silanols and intracrystalline defect sites such as "hydroxyl nests".[20] High rates of ^{18}O exchange have been observed by von Ballmoos[23] for ZSM-5 zeolites, lending support for the presence of such defects. Reaction of aluminum halides with these defects followed by ion exchange would result in the creation of Brønsted sites as depicted in Scheme I.

The incorporation of Al into the zeolite framework as a tetracoordinate species generates a negative framework charge. This can be balanced either by a haloaluminum cation (as illustrated) or by a proton. Subsequent NH_4^+ exchange and calcination converts all of the sites into Brønsted acid sites.

A similar mechanism may be invoked for the reaction with fluoaluminate complexes. However, in this case, alumination could proceed even in the absence of defect sites, due to the high reactivity of inorganic fluorides toward silica. Thus the direct substitution of framework Si may occur, as shown in Scheme II.

As shown previously, the alkaline fluoaluminate solution contained 4-coordinate Al species, revealed through ^{27}Al NMR. Such 4-coordinate species may be more effective than their 6-coordinate counterpart in the Al insertion reaction because of its smaller size, hence higher intracrystalline diffusivity. Four-coordinate species may also have some steric advantage in their initial interaction with framework defect sites.

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Folded and Extended Structures of Homooligopeptides from α,α-Dialkylated Glycines. A Conformational Energy Computation and X-ray Diffraction Study

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Abstract: Conformational energy computations on a derivative and a homodipeptide of α,α-di-*n*-propylglycine were performed. In both cases the N- and C-terminal groups are blocked as acetamido and methylamido moieties, respectively. To analyze the effect of side-chain length, we carried out computations also on *N*-acetyl-α-methyl-α-ethyl-D-glycine methylamide. Literature data on *N*-acetyl-α,α-dimethylglycine methylamide were compared with our results. It was found that the minimum energy conformations for the α,α-di-*n*-propylglycine derivative and homodipeptide correspond to the fully extended conformation. A comparison with the derivatives of α-methyl-α-ethyl-D-glycine and α,α-dimethylglycine indicates that the preference from a folded to a fully extended conformation increases with increasing bulkiness of the C^α-substituents. The results of the theoretical analysis of the conformation of the derivative and homodipeptide of α,α-di-*n*-propylglycine are in agreement with their conformational properties in the solid state, determined by X-ray diffraction and also described in this work. In this latter study the N- and C-terminal groups are blocked as trifluoroacetamido and *N'*,*N'*-dibenzylacylhydrazido moieties, respectively.

α,α-Dialkylated glycyl residues have been shown to represent a useful new type of conformational constraint in peptides.[2-4] Through this modification of the α-carbon, information may be obtained about the active conformation of a peptide at the receptor site and biological potency may be increased, possibly, at least in part, because of enhanced resistance to enzyme degradation. The replacement of the two α-hydrogens in glycyl derivatives by alkyl moieties has profound structural consequences. In particular, chirality may still be absent, as in α,α-dimethylglycine (also called α-aminoisobutyric acid, Aib), α,α-diethylglycine (Deg), α,α-di-*n*-propylglycine (Dpg), or may be introduced, as in α-methyl-α-ethylglycine (also called isovaline, Iva), depending on the nature of the replacements.

Among the α,α-dialkylated glycyl residues the only systematic conformational studies have been those on the Aib residue.[2-11] The inherent interest in Aib-rich peptides results not only from their restricted conformational space but also from their tendency to adopt ϕ,ψ sets of values typical of the 3_{10}- and α-helices. In addition, Aib residues characterize a family of naturally occurring membrane-active antibiotics, the peptaibol antibiotics.[4,9,10,11] Some of these antibiotics contain also a limited number of R-Iva residues (an R- or D-Iva residue is an L-alanine in which the α-hydrogen is replaced by an ethyl substituent).[12]

The structural modifications induced by substitution of protein amino acids by other α,α-dialkylated glycyl residues in bioactive

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peptides have not been explored so far, despite the interesting conformational properties likely to be conferred on such analogues. This may be due to the fact that it is generally assumed that *all* α,α-dialkylated glycyl residues would show conformational preferences strictly similar to those exhibited by their prototype Aib residue. However, the present and the following papers demonstrate unequivocally that this current view is not correct.

As a part of a program of investigation of the conformations adopted by α,α-dialkylated glycyl residues, we report in this paper the results of a conformational energy computation study of a derivative and a homodipeptide of the Dpg residue. In both cases the N- and C-terminal groups are blocked as acetamido (Ac–N-H–) and methylamido (–CONHMe) moieties, respectively. To investigate the effect of side-chain lengths, computations on Ac-D-Iva-NHMe were also performed. Literature data[2,3,5-8] on Ac-Aib-NHMe were compared with our results.

Furthermore, the results of the theoretical analysis of the conformation of the Dpg derivative and homodipeptide were compared with their conformational preferences in the solid state, determined by X-ray diffraction and also reported in this paper. In this latter study the N- and C-terminal groups are blocked as trifluoroacetamido (Tfa-NH–) and *N'*,*N'*-dibenzylacylhydrazido [–CO–NHN($CH_2C_6H_5$)$_2$ or –CO–DBH] moieties, respectively.[13] In contrast to Aib[4,14-23] and Iva[12] derivatives and homopeptides, already investigated by X-ray diffraction, such an experimental study has as yet not been reported for the Dpg analogues. Interestingly, in recent years the crystal structures of a number of linear Aib co-oligopeptides, including alamethicin itself,[24] have been solved by X-ray diffraction (for significant examples see ref 25–36).

Table I. Crystal Data for Tfa(Dpg)$_{1,2}$DBH

parameter	Tfa-Dpg-DBH	Tfa(Dpg)$_2$DBH
mol formula	$C_{24}H_{30}N_3O_2F_3$	$C_{32}N_{45}N_4O_3F_3$
mol wt (amu)	506.5	590.7
Crystal system	monoclinic	triclinic
space group	$P2_1/n$	$P\bar{1}$
Z, molecule/unit cell	8	2
a, Å	19.615 (6)	11.259 (1)
b, Å	12.284 (5)	12.729 (1)
c, Å	22.153 (6)	13.099 (1)
α, deg	90	65.21 (1)
β, deg	108.68 (3)	98.31 (1)
γ, deg	90	101.91 (1)
V, Å^3	5056.6	1644.1
d(exptl), g/cm^3	1.18	1.18
d(calcd), g/cm^3	1.181	1.179
radiation, Å	Cu Kα, λ = 1.5418 (Ni-filtered)	Cu Kα, λ = 1.5418 (Ni-filtered)
measured reflctns	4041	3187
reflctns with $I > 3\sigma(I)$	2720	2361
R factor (weighted)	0.072	0.076
temp. °C	23, ambient	23, ambient

Experimental Section

Conformational Energy Computations. The geometry of the Dpg residue was derived from the X-ray diffraction analyses of Tfa-(Dpg)$_{1,2}$DBH described in this work, while that of Iva was taken from literature data.[12] The geometries of the acetamido and methylamido blocking groups were those used by Momany et al.[37]

All C–H bond lengths were set equal to 1.09 Å according to Némethy et al.[38]

Conformational energies were calculated by employing the potential energy functions and energy parameters derived by Momany et al.[37] Consistent with this procedure, partial charges for the electrostatic contribution were obtained from CNDO/2 calculations performed on the *N*-acetyl-*N'*-methylamides of Iva and Dpg.

Conformational energies are expressed as $E = E - E_0$, where E_0 is the energy of the lowest energy conformation for a given compound.

The conformational space of Ac(Dpg)$_{1,2}$NHMe and Ac-D-Iva-NHMe was mapped by calculating the conformational energy at 10° intervals of all the ϕ, ψ, and χ angles, with the ω angles fixed at 180° and the methyl hydrogens fixed into staggered conformations.[39]

Minimum energy conformations were then obtained in all the low-energy regions located in the above search, minimizing the energy with respect to all dihedral angles of each residue by the Newton–Raphson method[40] employing analytical first and second derivatives. The precision in the determination of minima was set to about 0.1 deg for any of the variables.

All computations were performed with the new packages of fast programs NB/83 and OPT/83[41] operating on the UNIVAC 1100/80 computer of the Centro di Calcolo Interfacoltà at the University of Naples.

X-ray Diffraction. Colorless crystals of Tfa(Dpg)$_{1,2}$DBH[13] were grown from ethanol and acetone solutions, respectively.

Weissenberg photographs, because of the systematic absences, indicate the monoclinic and the triclinic systems for the Tfa-Dpg-DBH and the Tfa(Dpg)$_2$DBH crystals, respectively.

A CAD-4 Enraf Nonius diffractometer, equipped with PDP-8/E and a PDP-11/34 digital computers, was used for determination of the unit-cell dimensions, data collection, structure determination, and refinement for both crystals. Accurate unit-cell parameters, orientation matrix, and intensity data collection were performed with Cu K$_\alpha$ radiation. A summary of the crystal data for both structures is given in Table I.

The analysis of the peak profiles for both crystals suggested an ω-2θ scan mode with a range of (1.1 + 0.16 tan θ) for the peak measurements; background counts were taken at the end of each scan. A distance crystal-counter of 368 mm was used with a counter entrance aperture of

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Table II. Minimum Energy Conformations[a] for *N*-Acetyl-*N'*-methylamides of α,α-Dialkylated Glycines

compd	ϕ	ψ	$\chi^{1,1}$ [b]	$\chi^{2,1}$ [b]	ΔE	N[c]
Ac-Dpg-NHMe	−179.3	−178.6	58.6	−56.9	0.0	3
	−57.5	−52.6	177.2	61.9	3.59	2
	64.8	−168.0	−48.6	171.2	3.60	1
	60.3	49.3	−62.9	−176.8	3.75	2
	−65.6	170.3	68.3	49.6	4.91	1
$Ac(Dpg)_2NHMe$[g]	−179.3, −178.8	−179.4, −178.5	52.4, 64.0	−51.3, −63.1	0.0	1
Ac-D-Iva-NHMe	173.9	−52.9	163.4	−47.8	0.0	2
	−177.9[d]	−176.8	−171.7	−58.4	0.14	1
	−59.4	−48.0	−171.6	59.7	0.24	3
	−1758.5	55.0	163.2	−175.8	0.53	1
	66.2[d]	−172.1	161.4	−68.3	1.66	3
	−66.5	178.5	165.1	54.1	2.41	1
	63.0	32.7	172.7	−65.7	2.60	2
Ac-Aib-NHMe[e]	−55.5	−40.3			0.0	
	47.5	48.4			1.17	
	−62.3	171.8			3.15	
	−176.4	50.8			3.27	
	175.2	−47.1			3.75	
	180.0[d]	180.0			7.0[f]	

[a] The energies are given in units of kcal/mole. Only the conformations presenting a $\Delta E <$ kcal/mol with respect to the minimum energy conformation are given in the Table. All angles, ϕ, ψ, and χ^{ij}, are in the range $-180° \leq \phi,\psi,\chi^{ij} \leq 180°$. [b] In χ^{ij} index i refers to the bond about which the dihedral angle is calculated (i = 1 indicates the C^{α}–C^{β} bond, i = 2, the C^{β}–C^{γ}, etc), while index j refers to side-chain 1 or 2 bonded to the same C^{α}. [c] N indicates the number of minima in the same area of ϕ and ψ with different values of $\chi^{1,1}$ and/or $\chi^{2,1}$ (the values given are those of the deepest minimum). [d] This conformation is not present in Ac-Aib-NHMe as reported in ref 4. [e] Reference 4. [f] This minimum is given for comparison with analogous minima in the other compounds. [g] The first and second values refer to the first and second residues, respectively.

4 mm. The tube placed between the goniometer head and the detector was evacuated by using a vacuum pump. Prescan runs were made at a speed of 4°/min. Reflections with a net intensity $I \leq \sigma(I)$ 0.5 were flagged as "weak"; those at $I > \sigma(I)$ 0.5 were measured at lower speed in the range 1–4°/min, depending on the value $\sigma(I)/I$. The maximum time allowed for the scan was set to 60 s. Two intensity-control reflections were recorded every 60 min of X-ray exposure time; no significant change in their intensity was observed during data collection. Orientation checks were made with respect to the scattering vector of 25 strong reflections; when necessary, reorientation was made by using the high-angle reflections employed for determination of lattice constants and matrix determination of each crystal.

A total of 4041 and 3187 independent reflections were collected for Tfa-Dpg-DBH and $Tfa(Dpg)_2DBH$, respectively, and corrected for polarization and Lorentz factors; of these, 2720 and 2361 reflections, respectively, were considered "observed" and used in the calculations, since their values were greater than $3\sigma(I)$.

Both structures were solved with MULTAN in the form programmed by Germain et al.[42] The maps corresponding to the highest combined figures of merit revealed the position of most of the atoms in the molecules. Successive difference Fourier maps enabled us to locate unequivocally the rest of the atoms, with the exception of the fluorine atoms of the trifluoroacetyl groups. It was evident that these atoms were statistically positioned in two conformations almost equally represented in the crystals: in one, a C–F bond is eclipsed by the C(2)–O(1) bond; in the other, a C–F bond is eclipsed by the C(2)–N_1 bond. For the refinements, the standard least-squares procedure, minimizing the quantity $\sum w[|F_o^2 - F_c^2|)^2$ with w equal to $1/\sigma(F_o)^2$, was used. In the calculations the two sets of fluorine atoms were refined with isotropic temperature factors (the final B factors for the two sets of fluorine atoms present values on the average of 8.5 and 6.5). Anisotropic temperature factors for C, N, and O were used. Most of the hydrogen atoms were located with difference Fourier maps; the others were included in the calculations in their stereochemically expected positions with an isotropic temperature factor equal to the B equivalent of the carrier atom. The hydrogen atoms bonded to amide N atoms of both structures were refined in the last four cycles with fixed isotropic temperature factors.

Refinements were ended when the maximum shift in the atomic coordinates and anisotropic temperature factors was less than $^1/_5$ and $^1/_3$ of the corresponding standard deviations, respectively. The scattering factors for all atomic species were calculated from Cromer and Waber.[43] All calculations were carried out on a PDP-11/34 digital computer of the Centro di Metodologie Chimico-Fisiche of the University of Naples, using the SDP package of crystallographic programs. The final atomic parameters for both structures have been submitted as supplementary material. The final values of the weighted R factor for the 2720 and 2361 observed reflections were 0.072 and 0.076, respectively.

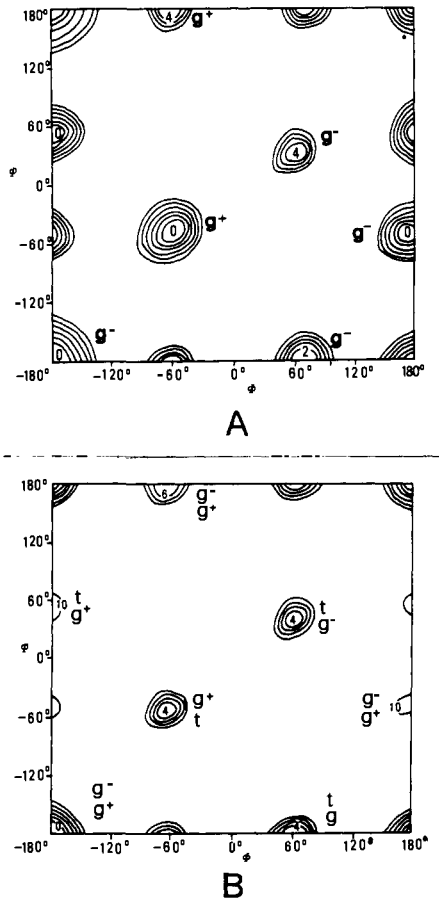

Figure 1. Conformational energy contour maps of (A) Ac-D-Iva-NHMe and (B) Ac-Dpg-NHMe. The contour lines are spaced 2 kcal/mol up to 10 kcal/mol over the 10° grid point of lowest energy for each map, located at (ϕ,ψ) = (180°,180°) in both maps. The preferred conformation of side chains in each region is specified by the labels g^+ (60°), t (180°), and g^- (−60°). ($\chi^{1,1}$ for A; $\chi^{1,1}$ (lower) and $\chi^{1,2}$ (upper) for B).

Results and Discussion

Figure 1 gives the conformational energy space of the blocked single residues Ac-D-Iva-NHMe and Ac-Dpg-NHMe. The

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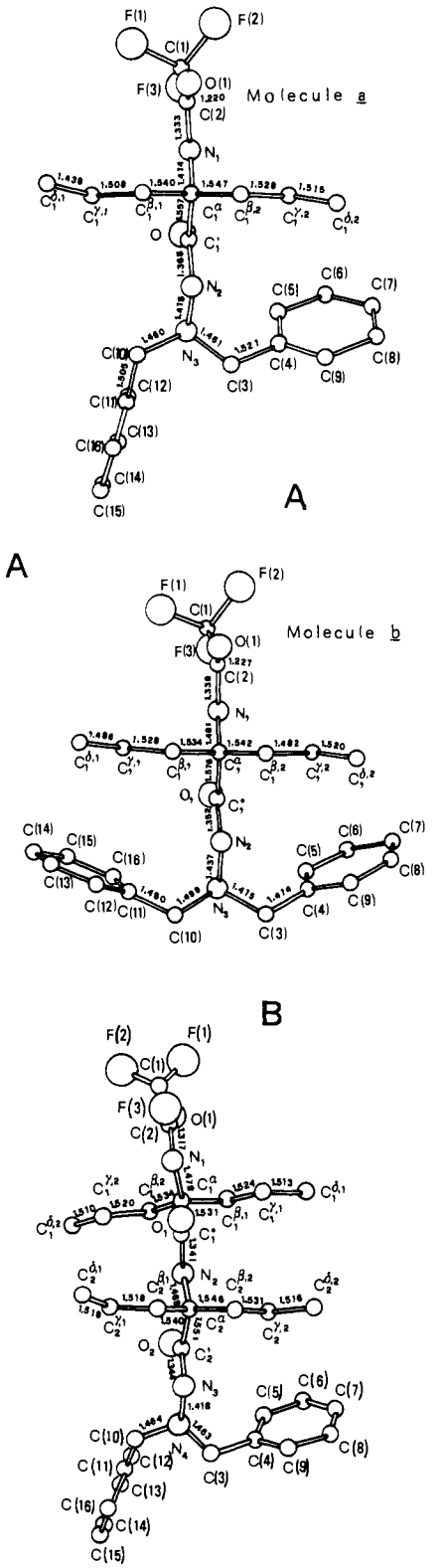

Figure 2. Molecular structures of (A) Tfa-Dpg-DBH showing bond lengths (Å) for the two independent molecules. Other bond lengths for molecule a: C(1)–C(2), 1.565, and C_1'–O_1, 1.209. For molecule b: C(1)–C(2), 1.578, and C_1'–O_1, 1.217. In (B) are shown bond lengths for Tfa(Dpg)$_2$DBH. Other bond lengths (not shown in the figure): C(1)–C(2), 1.541; C(2)–O(1), 1.218; C_1^{α}–C_1', 1.566; C_1'–O_1, 1.222; and C_2'–O_2, 1.216.

corresponding minimum energy conformations are given in Table II, together with literature data for Ac-Aib-NHMe[2,3,5-8] and the single minimum computed for Ac(Dpg)$_2$NHMe. Figures 2 and 3 show the molecular structures of Tfa(Dpg)$_{1,2}$DBH, respectively, determined by X-ray diffraction, with bond lengths and bond angles, respectively. Bond distances have not been corrected for thermal motions. The internal rotation angles describing the

Table III. Conformational Parameters[a] for the Amino Acid Residues of Tfa(Dpg)$_{1,2}$DBH

	Tfa-Dpg-DBH		Tfa(Dpg)$_2$DBH	
angle	molecule A[b]	molecule B[b]	residue 1	residue 2
ϕ	176.0	177.0	179.5	172.5
ψ	175.9	174.8	169.4	−179.4
ω	174.9	178.0	170.3	−177.7
$\chi^{1,1}$	58.1	51.3	59.3	54.9
$\chi^{2,1}$	−167.0	−173.8	−179.5	−165.6
$\chi^{1,2}$	−55.9	−53.5	−60.3	−58.0
$\chi^{2,2}$	−173.1	−174.5	178.1	173.7

[a] According to the IUPAC-IUB convention.[24] In the χ^{ij} notation i refers to the bond about which the angle is measured (i = 1 refers to C^{α}–C^{β}; i = 2 refers to C^{β}–C^{γ}), while j indicates the side chain (1 or 2) on the same residue. [b] In the same crystal, two molecules are present as independent units.

Table IV. Additional Internal Rotation Angles for Tfa(Dpg)$_{1,2}$DBH

	Tfa-Dpg-DBH[a]		
angle	molecule A	molecule B	Tfa-(DPg)$_2$DBH
C_1^{α}–N_1–C(2)–C(1)	−173	−171	−179
C_1^{α}–N_1–C(2)–O(1)	5	5	1
$C_1^{\beta,1}$–C_1^{α}–N_1–C(2)	60	61	63
$C_1^{\gamma,1}$–$C_1^{\beta,1}$–C_1^{α}–N_1	58	51	59
$C_1^{\beta,2}$–$C_1^{\gamma,1}$–$C_1^{\beta,1}$–C_1^{α}	−167	−174	−179
$C_1^{\beta,2}$–C_1^{α}–N_1–C(2)	−65	−65	−60
$C_1^{\beta,2}$–C_1^{α}–$C_1^{\beta,1}$–$C_1^{\gamma,1}$	177	−177	−177
$C_1^{\gamma,2}$–$C_1^{\beta,2}$–C_1^{α}–N_1	−56	−54	−60
$C_1^{\gamma,2}$–$C_1^{\beta,2}$–C_1^{α}–$C_1^{\beta,1}$	180	−179	176
$C_1^{\delta,2}$–$C_1^{\gamma,2}$–$C_1^{\beta,2}$–C_1^{α}	−173	−175	178
C_1'–C_1^{α}–N_1–C(2)	176	177	179
C_1'–C_1^{α}–$C_1^{\beta,1}$–$C_1^{\gamma,1}$	−53	−59	−53
C_1'–C_1^{α}–$C_1^{\beta,2}$–$C_1^{\gamma,2}$	57	59	54
O_1–C_1'–C_1^{α}–N_1	−6	−6	−13
O_1–C_1'–C_1^{α}–$C_1^{\beta,1}$	111	111	104
O_1–C_1'–C_1^{α}–$C_1^{\beta,2}$	−126	−126	−132
N_2–C_1'–C_1^{α}–N_1	176	175	169
N_2–C_1'–C_1^{α}–$C_1^{\beta,1}$	−68	−68	−73
N_2–C_1'–C_1^{α}–$C_1^{\beta,2}$	56	55	50
C_2^{α}–N_2–C_1'–C_1^{α}			170
C_2^{α}–N_2–C_1'–O_1			−7
$C_2^{\beta,2}$–C_2^{α}–N_2–C_1'			−70
$C_2^{\gamma,2}$–$C_2^{\beta,2}$–C_2^{α}–N_2			−58
$C_2^{\delta,2}$–$C_2^{\gamma,2}$–$C_2^{\beta,2}$–C_2^{α}			174
$C_2^{\beta,1}$–C_2^{α}–N_2–C_1'			53
$C_2^{\beta,1}$–C_2^{α}–$C_2^{\beta,2}$–$C_2^{\gamma,2}$			178
$C_2^{\gamma,1}$–$C_2^{\beta,1}$–C_2^{α}–N_2			55
$C_2^{\gamma,1}$–$C_2^{\beta,1}$–C_2^{α}–$C_2^{\beta,2}$			178
$C_2^{\delta,1}$–$C_2^{\gamma,1}$–$C_2^{\beta,1}$–C_2^{α}			−166
C_2'–C_2^{α}–N_2–C_1'			172
C_2'–C_2^{α}–$C_2^{\beta,2}$–$C_2^{\gamma,2}$			54
C_2'–C_2^{α}–$C_2^{\beta,1}$–$C_2^{\gamma,1}$			−59
O_2–C_2'–C_2^{α}–N_2			1
O_2–C_2'–C_2^{α}–$C_2^{\beta,2}$			−116
O_2–C_2'–C_2^{α}–$C_2^{\beta,1}$			120
N_3–C_2'–C_2^{α}–N_2			−179
N_3–C_2'–C_2^{α}–$C_2^{\beta,2}$			63
N_3–C_2'–C_2^{α}–$C_2^{\beta,1}$			−60
[a]N_4–N_3–C_2'–C_2^{α}	175	178	−178
[a]N_4–N_3–C_2'–O_2	−3	−1	2
[a]C(3)–N_4–N_3–C_2'	127	119	135
[a]C(4)–C(3)–N_4–N_3	−68	−64	−65
[a]C(5)–C(4)–C(3)–N_4	−30	−51	−39
[a]C(9)–C(4)–C(3)–N_4	152	131	141
[a]C(10)–N_4–N_3–C_2'	−108	−120	−99
[a]C(10)–N_4–C(3)–C(4)	171	178	170
[a]C(11)–C(10)–N_4–N_3	176	65	163
[a]C(11)–C(10)–N_4–C(3)	−63	−176	−72
[a]C(12)–C(11)–C(10)–N_4	−51	−130	−51
[a]C(16)–C(11)–C(10)–N_4	129	52	129

[a] For Tfa-Dpg-DBH, having only one Dpg residue, the index 2 in C_2', C_2^{α}, and O_2 must be read as 1 (e.g., C_1', C_1^{α}, O_1), while N_4 and N_3 must be read as N_3 and N_2, respectively.

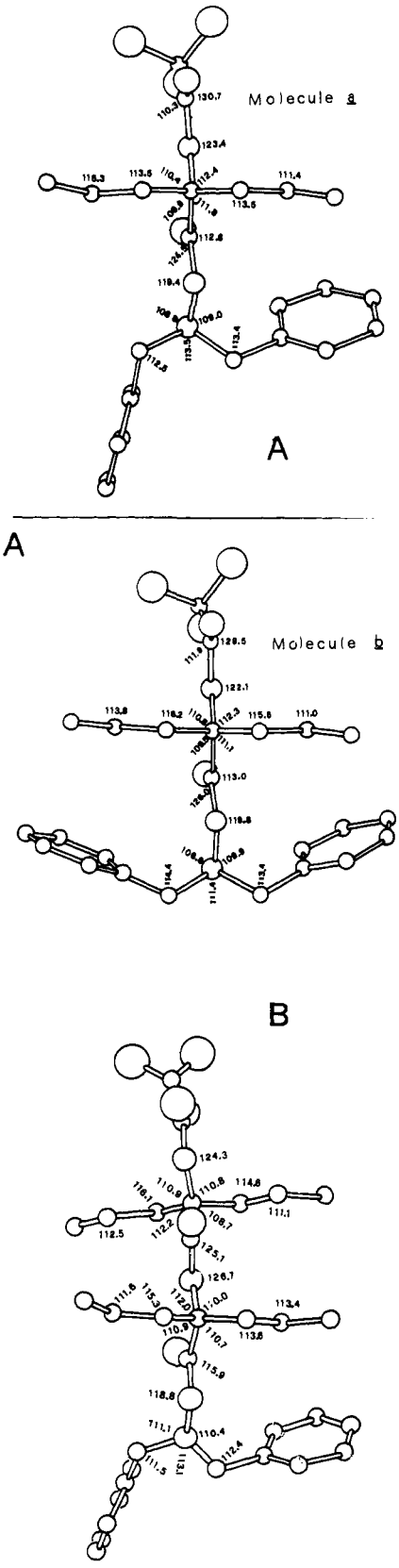

Figure 3. Molecular structures of (A) Tfa-Dpg-DBH and (B) Tfa-(Dpg)$_2$DBH showing bond angles. Additional bond angles for the molecular structure of Tfa-Dpg-DBH (molecule a): C(1)-C(2)-O(1), 119.0°; N_1-C_1^{α}-C_1', 101.1°; $C_1^{\beta,1}$-C_1^{α}-$C_1^{\beta,2}$, 110.9°; C_1^{α}-C_1'-O_1, 122.6°. For molecule b: C(1)-C(2)-O(1), 118.6°; N_1-C_1^{α}-C_1', 101.1°; $C^{\beta,1}$-C_1^{α}-$C_1^{\beta,2}$, 111.5°; C_1^{α}-C_1'-O_1, 121.0°. For Tfa(Dpg)$_2$DBH other bond angles (not shown in the figure): C(1)-C(2)-O(1), 118.2°; C-(1)-C(2)-N_1, 111.9°; O(1)-C(2)-N_1, 129.9°; N_1-C_1^{α}-C_1', 103.0°; $C_1^{\beta,1}$-C_1^{α}-$C_1^{\beta,2}$, 111.0°; C_1^{α}-C_1'-O_1, 120.2°; C_1^{α}-C_1'-N_2, 114.6°; N_2-C_2^{α}-C_2, 102.3°; $C_2^{\beta,1}$-C_2^{α}-$C_2^{\beta,2}$, 112.0°; C_2^{α}-C_2'-O_2, 121.9°.

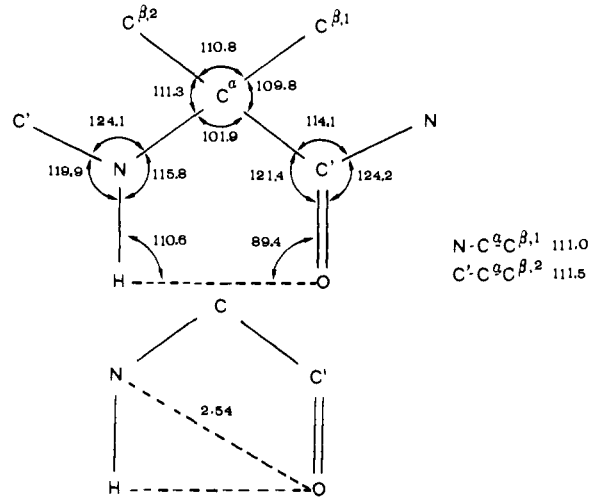

Figure 4. Parameters characterizing the C_5 ring structure. The values shown are the average of the observed H-bonded intramolecular structures.

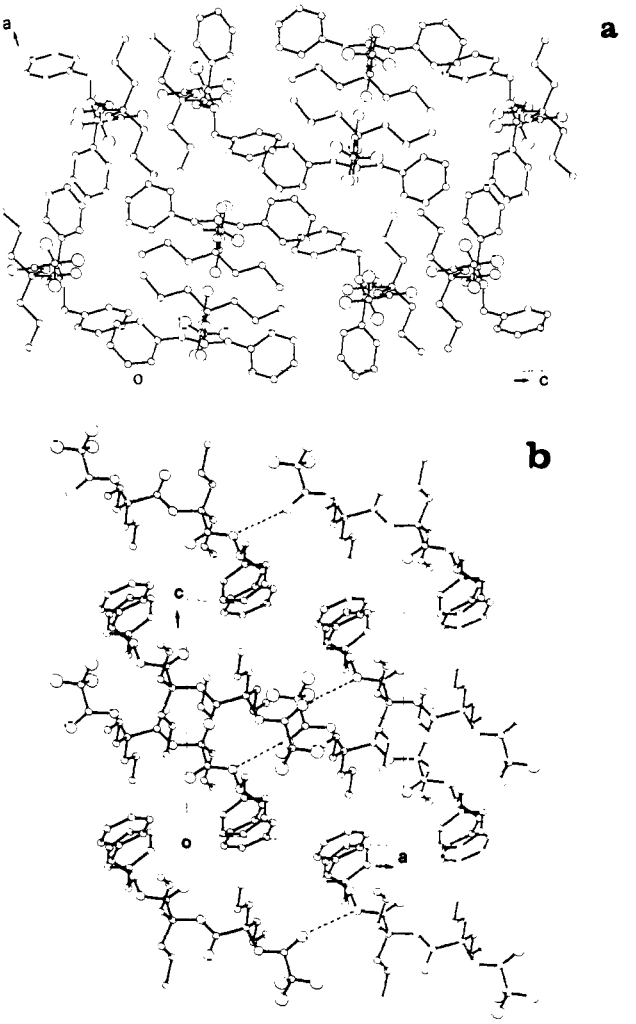

Figure 5. Intramolecular hydrogen bonds and modes of packing of the (a) Tfa-Dpg-DBH and (b) Tfa(Dpg)$_2$DBH molecules projected down the *b* axis.

conformations of the Dpg residues[44] in the two compounds are listed in Table III. The parameters characterizing the C_5 annular system[45] (see discussion below) are reported in Figure 4. Ad-

(44) IUPAC-IUB Commission on Biochemical Nomenclature: *Biochemistry* **1970**, *9*, 3471-3479.

ditional internal rotation angles are given in Table IV. The modes of packing of the two compounds are illustrated in Figure 5.

For $Ac(Dpg)_{1,2}NHMe$ the minimum energy conformations correspond to the fully extended structure (Table II). In both compounds this structure appears to be significantly more stable than any other. In the blocked dipeptide in practice this became the *only* minimum calculated. A comparison with Ac-D-Iva-NHMe and Ac-Aib-NHMe, with a methyl and an ethyl group or two methyl groups as substituents at the C^α carbon, indicates that, while long alkylated side chains (Dpg) induce the preferential formation of a *fully extended* backbone conformation, in the α,α-dimethylated residue (Aib) *folded* forms of either the 3_{10}- or α-helical type are the most stable conformations.[2,3,5-8] On the contrary, in the case of the Iva residue (with its side chains of intermediate bulkiness) several conformations, including the aforementioned extended and folded conformations, represent local minima of *comparable* energy.

In order to compare the results of the theoretical computations with the preferred conformations in the solid state of Dpg, Iva, and Aib derivatives and peptides, we decided to examine by X-ray diffraction $Tfa(Dpg)_{1,2}DBH$. Aib and Iva derivatives and homopeptides have already been studied by X-ray diffraction[12,14-23] [for Iva, only the structure of the N-monochloroacetylated (mClAc) derivative of the D-enantiomer has been determined[12]]; however, no such an experimental study has been reported so far for Dpg derivatives and peptides. The two blocking groups, Tfa and DBH, have been selected for this investigation because, inter alia, their concomitant presence induces a high crystallinity to the resulting compounds.[13] The crystal structures of only two trifluoroacetamides,[46,47] one Tfa amino acid (Tfa-Aib-OH)[17] and one Tfa peptide (Tfa-L-Lys-L-Ala-NH-C_6H_4-pCF_3, bound to the enzyme elastase)[48] have been solved. Conversely, the crystal structures of a number of acyl hydrazides are available.[49-56]

Bond distances of both $Tfa(Dpg)_{1,2}DBH$ have largely unexceptional values (Figure 2). The amide and peptide groups and the benzene rings show geometries close to the expected values.[57-59]

In both compounds a few bond angles, however, present a clear-cut trend (Figure 3): the $N-C^\alpha-C'$ angle of the Dpg residues has markedly smaller values than the tetrahedral value, while the angles $C^\alpha-C^{\beta 1}-C^{\gamma 1}$ and $C^\alpha-C^{\beta 2}-C^{\gamma 2}$ tend to be on the average larger than the tetrahedral angle. This result is good evidence for the presence of the strain introduced by intramolecularly H-bonded structures of the C_5 type.[45] $Tfa(Dpg)_2DBH$ represents the first peptide where two consecutive C_5 ring structures have been determined in the solid state. Figure 4 gives details of the parameters characterizing this conformation. The occurrence of this type of intramolecular H-bond is confirmed by the increase in the $C'-N-C^\alpha$ angle as compared to the average angle in peptide structures[58] and by the concomitant decrease with respect to the literature values[58] of the other angles on the nitrogen atom.

As shown in Table III, the Dpg residues in both compounds have backbone dihedral angles φ, ψ, and ω close to the fully extended, C_5 conformation.[45] Of the two *n*-propyl side chains on each Dpg residue, one has the g^- conformation and the other the g^+ conformation for the χ^1 dihedral angle, while for both side chains the χ^2 angles exhibit only the *trans* conformation. Such a conformation of the two *n*-propyl moieties of the Dpg residues allows the molecules to release the intramolecular main-chain–side-chain and side-chain–side-chain interactions and to adopt the C_5 backbone conformation.

The rotational disorder, typical of the trifluoroacetamido group,[46] unless rigidly bound in the active site of an enzyme,[48] is found also in these two compounds. In the structures of the amino acid derivative and the dipeptide, the $C_1^\alpha-C_1'-O_1-N_2$ and $C_2^\alpha-C_2'-O_2-N_3$ amide-type groups of the acylhydrazido moiety, respectively, are planar to within 0.04 Å.[49-56] In both structures the conformation is *Z* about the carbonyl carbon–nitrogen amide-type bond of the acylhydrazido moiety[49-56] (in other words, the –CO–NH group is *trans*, as expected for a secondary amide[58]) (Table IV). The *N',N'*-dibenzylacylhydrazido moieties in all molecules of both structures show a planar nitrogen atom linked to the terminal carbonyl group of the peptide chain and a tetrahedral nitrogen atom, disubstituted with two benzyl groups, which presents an average value of 110° for its angles.[49,50,56] Furthermore, the observed dihedral angles around the –NH–N bond show skew values with respect to the two methylene carbons of the benzyl groups (~+120°, ~−120°).[49,50,56] The conformation of the benzyl groups is of the type t,g^- in both groups of Tfa-$(Dpg)_2$DBH and in one molecule of the independent unit of Tfa-Dpg-DBH, whereas it is of the type g^-,g^+ in the other molecule of the independent unit of Tfa-Dpg-DBH.[49] In the Tfa-Dpg-DBH structure then, both conformations are observed, while in the $Tfa(Dpg)_2DBH$ structure only the t,g^- is seen. This demonstrates a certain degree of conformational freedom for the rotation around the $NH-N(CH_2-Ar)_2$ bonds, and the observed conformation is the result of minimization of crystal packing forces.

Additional, although indirect, support to the existence of the intramolecularly H-bonded C_5 conformation in the two compounds is given by the observation that the pertinent amide and peptide N—H groups and peptide and acylhydrazido C=O groups are not involved in the intermolecular H-bonding schemes (Figure 5). The molecules in the crystals are held together by van der Waals interactions and intermolecular H-bonds between the only N—H and C=O groups left (the trifluoroacetamido C=O and the acylhydrazido N—H groups). The $N_3\cdots O(1)$ distance in the dipeptide is 3.11 Å, while the $N_2\cdots O(1)$ distances for the two molecules in the independent unit of the amino acid derivative are 3.04 and 3.10 Å. The average N···O distance for a N—H···O=C H-bond in peptides is 2.92 Å.[60,61]

In summary, in this study we have shown that the most stable conformation calculated for Dpg derivatives and the homodipeptide is the fully extended conformation. As for the energy differences between the *higher energy* minima associated with the 3_{10}- and α-helical regions, in view of the assumptions on the geometrical parameters and small ΔE values between them, their rank order is merely indicative. We have also demonstrated that in the case of the Iva residue several conformations, including the fully extended and folded conformations, represent local minima of comparable energy. Interestingly, the most stable folded (helical) conformation of the D-Iva enantiomer exhibits a set of φ,ψ angles typical of an α-monoalkylated L-amino acid in a *right*-handed helical conformation. This important result allows us to clarify a previously unexplained finding, namely that the naturally occurring peptaibol antibiotics, known to adopt *right*-handed helical structures,[24] incorporate in their sequences D-Iva residues.[4,9-11] Finally, the conformational preferences of the Aib residue are

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again slightly different, in the sense that theoretical studies on Aib derivatives and homopeptides have provided strong support for the preference of this residue for ϕ,ψ values in the 3_{10}- and α-helical regions of the Ramachandran map.[2,3,5-8]

We have also been able to demonstrate that the results of our theoretical analysis of the conformation of the Dpg derivative and homodipeptide are in excellent accord with their conformational preferences in the solid state, determined by X-ray diffraction and also described in this paper; in particular, one intramolecularly H-bonded C_5 conformation is present in the amino acid derivative, while two such forms are found consecutively in the dipeptide. It seems, therefore, that the influence of the N- and C-blocking groups used in this work on the conformational preferences of the Dpg residue is negligible. In particular, the trifluoromethyl group of the Tfa moiety is not rigid, but rather it shows rotational isomerization even in the solid state. In addition, we are tempted to exclude an influence of the DBH blocking group in view of a comparison with the infrared absorption and ^{1}H NMR results on the corresponding *tert*-butyl ester peptides.[62]

The only Iva-containing compound so far investigated by X-ray diffraction, mClAc-D-Iva-OH,[12] also adopts a fully extended C_5 conformation in the solid state, that is, one of the minimum energy conformations calculated in this work for this residue. Clearly, however, the structures of several carefully selected Iva-containing peptides should be solved before we could have in hand a complete picture of the conformations adopted by this residue in the solid state. Suitable candidates for this investigation appear to be peptides long enough (N- and C-blocked tripeptides and longer peptides) to assume a 3_{10}- or an α-helical structure, particularly with sequences corresponding to segments of the Iva-containing peptaibol antibiotics.[4,9-11] This study will also provide an experimental support to the preferred screw sense of the helical structures of Iva-containing peptides suggested by the theoretical analysis described here.

Finally, the conformational properties of a number of Aib derivatives and linear homo- and co-oligopeptides have been determined in the solid state by X-ray diffraction.[4,14-36] As expected from the conformational energy computations,[2,3,5-8] all sets of ϕ,ψ angles (but one) are found in the region of the Ramachandran map that includes both the 3_{10}-helical and α-helices.

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Registry No. Ac-Dpg-NHMe, 93039-01-1; Ac-$(Dpg)_2$-NHMe, 93000-44-3; Ac-D-Iva-NHMe, 93000-45-4; Tfa-Dpg-DBH, 87112-93-4; Ifa-(Dpg)-DBH, 87112-98-9.

Supplementary Material Available: Listings of positional parameters for Tfa-Dpg-DBH and Tfa$(Dpg)_2$DBH (4 pages). Ordering information is given on any current masthead page.

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Folded and Extended Structures of Homooligopeptides from α,α-Dialkylated α-Amino Acids. An Infrared Absorption and ^{1}H Nuclear Magnetic Resonance Study

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Abstract: The conformational preferences of the N- and C-protected homopeptides from α,α-di-*n*-propylglycine (to the pentapeptide) in the solid state and in chloroform solution have been assessed by using infrared absorption and ^{1}H nuclear magnetic resonance. A comparison is made with the conformations adopted by the corresponding series from α-aminoisobutyric acid, also dialkylated at the α-carbon, and from L-norvaline, in which the single alkyl side chain is the same as those in α,α-di-*n*-propylglycine. The highest L-norvaline homopeptides exhibit a significant tendency for adopting an *intermolecularly* H-bonded β-structure, in contrast to the α,α-di-*n*-propylglycine and α-aminoisobutyric acid peptides where *intramolecular* H-bonding is the dominating factor. The likely absence of a conformational transition with increasing main-chain length and the exceptional structural stability upon heating of *all* the α,α-di-*n*-propylglycine homopeptides represent an additional relevant finding of the present work.

Structural restrictions of bioactive peptides via backbone modifications reduce the difficulties of the determination of the relationships between conformation and activity, an important goal of contemporary biochemistry.

In the preceding paper[2] we have shown by conformational energy computations that the preferred conformational space for the α,α-di-*n*-propylglycine (Dpg) residue occurs in the region of the fully extended structure. This theoretical result has been confirmed by an experimental investigation in the solid state on a Dpg derivative and a fully protected homodipeptide carried out by X-ray diffraction. In contrast, the α,α-dimethylglycine, or α-aminoisobutyric acid (Aib), residue, is known to prefer a conformation close to the region where the 3_{10}- and α-helices are found.[3]

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