(3) with a N(6)⋯O(3) distance of 2.94 Å. The mean values of torsion angles ϕ and ψ for the sequence Deg-1 to Deg-5 in the hexapeptide are +51.9 and +32.9°, respectively, as shown in *Fig. 4*, close to those expected for a left-handed

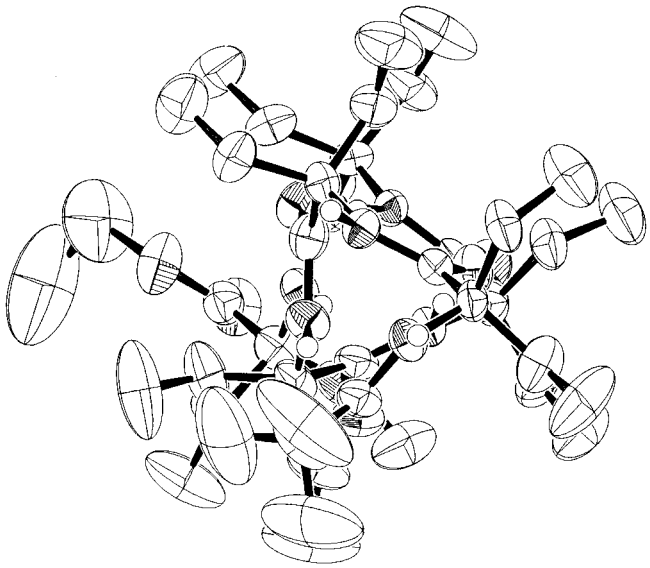


Fig. 5. *ORTEP Drawing of* **11** *as viewed along the helix axis* (ellipsoids at 50% probability)

3_{10}-helix (+57 and +30° resp.). *Fig. 4* shows only a left-handed 3_{10}-helical structure, but the enantiomer (average ϕ and ψ value $= -51.9$ and $-32.9°$, resp.) of the molecule exists in the crystal. The ϕ and ψ torsion angles (-47.6 and $-53.1°$, resp.) for Deg-6 at the C-terminus have opposite signs to those of the preceding Deg-1 to Deg-5 residues, corresponding to a change in the handedness of the helix. The right-handed (*P*) 3_{10}-helical molecules are connected with the left-handed (*M*) 3_{10}-helical molecules in a head-to-tail alignment, *via* intermolecular H-bonds. One is a H-bond between the H–N(1) peptide donor and the C(5)=O(5) carbonyl O-atom acceptor of a symmetry-related molecule ($x+1/2, -y+1, z+1/2$) with a N(1)···O(5) distance of 2.88 Å, and the other is a weak H-bond between the H–N(2) donor and the C(6)=O(6) acceptor of a symmetry-related molecule ($x+1/2, -y+1, z+1/2$) with a N(2)···O(6) distance of 3.19 Å as shown in *Fig. 6*. That is to say, the chains of intermolecular H-bonded molecules are of the (...*M*...*P*...*M*...*P*...) mode. The crystals of **11**, recrystallized from $CDCl_3$ or CH_2Cl_2/MeOH, also gave the same diffraction parameters (*Table 3*).

Solution Conformational Analysis. The conformational preferences of di- to hexapeptides **5a**, **8b**, **9**, **10**, and **11** were examined in a solvent of low polarity ($CDCl_3$) by using FT-IR absorptions at various concentrations in the range of 5.0–0.5 mM. 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 planar *C*5 conformation, whereas the NH groups of the Deg-1 and Deg-2 residues are free in the case of a 3_{10}-helical conformation. *Fig. 7* shows the IR absorption in the 3500–3300 cm^{-1} region at a peptide concentration of 1.0 mM. The bands at 3435–3450 cm^{-1} are assigned to free (solvated) peptide NH groups or to amide NH groups with a weak intramolecular H-bond of the C–F···H–N type, those at 3390–3400 cm^{-1} to amide NH groups with a relatively stronger C–F···H(N)···O=C intramolecular H-bond,

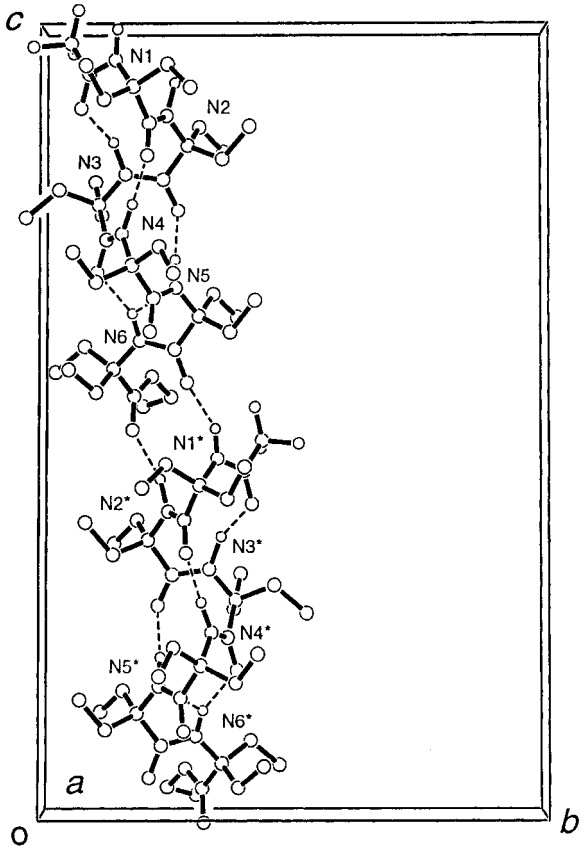


Fig. 6. *View of the crystal structure of* **11**. The four intramolecular and two intermolecular H-bonds are indicated as dashed lines. Head-to-tail H-bonding in hexpaptide **11** is shown.

and those at 3340 – 3360 cm^{-1} to peptide NH groups with N–H ··· O=C intramolecular H-bonds of different strength. The strong absorption at 3340 cm^{-1} of the dipeptide shifts to slightly higher wavenumbers (3360 cm^{-1}), and also the relative intensity of this absorption band increases gradually with increasing chain length. In the concentration range examined (5.0 – 0.5 mM), the IR absorption spectra of the hexapeptide **11** remain essentially unchanged.

To obtain more detailed information on the conformation of the homopeptides in $CDCl_3$ solution, ^{1}H-NMR techniques were applied especially to the hexapeptide **11**. In the ^{1}H-NMR spectrum of **11** in $CDCl_3$ at room temperature, the CF_3CO–N*H* signal at the N-terminus was unambiguously identified by its high-field position (δ 6.77 (br. *s*, 1 H)) [12], and the amide NH signal at the C-terminus (δ 8.00 (br. *s*, 1 H)) by analogy with the C-terminal NH signal of dipeptide **5b** (δ 7.96 (br. *s*, 1 H)). The precise assignments of the remaining internal four NH protons (Deg-2 to Deg-5) of **11** could not be made. The chemical shifts of all NH protons in hexapeptide **11** were essentially independent of the concentration in the examined range of 1.0 – 50 mM. The ^{1}H,^{1}H-

Table 1. *Selected Torsion Angles* [°] *for the Homopeptides* **8a, 10,** *and* **11**

Torsion angle	CF_3CO-(Deg)$_3$-OMe (**8a**)	CF_3CO-(Deg)$_5$-OEt (**10**)		CF_3CO-(Deg)$_6$-OEt (**11**)
		Molecule **A**	Molecule **B**	
ω_0	– 179.5	– 171.0	– 173.9	174.2
ϕ_1	– 178.1	– 53.0	– 55.5	52.5
ψ_1	180.0	– 40.8	– 36.5	40.8
ω_1	170.3	– 173.2	– 176.5	171.7
ϕ_2	59.6	– 55.6	– 55.7	57.4
ψ_2	44.5	– 20.9	– 18.7	22.0
ω_2	169.5	179.9	174.9	179.3
ϕ_3	178.4	– 52.7	– 46.1	52.4
ψ_3	– 178.5	– 25.3	– 35.3	27.4
ω_3	177.9	179.7	– 172.9	– 177.8
ϕ_4	–	– 52.5	– 55.7	45.9
ψ_4	–	– 36.9	– 34.4	33.9
ω_4	–	– 174.9	– 173.6	178.1
ϕ_5	–	43.2	42.0	51.5
ψ_5	–	52.8	52.0	40.5
ω_5	–	174.8	178.0	180.0
ϕ_6	–	–	–	– 47.6
ψ_6	–	–	–	– 53.1
ω_6	–	–	–	– 175.9
χ_1^1	56.5	180.0	– 178.3	– 179.0
χ_1^2	– 54.5	60.7	59.3	– 58.8
χ_2^1	– 66.0	– 178.4	62.0	– 57.6
χ_2^2	179.4	58.0	57.2	177.2
χ_3^1	– 64.9	58.9	62.8	– 55.9
χ_3^2	58.6	176.8 [a]	178.6	– 179.5
χ_4^1	–	62.5	57.6	177.6
χ_4^2	–	– 178.0	– 179.4	– 59.7
χ_5^1	–	– 62.6	– 63.7	– 178.3
χ_5^2	–	– 175.3	– 177.4	– 55.0
χ_6^1	–	–	–	177.4
χ_6^2	–	–	–	67.7

[a]) The C(γ)-atoms were disordered over two sites with occupancy factor 0.58 (χ_3^2 176.8) and 0.42 (χ_3^2 76.2), resp.

NOESY experiment of **11**, performed at room temperature, did not show any correlation among the amide NH signals; this correlation would be present in the case of a 3_{10}-helical conformation. The additional effects of the strong H-bonding acceptor solvent DMSO or the paramagnetic free radical 2,2,6,6-tetramethyl-1-piperidyloxyl (TEMPO) on the chemical shifts of NH signals were measured for the hexapaptide **11**, but the NH signals were almost insensitive to the addition of the two perturbing agents DMSO (0–10% (*v*/*v*)) and TEMPO ($0-5\cdot10^{-2}$% (*w*/*v*)), as shown in *Fig. 8*. To detect minor conformations in $CDCl_3$ solution, ^{1}H-NMR spectra of **11** were measured at low temperature. Unfortunately, the ^{1}H-NMR spectrum of **11** exhibited only six signals due to the NH protons, even at $-50°$, and no broadening of signals occurred; almost no differences were observed between the spectra measured at room temperature and at $-50°$.

Table 2. *Intra- and Intermolecular H-Bond Parameters for the Homopeptides* **8a**, **10**, *and* **11**

Peptide	Donor H–D	Acceptor A	Distance D···A [Å]	Angle D–H···A [°]	Symmetry operations
CF_3CO-(Deg)$_3$-OMe (**8a**)	H–N(1)	O(1)	2.54	110	x, y, z
	H–N(3)	O(3)	2.62	111	x, y, z
	H–N(2)	O(2)	2.97	116	$-x+3/2, y+1/2, -z+1/2$
CF_3CO-(Deg)$_5$-OEt (**10**)	H–N(3)	O(0)	3.05	165	x, y, z
Molecule **A**	H–N(4)	O(1)	3.15	176	x, y, z
	H–N(5)	O(2)	2.97	160	x, y, z
	H–N(1)	O(4)	2.77	167	$x, y, z+1$
Molecule **B**	H–N(3)	O(0)	3.02	162	x, y, z
	H–N(4)	O(1)	3.11	177	x, y, z
	H–N(5)	O(2)	3.07	156	x, y, z
	H–N(1)	O(4)	2.82	168	$x, y, z-1$
CF_3CO-(Deg)$_6$-OEt (**11**)	H–N(3)	O(0)	2.94	146	x, y, z
	H–N(4)	O(1)	3.07	177	x, y, z
	H–N(5)	O(2)	2.96	175	x, y, z
	H–N(6)	O(3)	2.94	154	x, y, z
	H–N(1)	O(5)	2.88	146	$x+1/2, -y+1, z+1/2$
	H–N(2)	O(6)	3.19	161	$x+1/2, -y+1, z+1/2$

Table 3. *Crystal and Diffraction Parameters*

	CF_3CO-(Deg)$_3$-OMe (**8a**)	CF_3CO-(Deg)$_5$-OEt (**10**)	CF_3CO-(Deg)$_6$-OEt (**11**)
Empirical formula	$C_{21}H_{36}F_3N_3O_5$	$C_{68}H_{120}F_6N_{10}O_{14}$	$C_{40}H_{71}F_3N_6O_8$
M_r	467.53	1415.74	821.03
Color/habit	colorless, needle	colorless, prism	colorless, block
Crystal size [mm]	$0.50 \times 0.20 \times 0.20$	$0.40 \times 0.40 \times 0.20$	$0.30 \times 0.30 \times 0.10$
Crystal system	monoclinic	triclinic	monoclinic
Lattice parameters			
a, b, c [Å]	13.658(2), 10.785(3), 18.228(2)	17.910(2), 19.640(3), 12.021(2)	9.504(2), 18.035(3), 27.893(2)
α, β, γ [°]	90, 101.919(8), 90	101.60(1), 104.28(1), 89.77(1)	90, 97.76(2), 90
V [Å^3]	2627.0(7)	4009.4(10)	4737(1)
Space group	$P2_1/n$ (No. 14)	$P\bar{1}$ (No. 2)	$P2_1/n$ (No. 14)
Z value	4	2	4
D_{calc} (g/cm^3)	1.182	1.173	1.151
μ (CuK_α)	8.31	7.58	7.28
No. of observations	1913 ($I > 3.0\ \sigma(I)$)	5134 ($I > 3.0\ \sigma(I)$)	2721 ($I > 2.5\ \sigma(I)$)
No. of variables	290	964	515
R, R_w	0.070, 0.059	0.061, 0.061	0.067, 0.062
crystallizing solvent	MeOH	MeOH	MeOH

Discussion. – The conformations of the penta- and hexapaptide **10** and **11** in the solid state are very different from those reported by *Toniolo* and co-workers [5]. They reported that the pentapeptide containing Deg with a *tert*-butyl ester as the C-terminal protecting group preferred a fully extended *C5*-structure in the solid state. However, our results show that the 3_{10}-helical conformations are preferred in the solid state for **10**. *Fig. 9* shows the structure of **10**, as established by X-ray analysis, superimposed on the

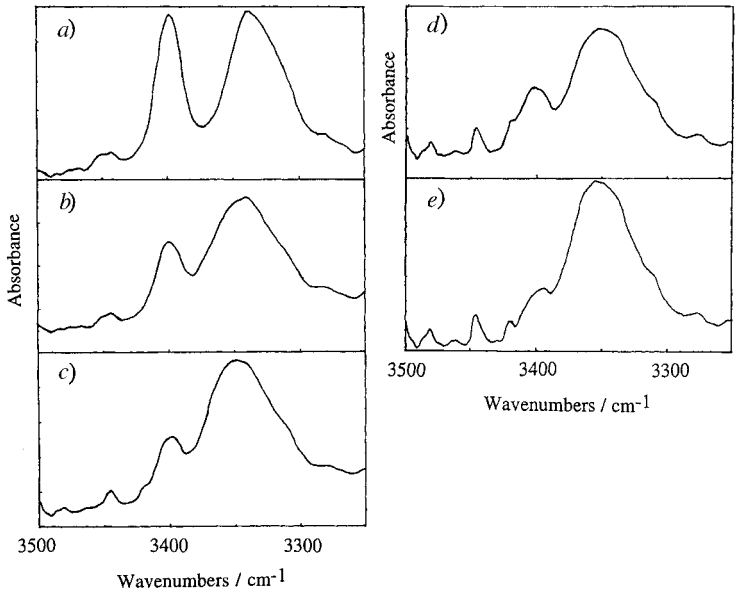


Fig. 7. *FT-IR Absorption spectra* (3500–3250 cm^{-1} region) *of the* CF_3CO-$(Deg)_n$-OEt ($n = 2–6$) *homopeptides in* $CDCl_3$ *solution* (peptide concentration 1.0 mM): a) n = *2*, b) n = *3*, c) n = *4*, d) n = *5* and e) n = *6*

conformation of the pentapeptide calculated by computer energy minimization. The 3_{10}-helical conformation determined by X-ray analysis and that obtained by computer calculation are very similar.

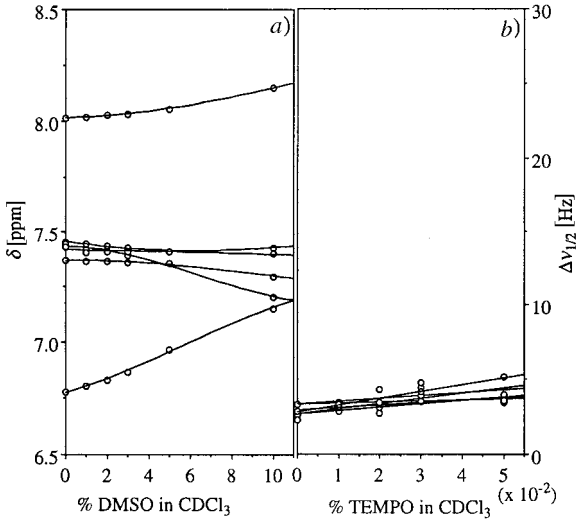


Fig. 8. a) *Plot of NH chemical shifts in the* ^1H*-NMR spectra of hexapeptide* **11** *as a function of increasing percentages of DMSO* (v/v) *added to the* $CDCl_3$ *solution* (peptide concentration 1.0 mM) *and* b) *plot of the bandwidth of the NH protons of* **11** *as a function of increasing percentages of TEMPO* (w/v) *added to the* $CDCl_3$ *solution* (peptide concentration 1.0 mM)

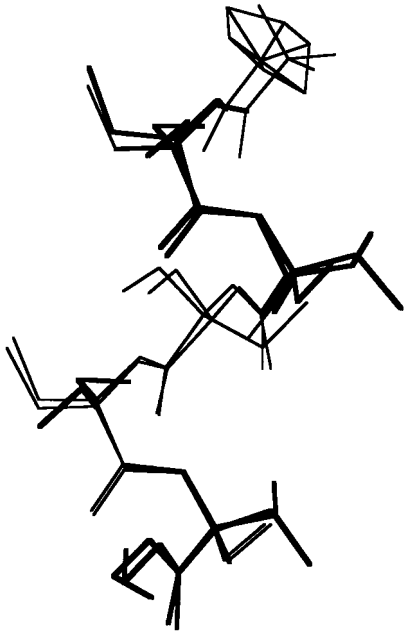


Fig. 9. *Molecule* **A** *of pentapeptide* **10** *as determined by X-ray crystallographic analysis, superimposed on the minimal-energy conformation of the pentapeptide calculated by MacroModel* [19]. The rotational disorder of the trifluoroacetyl function is shown in the structure determined by X-ray analysis.

The IR spectrum of pentapeptide CF_3CO-$(Deg)_5$-OEt (**10**) is very similar to that of CF_3CO-$(Deg)_5$-O-*t*-Bu reported by *Toniolo* and co-workers [5]. These IR absorption data tentatively suggest that the largely populated structure of homopeptides prepared from Deg in $CDCl_3$ solution is not a 3_{10}-helical structure, but a fully extended *C*5 conformation. In the ^{1}H-NMR spectrum of hexapeptide **11**, the internal four NH protons (Deg-2 to Deg-5) appear in the narrow region of δ 7.36–7.45, suggesting that these internal NH protons exist under closely related circumstances in $CDCl_3$ solution. The NH signals of **11** were almost insensitive to the addition of DMSO and TEMPO which also supports that the *C*5 conformation is preferred in $CDCl_3$ solution. The absence of splitting and broadening of the NH signals in the ^{1}H-NMR spectrum of **11** measured at $-50°$ can be attributed to the presence of either only a single conformer (minor conformers in very minute amount) or several conformers in very fast exchange. However, a planar structure existing only in $CDCl_3$ solution would be ruled out, because the crystals, recrystallized from $CDCl_3$, also afforded the same diffraction parameters as those obtained from the crystals recrystallized from MeOH. The dominant conformation in the $CDCl_3$ solution is a planar structure, and this planar conformation in solution is consistent with the results reported by *Toniolo* and co-workers [5].

Conclusions. – The preferred conformations of the ethyl ester penta- and hexapeptides **10** and **11**, respectively, prepared from Deg were 3_{10}-helical structures in the solid state. We established the dominant conformation of **11** in $CDCl_3$ solution to

be fully extended planar (*C*5) structure. Thus the preferred conformation of **11** in $CDCl_3$ solution and that in the solid state are drastically different. Two intermolecular H-bonds are present in the 3_{10}-helical structure of **11**, but none in the planar (*C*5) structure, and therefore intermolecular H-bonds in a minor 3_{10}-helical conformation in solution would affect the nucleation events. In the case of *tert*-butyl ester C-terminal protecting groups [11], the bulky ester prevents the formation of intermolecular H-bonds in the 3_{10}-helical structure, therefore the extended planar structures would be adopted in the solid state. Although 3_{10}-helical structures were reported for heteropeptides containing dipropylglycine and dibutylglycine [6], the results presented here establish for the first time the 3_{10}-helical structure as the minimum-energy conformation also for homopeptides prepared from Deg.

Experimental Part

General. General procedures for syntheses according to previous reports [11][15]. CC = Column chromatography. IR Spectra (cm^{-1}): *Jasco-A-100* spectrometer for conventional measurements (KBr and neat) and *Jasco-FT-IR-420* spectrophotometer for $CDCl_3$ solns. using 0.1-mm path length of a NaCl cell. ^{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* spectrometer. Elemental analyses were performed in the Analytical Center of the Faculty of Science at Kyushu Unitersity.

Diethylglycine Hydrochloride (= *2-Amino-2-ethylbutanoic Acid Hydrochloride*; Deg · HCl; **1**). A mixture of diethyl ketone (63 ml, 624 mmol), KCN (37.2 g, 572 mmol), and NH_4Cl (31.3 g, 585 mmol) in H_2O (170 ml) was heated at 55–60° for 8 h. After being cooled to r.t., the mixture was extracted with Et_2O, the extract dried ($MgSO_4$) and evaporated, and the residue dissolved in conc. aq. HCl soln. (350 ml). After refluxing for 3 days, the soln. was concentrated to 1/3 volume and left at r.t. for 24 h. The precipitated crystals **1** were collected (38–60 g, 40–63%). M.p. 245–248° (sublimed). IR (KBr): 3200, 3160, 2900 (br.), 1710 (br.). ^{1}H-NMR (270 MHz, (D_6)DMSO); 8.42 (br. *s*, 1 H); 4.25 (br. *s*, 3 H); 1.79 (*q*, *J* = 7.4, 4 H); 0.87 (*t*, *J* = 7.4, 6 H). Anal. calc. for $C_6H_{14}ClNO_2$: C 42.99, H 8.42, N 8.36, found: C 43.00, H 8.40, N 8.43.

2,2-Diethyl-N-*(trifluoroacetyl)glycine* (= *2-Ethyl-2-[(trifluoroacetyl)amino]butanoic Acid*; CF_3CO-Deg; **2**). A mixture of **1** (10.0 g, 59.7 mmol) in $(CF_3CO)_2O$ (30 ml) was stirred at r.t. for 5 days. The mixture was poured into 5% aq. $NaHCO_3$ soln. and the soln. acidified with solid citric acid. The acidic soln. was extracted with $CHCl_3$ and the extract dried ($MgSO_4$) and evaporated: **2** (8.4 g, 62%). Colorless crystals. M.p. 116–117° (from $CHCl_3$). IR (KBr): 3350, 3100 (br.), 1730, 1700. ^{1}H-NMR (270 MHz, $CDCl_3$); 8.61 (br. 1 H); 7.24 (br. *s*, 1 H); 2.51 (*qd*, *J* = 7.4, 14.8, 2 H); 1.95 (*qd*, *J* = 7.4, 14.8, 2 H); 0.84 (*t*, *J* = 7.4, 3 H). FAB-MS: 228.2 ([M^+ + H]$^+$), 182.1. Anal. calc. for $C_8H_{12}F_3NO_3$: C 42.30, H 5.32, N 6.17; found: C 42.35, H 5.35, N 6.25.

*4,4-Diethyl-2-(trifluoromethyl)oxazol-5(4*H*)-one* (**3**). A soln. of **2** (5.0 g, 22.0 mmol) in thionyl chloride (50 ml, 685 mmol) was heated at 50° for 5 h. After removal of $SOCl_2$, the oily residue was distilled under reduced pressure to afford **3** (2.9 g, 63%). Colorless oil. B.p. 83–84°/110 Torr. IR (neat): 1830. ^{1}H-NMR (270 MHz, $CDCl_3$); 1.95 (*q*, *J* = 7.4, 4 H); 0.85 (*t*, *J* = 7.4, 6 H). Compound **3** was very sensitive to air, and was easily converted to the acid **2**.

Diethylglycine Methyl Ester (= *Methyl 2-Amino-2-ethylbutanoate;* Deg-OMe; **4a**). A soln. of **1** (4.0 g, 23.8 mmol) and $SOCl_2$ (6.0 ml, 82.2 mmol) in MeOH (120 ml) was refluxed for 24 h. After removal of MeOH, the oily residue was diluted with 5% aq. $NaHCO_3$ soln. and extracted with $CHCl_3$ and the extract dried ($MgSO_4$) and evaporated: crude **4a** (2.3 g, 66%) which was used in the next reaction without purification. Colorless oil. IR (neat): 3390 (br.), 1725. ^{1}H-NMR (270 MHz, $CDCl_3$): 3.72 (*s*, 3 H); 1.80 (*qd*, *J* = 7.4, 14.8, 2 H); 1.70 (br. *s*, 2 H); 1.56 (*qd*, *J* = 7.4, 14.8, 2 H); 0.85 (*t*, *J* = 7.4, 6 H).

Diethylglycine Ethyl Ester (= *Ethyl 2-Amino-2-ethylbutanoate*; Deg-OEt; **4b**). Ester **4b** was prepared from **1** as described for **4a** and used without purification. Yield 70%. Colorless oil. IR (neat): 3380 (br.), 1720. ^{1}H-NMR (270 MHz, $CDCl_3$): 4.18 (*q*, *J* = 6.9, 2 H); 1.82 (*qd*, *J* = 7.4, 14.8, 2 H); 1.56 (*qd*, *J* = 7.4, 14.8, 2 H); 1.28 (*t*, *J* = 6.9, 3 H); 0.86 (*t*, *J* = 7.4, 3 H).

Methyl 2-Ethyl-2-{{2-ethyl-1-oxo-2-[(trifluoroacetyl)amino]butyl}amino}butanoate (CF_3CO-Deg-Deg-OMe; **5a**). A soln. of **3** (1.88 g, 8.99 mmol) and **4a** (1.95 g, 13.4 mmol) in MeCN (20 ml) was refluxed for 4 days. Evaporation afforded an oily residue which was purified by CC (silica gel, 10% AcOEt/hexane): **5a** (2.87 g,

90%). Colorless crystals. M.p. 96–97°. IR (KBr): 3370, 3270, 1720, 1700, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.95 (br. *s*, 1 H); 6.76 (br. *s*, 1 H); 3.82 (*s*, 3 H); 2.66 (*qd*, *J* = 7.3, 14.6, 2 H); 2.45 (*qd*, *J* = 7.3, 14.6, 2 H); 1.84 (*qd*, *J* = 7.3, 14.6, 2 H); 1.72 (*qd*, *J* = 7.3, 14.6, 2 H); 0.83 (*t*, *J* = 7.3, 6 H); 0.76 (*t*, *J* = 7.3, 6 H). FAB MS: 355.2 ($[M+H]^+$). Anal. calc. for $C_{15}H_{25}F_3N_2O_4$: C 50.84, H 7.11, N 7.91; found: C 50.92, H 7.14, N 7.84.

Ethyl 2-Ethyl-2-{[2-ethyl-1-oxo-2-[(trifluoroacetyl)amino]butyl]amino}butanoate (CF_3CO-Deg-Deg-OEt; **5b**). As described for **5a**, from **3** and **4b**: 99% of **5b**. M.p. 81–82°. IR (KBr): 3350, 3250, 1730, 1690, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$); 7.96 (br. *s*, 1 H); 6.80 (br. *s*, 1 H); 4.28 (*q*, *J* = 7.1, 2 H); 2.69 (*qd*, *J* = 7.4, 14.8, 2 H); 2.46 (*qd*, *J* = 7.4, 14.8, 2 H); 1.86 (*qd*, *J* = 7.4, 14.8, 2 H); 1.75 (*qd*, *J* = 7.4, 14.8, 2 H); 1.33 (*t*, *J* = 7.1, 3 H); 0.83 (*t*, *J* = 7.4, 6 H); 0.76 (*t*, *J* = 7.4, 6 H). FAB-MS: 369.2 ($[M+H]^+$). Anal. calc. for $C_{16}H_{27}F_3N_2O_4$: C 52.17, H 7.39, N 7.60; found: C 52.05, H 7.37, N 7.45.

2-Ethyl-2-{[2-ethyl-1-oxo-2-[(trifluoroacetyl)amino]butyl]amino}butanoic Acid (CF_3CO-Deg-Deg-OH **6**). A soln. of **5a** (615 mg, 1.74 mmol) and NaOH (1.00 g, 25.0 mmol) in dioxane (7 ml) and H_2O (10 ml) was stirred for 2 days. The mixture was diluted with H_2O and washed with $CHCl_3$. The aq. soln. was acidified with 10% aq. HCl soln. and extracted with $CHCl_3$ and the org. phase dried ($MgSO_4$) and evaporated: **6** (350 mg, 59%). Colorless crystals. The anal. sample was recrystallized from $CHCl_3$. M.p. 136–137°. IR (KBr): 3380, 3300, 3000 (br.), 1710 (br.), 1670. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.94 (br. *s*, 1 H); 6.63 (br. *s*, 1 H); 6.50 (br. 1 H); 2.65 (*qd*, *J* = 7.3, 14.6, 2 H); 2.45 (*qd*, *J* = 7.3, 14.6, 2 H); 1.90 (*qd*, *J* = 7.3, 14.6, 2 H); 1.69 (*qd*, *J* = 7.3, 14.6, 2 H); 0.84 (*t*, *J* = 7.3, 12 H). EI-MS: 341.2 (2, M^+), 182 (100). EI-HR-MS: 340.1626 ($C_{14}H_{23}F_3N_2O_4^+$, M^+; calc. 340.1610). Anal. calc. for $C_{14}H_{23}F_3N_2O_4$: C 49.41, H 6.81, N 8.23; found: C 49.44, H 6.87, N 8.11.

Methyl Trifluoroacetyl-diethylglycyl-diethylglycyl-diethylglycinate (CF_3CO-Deg-Deg-Deg-OMe; **8a**). A mixture of **6** (134 mg, 0.394 mmol) and *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC) (100 mg, 0.522 mmol) in MeCN (5 ml) was stirred at r.t. Amine **4a** (150 mg, 1.03 mmol) was added to the soln. and the mixture was refluxed for 14 days. After evaoporation, the residue was purified by CC (silica gel). Elution with 15% AcOEt/hexane afforded **7** (96 mg, 75%), and elution with 20% AcOEt/hexane gave **8a** (12.8 mg, 7%).

Data of **7**: Colorless oil. IR (neat): 3375, 1835, 1730, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.48 (br. *s*, 1 H); 2.54 (*qd*, *J* = 7.4, 14.8, 2 H); 1.80–2.00 (*m*, 6 H); 0.87 (*t*, *J* = 7.4, 6 H); 0.83 (*t*, *J* = 7.4, 6 H). EI-MS: 322.1 (3, M^+), 294.1 (38), 265.1 (100), 225.1 (24), 182.1 (66).

Data of **8a**: Colorless crystals. M.p. 148–149° (from MeOH). IR (KBr): 3375, 3320, 3275, 1720, 1645. ^{1}H-NMR (270 MHz, $CDCl_3$); 7.99 (br. *s*, 1 H); 7.38 (br. *s*, 1 H); 6.73 (br. *s*, 1 H); 3.82 (*s*, 3 H); 2.55–2.75 (*m*, 4 H); 2.46 (*qd*, *J* = 7.4, 14.8, 2 H); 1.60–1.92 (*m*, 6 H); 0.83 (*t*, *J* = 7.4, 6 H); 0.76 (*t*, *J* = 7.4, 12 H). FAB-MS: 490.3 ($[M+Na]^+$), 468.3 ($[M+H]^+$). Anal. calc. for $C_{21}H_{36}F_3N_3O_5$: C 53.95, H 7.76, N 8.99; found: C 54.19, H 7.71, N 8.89.

Ethyl Trifluoroacetyl-diethylglycyl-diethylglycyl-diethylglycinate (CF_3CO-Deg-Deg-Deg-OEt; **8b**). $NaBH_4$ (2.0 g, 52.9 mmol) was added to the stirred soln. of **5b** (2.00 g, 5.43 mmol) in EtOH (70 ml), and the mixture was refluxed for 2 h. More $NaBH_4$ (500 mg, 13.2 mmol) was added and the mixture refluxed for 2 h. The mixture was then diluted with H_2O (50 ml) and the EtOH evaporated. The aq. soln. was acidified with 5% aq. HCl soln. and washed with Et_2O. 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 (*ca.* 1.4 g) dissolved in MeCN (30 ml). Then **3** (1.45 g, 6.93 mmol) was added and the mixture refluxed for 3 days. Evaporation gave an oily residue which was purified by CC (silica gel, 20% AcOEt/hexane): **8b** (1.90 g, 73%). Colorless crystals. M.p. 156–157° (recryst. from MeOH/$CHCl_3$). IR (KBr): 3400, 3350, 3320, 1730, 1660. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.00 (br. *s*, 1 H); 7.41 (br. *s*, 1 H); 6.78 (br. *s*, 1 H); 4.28 (*q*, *J* = 7.3, 2 H); 2.55–2.80 (*m*, 4 H); 2.43 (*qd*, *J* = 7.4, 14.8, 2 H); 1.60–1.95 (*m*, 6 H); 1.32 (*t*, *J* = 7.3, 3 H); 0.83 (*t*, *J* = 7.4, 6 H); 0.77 (*t*, *J* = 7.4, 12 H). FAB-MS: 504.3 ($[M+Na]^+$), 482.3 ($[M+H)^+$]. Anal. calc. for $C_{22}H_{38}F_3N_3O_5$: C 54.87, H 7.95, N 8.73; found: C 54.94, H 7.94, N 8.73.

Ethyl Trifluoroacetyl-diethylglycyl-diethylglycyl-diethylglycyl-diethylglycinate (CF_3CO-Deg-Deg-Deg-Deg-OEt; **9**). $NaBH_4$ (2.0 g, 52.9 mmol) was added to the stirred soln. of **8b** (1.80 g, 3.74 mmol) in EtOH (100 ml), and the mixture was refluxed for 1 h. More $NaBH_4$ (500 mg, 13.2 mmol) was added and the mixture refluxed for 1 h. The mixture was then diluted with H_2O (80 ml) and the EtOH evaporated. After workup as described for **8b**, the residue, **2** (1.00 g, 4.40 mmol), and EDC (820 mg, 4.28 mmol) in MeCN (50 ml) were refluxed for 3 days. After evaporation, the residue was diluted with $CHCl_3$, the soln. washed with H_2O, dried ($MgSO_4$), and evaporated, and the oily residue purified by CC (silica gel, 30% AcOEt/hexane): **9** (1.78 g, 80%). Colorless crystals. M.p. 200.5–201.5° (recryst. from EtOH). IR (KBr): 3400, 3350, 1720, 1675, 1650. ^{1}H-NMR (270 MHz, $CDCl_3$); 8.02 (br. *s*, 1 H); 7.44 (br. *s*, 1 H); 7.38 (br. *s*, 1 H); 6.77 (br. *s*, 1 H); 4.28 (*q*, *J* = 6.9, 2 H); 2.55–2.75 (*m*, 6 H); 2.46 (*qd*, *J* = 7.3, 14.6, 2 H); 1.65–1.94 (*m*, 8 H); 1.32 (*t*, *J* = 6.9, 3 H); 0.74–0.90 (*m*, 24 H). FAB-MS: 617.4 ($[M+Na]^+$), 595.4 ($[M+H]^+$). Anal. calc. for $C_{28}H_{49}F_3N_4O_6$: C 56.55, H 8.31, N 9.42; found: C 56.66, H 8.35, N 9.39.

Ethyl Trifluoroacetyl-diethylglycyl-diethylglycyl-diethylglycyl-diethylglycyl-diethylglycinate (CF_3CO-Deg-Deg-Deg-Deg-Deg-OEt; **10**). As described for **9**, from **9** and **2**: 81%. M.p. 246–247.5° (recryst. from MeOH). IR (KBr): 3350 (br.), 3320 (br.), 3200, 1720, 1700, 1660, 1630. ^{1}H-NMR (270 MHz, $CDCl_3$); 8.01 (br. *s*, 1 H); 7.45 (br. *s*, 1 H); 7.41 (br. *s*, 1 H); 7.37 (br. *s*, 1 H); 6.77 (br. *s*, 1 H); 4.28 (*q*, *J* = 7.0, 2 H); 2.50–2.75 (*m*, 8 H); 2.45 (*qd*, *J* = 7.4, 14.8, 2 H); 1.55–1.95 (*m*, 10 H); 1.35 (*t*, *J* = 7.0, 3 H); 0.74–0.90 (*m*, 30 H). FAB-MS: 730.5 ($[M+Na]^+$), 708.5 ($[M+H]^+$). Anal. calc. for $C_{34}H_{60}F_3N_5O_7$: C 57.69, H 8.54, N 9.89; found: C 57.72, H 8.51, N 9.81.

Ethyl Trifluoroacetyl-diethylglycyl-diethylglycyl-diethylglycyl-diethylglycyl-diethylglycyl-diethylglycinate (CF_3CO-Deg-Deg-Deg-Deg-Deg-Deg-OEt; **11**). As described for **9**, from **10** and **2**. Purification by CC (silica gel, 10% MeOH/$CHCl_3$) afforded **11** (54%). Colorless crystals. M.p. 280–282° (recryst. from MeOH). IR (KBr): 3350 (br.), 3320 (br.), 3225, 1710, 1660 (br.). ^{1}H-NMR (500 MHz, $CDCl_3$); 8.00 (br. *s*, 1 H); 7.45 (br. *s*, 1 H); 7.42 (br. *s*, 1 H); 7.40 (br. *s*, 1 H); 7.36 (br. *s*, 1 H); 6.77 (br. *s*, 1 H); 4.27 (*q*, *J* = 7.1, 2 H); 2.57–2.67 (*m*, 10 H); 2.44 (*qd*, *J* = 7.3, 14.6, 2 H); 1.84 (*qd*, *J* = 7.3, 14.6, 2 H); 1.65–1.78 (*m*, 10 H); 1.33 (*t*, *J* = 7.1, 3 H); 0.80–0.88 (*m*, 30 H); 0.77 (*t*, *J* = 7.3, 6 H). FAB-MS: 843.5 ($[M+Na]^+$), 821.5 (M^+). Anal. calc. for $C_{40}H_{71}F_3N_6O_8$: C 58.52, H 8.72, N 10.24; found: C 58.55, H 8.78, N 10.18.

X-Ray Diffraction. Crystals were grown from MeOH solns. by slow evaporation. Data collection for three peptides was performed on a *Rigaku-AFC5R* diffractometer, Ni-foil filtered Cu$K\alpha$ radiation. Crystal and collection parameters are listed in *Table 3*. All three crystals remained stable at r.t. during the X-ray data collection. The structures were solved by direct methods using SIR92 [16] and expanded using *Fourier* techniques [17]. 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 **8a** gave a conventional *R* factor of 0.070 ($Rw = 0.059$) based on 1913 ($I > 3.0\,\sigma(I)$) reflections, and the largest peak and hole in the final difference *Fourier* map were 0.20 and -0.17 e·Å^{-3}. Two independent molecules (**A** and **B**) existed in the asymmetric unit of the pentapeptide **10**. Rotational disorders typical of the trifluoroacetyl functions were observed in both molecules **A** and **B**. The $C(\gamma)$ atoms of the Deg-3 side chain in molecule **A** were disordered over two sites with the occupancy factors 0.58 and 0.42 for the major and minor component, resp. In the $C(\beta)$ atoms of the ethyl ester moiety at the C-terminal protecting group of peptide **A**, the disorders were also observed. Their occupancy factors were refined to values of 0.68 and 0.32, resp. The *R* factor was 0.061 ($Rw = 0.061$) for 5134 data ($I > 3.0\,\sigma(I)$), and the largest peak and hole in the final difference *Fourier* map were 0.24 and -0.30 e·Å^{-3}. For the hexapeptide **11**, the *R* factor was 0.067 ($Rw = 0.062$) for 2721 data ($I > 2.5\,\sigma(I)$), and the largest peak and hole in the final difference *Fourier* map were 0.31 and -0.24 e·Å^{-3}. All calculations were performed using the teXsan [18] 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-113401, 113402, and 113403. 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).

Molecular-Mechanics Calculation. Conformational-energy calculations were performed by using the package of MacroModel Ver. 5.5 [19]. The parameters used were as follows: conformational search, Monte Carlo method; force field, AMBER*, 2000 structures were minimized; solvent, water.

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