

## A Helical Dpg Homo-peptide

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The first X-ray diffraction structure analysis of a helical homo-peptide of C<sup>α</sup>-dipropylglycine (Dpg) has been performed for Tfa-(Dpg)<sub>3</sub>-DBH monohydrate.

In recent years conformational energy computations and solution- and crystal-state structural analyses of a variety of derivatives and short peptides from the C<sup>α</sup>-disubstituted α-amino acids Deg (C<sup>α</sup>-diethylglycine) and Dpg (C<sup>α</sup>-dipropylglycine) have been carried out.<sup>1-12</sup> It was found that: (a) the conformational space available for exploration by these residues is severely restricted; and (b) the minimum energy conformation, corresponding to the fully-extended (C<sub>5</sub>) structure,<sup>13</sup> is that commonly observed experimentally. A comparison with peptides of Aib (α-aminoisobutyric acid, or C<sup>α</sup>-dimethylglycine), Iva (isovaline, or C<sup>α</sup>-methyl, C<sup>α</sup>-ethylglycine), and Ac<sub>n</sub>c (1-aminocycloalkane-1-carboxylic acid),<sup>7-11</sup> where the occurrence of the fully-extended structure is a rare event, indicates that this conformation becomes more stable than the α/3<sub>10</sub>-helical structures when the two side-chain C<sup>β</sup> atoms are symmetrically substituted, but not interconnected in a cyclic system.

In this paper we describe the results of our X-ray diffraction analysis of the terminally-blocked homo-tripeptide Tfa-(Dpg)<sub>3</sub>-DBH (Tfa, trifluoroacetyl; DBH, N',N'-dibenzylhydrazido). This is the first example of a helical conformation observed for a homo-peptide of either the Deg or the Dpg residue. As shown by theoretical calculations,<sup>7</sup> for these residues helical conformations, although of higher energy, are nevertheless possible.

### Experimental

Tfa-(Dpg)<sub>3</sub>-DBH was obtained in excellent yield (86%) by melting together the (4H)-oxazol-5-one of Tfa-Dpg-OH and H-(Dpg)<sub>2</sub>-DBH.<sup>14,15</sup> Colourless crystals, suitable for X-ray diffraction analysis, of Tfa-(Dpg)<sub>3</sub>-DBH monohydrate were grown from an isopropyl alcohol-acetone mixture by slow evaporation.

*Crystallography.*—Preliminary Weissenberg photographs were used to determine the crystal system and the space group. A CAD-4 Enraf-Nonius diffractometric system, equipped with PDP-8 and PDP-11 digital computers was used for determination of the unit cell constants, data collection, structure determination and refinement.

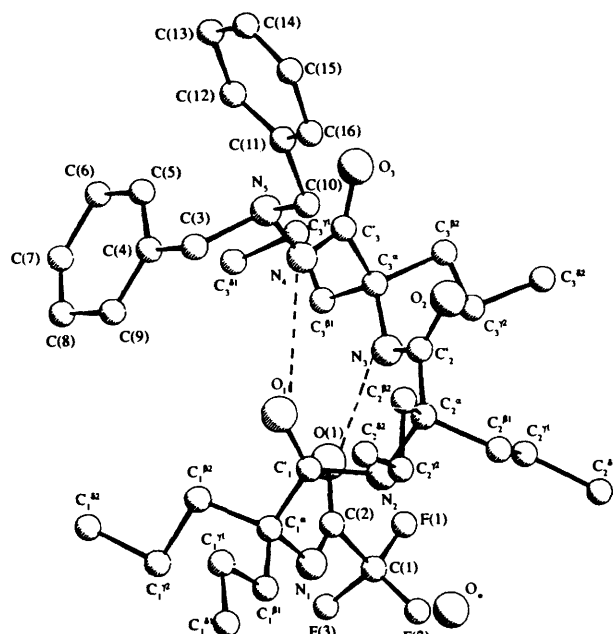
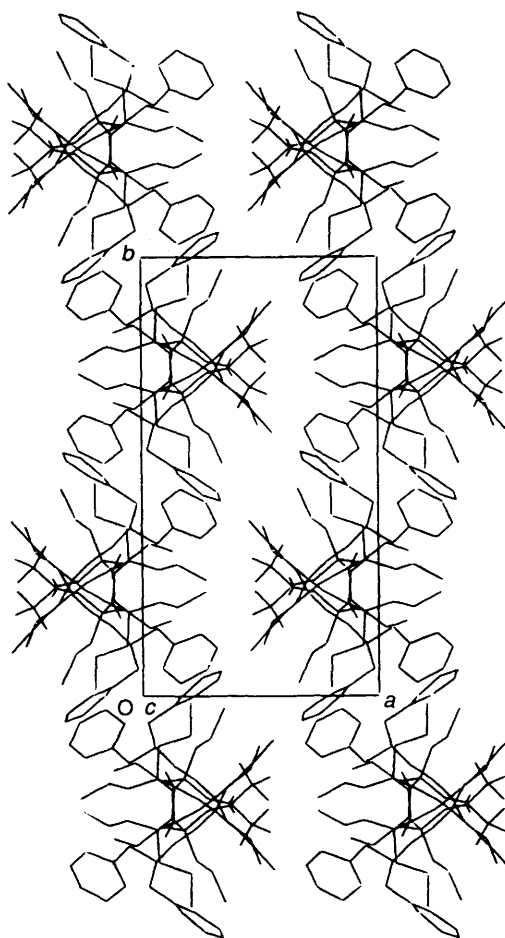
*Crystallographic data.* Monoclinic, space group P2<sub>1</sub>/c, *a* = 15.907(1), *b* = 20.481(5), *c* = 20.070(1) Å, β = 135.74(8)°, *V* = 4563.1(3) Å<sup>3</sup>, *Z* = 4, *D<sub>x</sub>* = 1.065 mg m<sup>-3</sup>, *D<sub>m</sub>* = 1.06 mg m<sup>-3</sup> (floatation), *F*(000) = 404. The analysis of the peak profile suggested an ω-2θ scan mode with a range of (1.1 + 0.20tanθ)° for the peak measurements; background counts were taken at both sides of each scan. A distance crystal-counter of 368 mm was used with a counter entrance aperture of 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<sup>-1</sup>. Reflections with a net intensity *I* ≤ 0.5 σ(*I*)

were flagged as 'weak'; those with *I* > 0.5 σ(*I*) were measured at lower speed in the range 1-4° min<sup>-1</sup>, depending on the value σ(*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. A total of 5947 independent reflections were measured using Cu-Kα radiation (λ = 1.5418 Å) and corrected for Lorentz and polarization factors. No absorption correction was applied because of the size of the crystal (0.2 × 0.3 × 0.2 mm); only 1153 reflections were considered 'observed', having net intensity *I* greater than 3σ(*I*). The structure was solved with MULTAN:<sup>16</sup> the *E*-map corresponding to the highest combined figure of merit revealed the positions of most of the atoms in the molecule. By successive difference Fourier maps it was possible to locate the rest of the atoms and to realize that statistical disorder was affecting both the *N*-terminal trifluoroacetyl group and one of the Dpg propyl side chains. In both cases it was soon evident that the atoms belonging to these groups were statistically positioned in two conformations almost equally represented in the crystal. In one conformation of the trifluoroacetyl group 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. The side chains in one of the propyl groups of the *C*-terminal Dpg residue are found in the two possible conformations for this alkyl group in which the torsion angles (χ<sup>1</sup>, χ<sup>2</sup>) are either (*g*<sup>+</sup>, *t*) or (*t*, *t*) with occupancy factors of 0.75 and 0.25, respectively. These conformations are also the only ones observed for all other propyl groups in the structure. In the calculations the two sets of disordered groups (trifluoroacetyl and one propyl) were refined with isotropic thermal parameters. All the remaining C, N and O atoms were refined anisotropically. Most of the hydrogen atoms were located by difference Fourier maps; the others were included in their stereochemically expected positions with isotropic thermal factors equal to the *B* equivalent of the carrier atom. The scattering factors for all atomic species were calculated from Cromer and Waber.<sup>17</sup> All measurements and calculations were carried out at the *Centro Interdipartimentale di Metodologie Chimico-fisiche* of the University of Naples. The final value for the weighted *R* factor is 0.095 for the 1153 observed reflections. This rather high value reflects the poor quality of the crystal and, in part, is due to the statistical and thermal disorder of the structure. Atomic coordinates, bond lengths and angles are given in Tables 1-3. Torsion angles and thermal parameters are available from the Cambridge Crystallographic Data Centre.\*

\* For details of the CCDC deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1992, issue 1.

**Table 1** Positional parameters with esds in parentheses for Tfa-(Dpg)<sub>3</sub>-DBH

Atom	x	y	z
F(1)	0.589(1)	0.345(1)	0.097(1)
F(2)	0.474(1)	0.260(1)	0.013(1)
F(3)	0.462(1)	0.313(1)	0.101(1)
C(1)	0.537(1)	0.294(1)	0.097(1)
C(2)	0.632(1)	0.2480(8)	0.1824(9)
O(1)	0.6185(8)	0.2296(6)	0.2312(6)
N(1)	0.7272(8)	0.2364(6)	0.1973(6)
C(A1)	0.826(1)	0.1910(8)	0.2743(8)
C(B11)	0.922(1)	0.1982(9)	0.2756(9)
C(G11)	1.031(1)	0.154(1)	0.347(1)
C(D11)	1.127(1)	0.171(1)	0.349(1)
C(B12)	0.780(1)	0.1213(8)	0.2574(9)
C(G12)	0.722(1)	0.0962(9)	0.1608(9)
C(D12)	0.660(1)	0.026(1)	0.141(1)
C'(1)	0.872(1)	0.2128(8)	0.3653(8)
O(1)	0.9092(7)	0.1738(5)	0.4305(6)
N(2)	0.8838(8)	0.2805(6)	0.3839(6)
C(A2)	0.936(1)	0.3079(8)	0.4771(8)
C(B21)	0.931(1)	0.3839(9)	0.4595(9)
C(G21)	0.803(1)	0.410(1)	0.388(1)
C(D21)	0.803(1)	0.186(1)	0.369(1)
C(B22)	1.069(1)	0.2882(9)	0.5589(9)
C(G22)	1.148(1)	0.298(1)	0.542(1)
C(B22)	1.270(2)	0.262(1)	0.616(1)
C'(2)	0.872(1)	0.2906(8)	0.5019(9)
O(2)	0.9165(8)	0.3055(6)	0.5799(6)
N(3)	0.7653(8)	0.2614(6)	0.4343(6)
C(A3)	0.701(1)	0.2345(8)	0.4547(8)
C(B31)	0.601(1)	0.1903(9)	0.3733(9)
C(G31)	0.533(2)	0.152(1)	0.387(1)
C(D31)	0.444(2)	0.100(2)	0.301(2)
C(B32)	0.645(1)	0.2903(9)	0.4650(9)
C(G32)	0.552(1)	0.331(1)	0.371(1)
C(D32)	0.509(2)	0.388(1)	0.387(1)
C'(3)	0.783(1)	0.1927(8)	0.5442(8)
O(3)	0.7777(7)	0.1907(6)	0.6029(6)
N(4)	0.8690(9)	0.1604(7)	0.5594(7)
N(5)	0.9461(9)	0.1178(7)	0.6378(7)
C(3)	0.972(1)	0.060(1)	0.605(1)
C(4)	0.861(1)	0.020(1)	0.528(1)
C(5)	0.789(1)	0.001(1)	0.537(1)
C(6)	0.681(2)	-0.036(1)	0.464(1)
C(7)	0.674(2)	-0.056(1)	0.396(1)
C(8)	0.738(2)	-0.040(1)	0.382(1)
C(9)	0.847(2)	-0.000(1)	0.454(1)
C(10)	1.059(1)	0.151(1)	0.720(1)
C(11)	1.132(1)	0.117(1)	0.816(1)
C(12)	1.082(2)	0.063(1)	0.816(1)
C(13)	1.161(2)	0.032(1)	0.913(1)
C(14)	1.267(2)	0.060(1)	0.987(1)
C(15)	1.313(2)	0.109(1)	0.980(1)
C(16)	1.250(1)	0.140(1)	0.893(1)
O(W)	0.858(1)	0.3757(8)	0.2572(8)

**Fig. 1** Molecular structure of Tfa-(Dpg)<sub>3</sub>-DBH monohydrate with numbering of the atoms. The two intramolecular hydrogen bonds are indicated by dashed lines. In this figure the right-handed 3<sub>10</sub>-helical structure is shown.**Fig. 2** Mode of packing of the Tfa-(Dpg)<sub>3</sub>-DBH molecules projected down the *c* axis

## Results and Discussion

Fig. 1 shows the molecular structure of Tfa-(Dpg)<sub>3</sub>-DBH. Bond lengths have not been corrected for thermal motion (in a few cases large deviations are present, reflecting the disorder observed in the crystal). The amide<sup>18,19</sup> and peptide groups<sup>20</sup> and the benzene rings show geometries close to the expected values.

The three Dpg residues have the following backbone torsion angles: \*  $\phi_1 = \pm 54.8^\circ$ ,  $\psi_1 = \pm 39.4^\circ$ ;  $\phi_2 = \pm 59.9^\circ$ ,  $\psi_2 = \pm 10.2^\circ$ ;  $\phi_3 = \pm 48.3^\circ$ ,  $\psi_3 = \pm 32.9^\circ$ . The average values for  $\phi, \psi$  are  $\pm 54.3^\circ$  and  $\pm 27.5^\circ$ , respectively, falling in the helical

\* Peptide torsion angles are defined according to the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature.<sup>21</sup>

region of the conformational map. In this centrosymmetric crystal, because of the absence of chiral atoms in the tripeptide, molecules with both helical handedness are observed. This

**Table 2** Bond lengths/Å for Tfa-(Dpg)<sub>3</sub>-DBH<sup>a</sup>

Bond	Bond	Bond
F(1)-C(1) 1.33(3)	C(A2)-C(B22) 1.53(2)	N(4)-N(5) 1.41(2)
F(2)-C(1) 1.39(3)	C(A2)-C'(2) 1.46(3)	N(5)-C(3) 1.54(3)
F(3)-C(1) 1.31(4)	C(B21)-C(G21) 1.52(2)	N(5)-C(10) 1.47(2)
C(1)-C(2) 1.54(2)	C(G21)-C(D21) 1.60(3)	C(3)-C(4) 1.51(2)
C(2)-O(1) 1.20(3)	C(B22)-C(G22) 1.53(4)	C(4)-C(5) 1.34(4)
C(2)-N(1) 1.34(2)	C(G22)-C(D22) 1.55(2)	C(4)-C(9) 1.40(2)
N(1)-C(A1) 1.50(2)	C'(2)-O(2) 1.21(2)	C(5)-C(6) 1.44(2)
C(A1)-C(B11) 1.51(3)	C'(2)-N(3) 1.33(2)	C(6)-C(7) 1.36(4)
C(A1)-C(B12) 1.53(2)	N(3)-C(A3) 1.46(3)	C(7)-C(8) 1.28(5)
C(A1)-C'(1) 1.47(2)	C(A3)-C(B31) 1.51(2)	C(8)-C(9) 1.47(3)
C(B11)-C(G11) 1.52(2)	C(A3)-C(B32) 1.55(3)	C(10)-C(11) 1.53(3)
C(G11)-C(D11) 1.54(4)	C(A3)-C'(3) 1.52(2)	C(11)-C(12) 1.35(3)
C(B12)-C(G12) 1.52(2)	C(B31)-C(G31) 1.51(4)	C(11)-C(16) 1.41(2)
C(G12)-C(D12) 1.61(3)	C(G31)-C(D31) 1.63(4)	C(12)-C(13) 1.50(3)
C'(1)-O(1) 1.26(2)	C(B32)-C(G32) 1.56(2)	C(13)-C(14) 1.33(2)
C'(1)-N(2) 1.41(2)	C(G32)-C(D32) 1.49(4)	C(14)-C(15) 1.31(4)
N(2)-C(A2) 1.51(2)	C'(3)-O(3) 1.24(3)	C(15)-C(16) 1.39(3)
C(A2)-C(B21) 1.58(2)	C'(3)-N(4) 1.34(2)	

<sup>a</sup> Numbers in parentheses are estimated standard deviations in the least significant digits.

**Table 3** Bond angles/° for Tfa-(Dpg)<sub>3</sub>-DBH<sup>a</sup>

Angle	Angle	Angle
F(1)-C(1)-F(2) 107.0(2)	N(2)-C(A2)-C(B22) 110.0(2)	O(3)-C'(3)-N(4) 121.0(1)
F(1)-C(1)-F(3) 111.0(2)	N(2)-C(A2)-C'(2) 116.0(1)	C'(3)-N(4)-N(5) 119.0(2)
F(1)-C(1)-C(2) 111.0(1)	C(B21)-C(A2)-C(B22) 108.0(1)	N(4)-N(5)-C(3) 107.0(1)
F(2)-C(1)-F(3) 110.0(2)	C(B21)-C(A1)-C'(2) 112.0(2)	N(4)-N(5)-C(10) 111.0(1)
F(2)-C(1)-C(2) 109.0(2)	C(B22)-C(A2)-C'(2) 109.0(1)	C(3)-N(5)-C(10) 110.0(1)
F(3)-C(1)-C(2) 109.0(2)	C(A2)-C(B21)-C(G21) 112.0(1)	N(5)-C(3)-C(4) 112.0(2)
C(1)-C(2)-O(1) 119.0(2)	C(B21)-C(G21)-C(D21) 110.0(1)	C(3)-C(4)-C(5) 120.0(2)
C(1)-C(2)-N(1) 114.0(2)	C(A2)-C(B22)-C(G22) 117.0(1)	C(3)-C(4)-C(9) 116.0(2)
O(1)-C(2)-N(1) 127.0(1)	C(B22)-C(G22)-C(O22) 113.0(2)	C(5)-C(4)-C(9) 124.0(2)
C(2)-N(1)-C(A1) 122.0(2)	C(A2)-C'(2)-O(2) 118.0(1)	C(4)-C(5)-C(6) 122.0(2)
N(1)-C(A1)-C(B11) 105.0(1)	C(A2)-C'(2)-N(3) 117.0(1)	C(5)-C(6)-C(7) 111.0(3)
N(1)-C(A1)-C(B12) 111.7(9)	O(2)-C'(2)-N(3) 125.0(2)	C(6)-C(7)-C(8) 130.0(2)
N(1)-C(A1)-C'(1) 108.0(1)	C'(2)-N(3)-C(A3) 122.0(1)	C(7)-C(8)-C(9) 119.0(3)
C(B11)-C(A1)-C(B12) 114.0(2)	N(3)-C(A3)-C(B31) 109.0(2)	C(4)-C(9)-C(8) 113.0(3)
C(B11)-C(A1)-C'(1) 111.0(1)	N(3)-C(A3)-C(B32) 110.0(1)	N(5)-C(10)-C(11) 115.0(2)
C(B12)-C(A1)-C'(1) 107.0(2)	N(3)-C(A3)-C'(3) 111.0(1)	C(10)-C(11)-C(12) 117.0(1)
C(A1)-C(B11)-C(G11) 114.0(2)	C(B31)-C(A3)-C(B32) 109.0(1)	C(10)-C(11)-C(16) 116.0(2)
C(B11)-C(G11)-C(D11) 109.0(2)	C(B31)-C(A3)-C'(3) 107.0(1)	C(12)-C(11)-C(16) 126.0(2)
C(A1)-C(B12)-C(G12) 111.0(2)	C(B32)-C(A3)-C'(3) 110.0(2)	C(11)-C(12)-C(13) 114.0(1)
C(B12)-C(G12)-C(D12) 109.0(2)	C(A3)-C(B31)-C(G31) 116.0(2)	C(12)-C(13)-C(14) 118.0(2)
C(A1)-C'(1)-O(1) 123.0(1)	C(B31)-C(G31)-C(D31) 110.0(3)	C(13)-C(14)-C(15) 125.0(2)
O(A1)-C'(1)-N(2) 119.0(1)	C(A3)-C(B32)-C(G32) 112.0(2)	C(14)-C(15)-C(16) 122.0(2)
O(1)-C'(1)-N(2) 118.0(1)	C(B32)-C(G32)-C(D32) 110.0(2)	C(11)-C(16)-C(15) 115.0(2)
C'(1)-N(2)-C(A2) 123.0(1)	C(A3)-C'(3)-O(3) 124.0(2)	
N(2)-C(A2)-C(B21) 101.0(1)	C(A3)-C'(3)-N(4) 115.0(2)	

<sup>a</sup> Numbers in parentheses are estimated standard deviations in the least significant digits.

incipient  $3_{10}$ -helical conformation<sup>8-11</sup> is stabilized by two intramolecular hydrogen bonds of the 1 $\leftarrow$ 4 type [the N<sub>3</sub>-H...O(1) and N<sub>4</sub>-H...O<sub>1</sub> distances are 2.98 and 3.09 Å, respectively<sup>22,23</sup>] with the formation of C<sub>10</sub> structures<sup>13</sup> (type III or III'  $\beta$ -turns<sup>24</sup> for right- or left-handed helices, respectively).

In a Dpg molecule in the right-handed helical conformation the  $\chi^1$  torsion angles of the two propyl side chains can adopt either the *g*<sup>+</sup> or the *t* conformation ( $\approx +60^\circ$  and  $\approx 180^\circ$ , respectively), while the  $\chi^2$  angles assume values close to the *t* conformation.<sup>7</sup> Such conformations for the propyl moieties allow the Dpg molecules to release the intra- and intermolecular main-chain-to-side-chain interactions. In Tfa-(Dpg)<sub>3</sub>-DBH the ( $\chi^1, \chi^2$ ) values for the two propyl side chains of the N-terminal residue are (*t, t*) and (*g*<sup>+</sup>, *t*), those for the central residue are (*g*<sup>+</sup>, *t*) and (*g*<sup>+</sup>, *t*), while those for the C-terminal residue are (*t, t*) [or (*g*<sup>+</sup>, *t*) for the statistically disordered propyl group] and (*g*<sup>+</sup>, *t*).

The rotational disorder, typical of the trifluoroacetamido group,<sup>25-28</sup> unless rigidly bound in the active site of an enzyme,<sup>29</sup> is found also in this compound. In the structure the amide-type group of the acylhydrazido moiety is planar within 0.01 Å.<sup>1,28</sup> The conformation about the carbonyl carbon-nitrogen amide-type bond is *Z* (in other words, the CO-NH is *trans*, as expected for a secondary amide).<sup>18,19</sup> The N',N'-dibenzylacylhydrazido moiety shows a planar nitrogen atom linked to the terminal carbonyl group of the peptide chain and a tetrahedral nitrogen atom, substituted with two benzyl groups, which presents an average value of 110° for its bond angles. Furthermore, the observed dihedral angles around the N-N bond show values of  $-95^\circ$  and  $144^\circ$  with respect to the two methylene carbons of the benzyl groups; these values deviate slightly from the canonical skew values (120°). It is reasonable to assume that these deviations would represent the results of short- and medium-range interactions between atoms of the

benzyl groups and those of the propyl side chains. The conformation of the benzyl groups is of the  $t_g^-$  type: the dihedral angles N(4)–N(5)–C(10)–C(11) and N(4)–N(5)–C(3)–C(4) have values of  $162^\circ$  and  $-65^\circ$ , respectively.

In the crystal the molecules are held together by the formation of two intermolecular hydrogen bonds also involving the cocrystallized water molecule (Fig. 2). These interactions are N(1)···O(3) (2.94 Å)<sup>22,23</sup> and O(W)···O(3) (2.72 Å).<sup>30–32</sup> The N(2)–H donor group does not participate in the hydrogen bonding scheme, as usually observed in the packing modes of  $3_{10}$ -helical molecules.<sup>8,11</sup> The hydrogen bonded molecules, related by the glide plane along the  $c$  direction form long rows. These rows, packing together in the other direction with a hexagonal arrangement, are stabilized by van der Waals interactions involving the hydrophobic phenyl and propyl groups.

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