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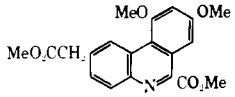

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(20) Of interest is the recent report [S. D. Jolad, J. J. Hoffman, S. J. Torrance, R. M. Wiedhopf, J. R. Cole, S. K. Arora, R. B. Bates, R. L. Gargiulo, and G. R. Kriek, *J. Am. Chem. Soc.*, **99**, 8040 (1977)] on the structure of bouvardin and deoxybouvardin, cyclic hexapeptides from the plant *Bouvardia ternifolia*, which contain a dimeric amino acid derived from oxidative coupling of two tyrosines which are joined in a cis amide bond; in bouvardin one of the tyrosines is hydroxylated at the β position. Such compounds may be far more common than hitherto recognized, having escaped detection by virtue of their lability under traditional degradation conditions.
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(36) NOTE ADDED IN PROOF. Ristomycinic acid obtained from ristomycin has now been established to have structure **12**; see T. M. Harris, C. M. Harris, J. R. Fehlner, R. Bognar, and F. Sztaricskai, *J. Org. Chem.*, in press.

Crystal and Molecular Structure of the Cyclic Hexapeptide *cyclo*-(Gly-Pro-*d*-Phe)$_2$

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Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616. *Received June 29, 1978*

Abstract: The crystal structure of *cyclo*-(Gly-Pro-*d*-Phe)$_2$ (GPF) has been determined by single-crystal X-ray diffraction and refined by block-diagonal least squares to an R value of 0.099. The crystals are monoclinic, $P2_1$, with cell constants of a = 19.694 (1) Å, b = 9.005 (1) Å, c = 10.357 (1) Å, and β = 104.05 (1)°. Although the crystal structure contains dimethyl sulfoxide, the conformation of GPF is similar to that of the hexapeptide *cyclo*-(Ala-Pro-*d*-Phe)$_2$, which has a crystal structure containing water. The structure of GPF consists of two type II β turns without strong 4 → 1 hydrogen bonds.

Introduction

In recent years there has been a steady increase in the frequency of reports in the literature of conformational studies of oligopeptides by either NMR experiments or energy calculations. Although several classes of compounds have been considered, the cyclic hexapeptides have been found amenable to both approaches since they have fewer degrees of freedom than do the analogous acyclic peptides yet still retain sufficient flexibility so that their conformation is not strictly dominated by nearest-neighbor interactions.

Since cyclic hexapeptides without other constraints still possess too many degrees of freedom, we have been interested in the restricted conformations of compounds with the sequence *cyclo*-(1-X-1-Pro-*d*-Phe)$_2$ in which the existence of two Pro residues restricts the available conformational space the peptide may occupy. These compounds have been postulated[1,2] to possess C_2 symmetry with the 1-Pro in the 2 position of a type II β turn which is stabilized by a 4 → 1 hydrogen bond between the N-H of X in position 1 and the C=O of the symmetry-related X in position 4. We have previously determined the crystal structure of *cyclo*-(1-Ala-1-Pro-*d*-Phe)$_2$,[3] hereafter referred to as APF, which has a conformation qualitatively similar to that postulated by NMR[1] but does not possess the anticipated strong 4 → 1 hydrogen bonds, although it does adapt a conformation characteristic of double type II β turns.

However, the more interesting result from the crystal structure of APF was not the agreement of the X-ray and NMR experiments but rather the hydration that accompanied the crystal structure. Since the peptide literally lies in a sea of solvent such that there are no peptide–peptide intermolecular hydrogen bonds, it is a prime example for studying the influence of water on its conformation. In order to more fully understand the influence of hydration (which must be the dominating intermolecular force in solution) on peptide conformation, we have continued to examine crystals of the sequence *cyclo*-(1-X-1-Pro-*d*-Phe)$_2$ and report in this paper the crystal

0002-7863/79/1501-0445$01.00/0

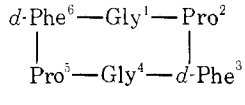
Table I. Fractional Atomic Coordinates and esd's

	x	y	z
N_1	0.5973 (5)	0.3326 (0)	0.1321 (11)
O_1	0.7096 (4)	0.2466 (14)	0.3227 (9)
C_1	0.7208 (6)	0.3275 (17)	0.2410 (11)
C_1^{α}	0.6664 (6)	0.3800 (19)	0.1166 (12)
O_2	0.7804 (5)	0.5480 (13)	0.4923 (10)
N_2	0.7838 (5)	0.3958 (15)	0.2569 (9)
C_2	0.8081 (6)	0.4229 (16)	0.4972 (12)
C_2^{α}	0.8370 (7)	0.3762 (18)	0.3815 (11)
C_2^{β}	0.8979 (7)	0.4698 (24)	0.3629 (14)
C_2^{γ}	0.8827 (9)	0.5117 (27)	0.2225 (16)
C_2^{σ}	0.8049 (7)	0.5045 (20)	0.1715 (14)
N_3	0.8181 (5)	0.3359 (13)	0.6035 (8)
O_3	0.7244 (5)	0.3597 (16)	0.8610 (8)
C_3	0.7352 (6)	0.3293 (16)	0.7534 (12)
C_3^{α}	0.8059 (6)	0.3819 (16)	0.7259 (11)
C_3^{β}	0.8679 (7)	0.3282 (21)	0.8392 (12)
C_3^{γ}	0.9338 (7)	0.4095 (21)	0.8368 (13)
$C_3^{\delta 1}$	0.9453 (8)	0.5515 (26)	0.8896 (17)
$C_3^{\delta 2}$	0.9770 (7)	0.3562 (21)	0.7668 (17)
$C_3^{\epsilon 1}$	1.0089 (11)	0.6334 (29)	0.8761 (26)
$C_3^{\epsilon 2}$	1.0404 (9)	0.4374 (33)	0.7569 (20)
C_3^{η}	1.0528 (9)	0.5714 (35)	0.8167 (25)
N_4	0.6904 (4)	0.2653 (13)	0.6552 (9)
O_4	0.5974 (4)	0.1777 (14)	0.4406 (8)
C_4	0.5740 (7)	0.1955 (17)	0.5398 (12)
C_4^{α}	0.6198 (7)	0.2291 (17)	0.6716 (12)
N_5	0.5035 (5)	0.2002 (12)	0.5255 (10)
O_5	0.4546 (6)	0.4092 (11)	0.3243 (8)
C_5	0.4612 (6)	0.2839 (13)	0.2969 (12)
C_5^{α}	0.4586 (6)	0.1599 (16)	0.4000 (13)
C_5^{β}	0.3864 (7)	0.1556 (19)	0.4325 (14)
C_5^{γ}	0.3994 (8)	0.1443 (33)	0.5721 (17)
C_5^{δ}	0.4688 (7)	0.2100 (19)	0.6333 (12)
N_6	0.4721 (5)	0.2380 (12)	0.1817 (9)
O_6	0.5419 (4)	0.4339 (12)	−0.0644 (8)
C_6	0.5400 (6)	0.3674 (15)	0.0385 (12)
C_6^{α}	0.4694 (6)	0.3402 (17)	0.0727 (11)
C_6^{β}	0.4113 (7)	0.3016 (18)	−0.0511 (13)
C_6^{γ}	0.3395 (7)	0.3328 (18)	−0.0257 (13)
$C_6^{\delta 1}$	0.3067 (8)	0.4551 (22)	−0.0776 (20)
$C_6^{\delta 2}$	0.3089 (7)	0.2398 (18)	0.0486 (13)
$C_6^{\epsilon 1}$	0.2443 (9)	0.4988 (27)	−0.0469 (26)
$C_6^{\epsilon 2}$	0.2477 (7)	0.2762 (21)	0.0799 (15)
C_6^{η}	0.2143 (9)	0.4011 (32)	0.0274 (20)
S	0.1437 (3)	0.4128 (9)	0.4742 (6)
O_S	0.1123 (8)	0.5654 (19)	0.4292 (15)
C_{S1}	0.2336 (16)	0.4143 (45)	0.4766 (29)
C_{S2}	0.1319 (16)	0.3367 (42)	0.3405 (30)

Table II. Calculated Hydrogen Coordinates

$H(C_1^{\alpha})$	0.6676	0.4912	0.1128
$H(C_1^{\alpha})$	0.6754	0.3360	0.0362
$H(C_2^{\alpha})$	0.8444	0.2666	0.4006
$H(C_2^{\beta})$	0.9447	0.4083	0.3898
$H(C_2^{\beta})$	0.9065	0.5590	0.4247
$H(C_2^{\gamma})$	0.9018	0.6180	0.2124
$H(C_2^{\gamma})$	0.9079	0.4449	0.1697
$H(C_2^{\delta})$	0.8122	0.4728	0.0848
$H(C_2^{\delta})$	0.7810	0.6040	0.1627
$H(C_3^{\alpha})$	0.8135	0.4917	0.7196
$H(C_3^{\beta})$	0.8759	0.2188	0.8235
$H(C_3^{\beta})$	0.8564	0.3425	0.9240
$H(C_3^{\delta 1})$	0.9141	0.5973	0.9419
$H(C_3^{\delta 2})$	0.9644	0.2590	0.7129
$H(C_3^{\epsilon 1})$	1.0163	0.7406	0.9102
$H(C_3^{\epsilon 2})$	1.0773	0.3920	0.7090
$H(C_3^{\eta})$	1.0974	0.6349	0.8118
$H(C_4^{\alpha})$	0.6220	0.1469	0.7356
$H(C_4^{\alpha})$	0.6002	0.3212	0.7092
$H(C_5^{\alpha})$	0.4768	0.0703	0.3632
$H(C_5^{\beta})$	0.3569	0.0707	0.3874
$H(C_5^{\beta})$	0.3586	0.2515	0.3994
$H(C_5^{\gamma})$	0.3970	0.0394	0.5978
$H(C_5^{\beta})$	0.3607	0.2015	0.6036
$H(C_5^{\delta})$	0.4943	0.1545	0.7148
$H(C_5^{\delta})$	0.4653	0.3188	0.6615
$H(C_6^{\alpha})$	0.4600	0.4400	0.1200
$H(C_6^{\beta})$	0.4149	0.1939	−0.0752
$H(C_6^{\beta})$	0.4172	0.3640	−0.1287
$H(C_6^{\delta 1})$	0.3272	0.5212	−0.1405
$H(C_6^{\delta 2})$	0.3323	0.1419	0.0812
$H(C_6^{\epsilon 1})$	0.2224	0.6013	−0.0702
$H(C_6^{\epsilon 2})$	0.2275	0.2125	0.1403
$H(C_6^{\eta})$	0.1648	0.4188	0.0374
$H(N_1)$	0.5920	0.2754	0.2138
$H(N_3)$	0.8348	0.2308	0.5959
$H(N_4)$	0.7035	0.2394	0.5692
$H(N_6)$	0.4842	0.1307	0.1709

structure of *cyclo*-(Gly-l-Pro-*d*-Phe)$_2$, hereafter referred to as GPF, grown from a dimethyl sulfoxide (Me_2SO)-water solution.



Experimental Section

A sample of *cyclo*-(Gly-l-Pro-*d*-Phe)$_2$, first synthesized[4] by Pease, was kindly provided by Dr. K. Kopple of our department. A plate-like crystal, grown from Me_2SO–water solution by slow evaporation and measuring 0.09 × 0.28 × 0.30 mm, was used for data collection. The space group was determined to be $P2_1$ ($P2_1/m$ is not a possible choice since the sample is optically active) with lattice constants a = 19.694 (1) Å, b = 9.005 (1) Å, c = 10.357 (1) Å, and β = 104.05 (1)°. The experimental density was found to be 1.31 ± 0.01 g cm^{-3} by flotation in a mixture of chloroform and benzene. If each unit cell contains two peptides and two Me_2SO molecules, the calculated density is 1.268 g cm^{-3} for Z = 2 of $C_{32}H_{38}N_6O_6 \cdot C_2H_6SO$. (The two most prominent peaks in a mass spectrum of a dry crystal correspond to $(CH_3)_2SO^+$ (*m/e* 78) and CH_3SO^+ (*m/e* 63).)

Three-dimensional intensity data were collected using nickel filtered copper Kα radiation to a 2θ maximum of 125°. A θ–2θ scan rate of 2° min^{-1} with a variable scan width and 10-s background measurements at both extremities of the scan were used to measure 3080 independent reflections. Throughout the data collection three standard reflections, which showed a systematic decay of approximately 4%, were monitored every 50 reflections. Absorption was corrected for as a function of ϕ (maximum deviation of a ϕ scan at χ = 90 was 19%; linear μ = 12.4 cm^{-1}), crystal decay as a linear function of exposure time, and Lorentz-polarization in the usual manner. The structure amplitudes and their estimated errors were calculated from the expressions $F_o = (QI_n)^{1/2}$ and $\sigma^2(F_o) = (Q/4I_n)[I_s + (t_s/t_b)^2 I_b + (0.02I_n)^2]$ where Q contains corrections for Lorentz-polarization, absorption, decay, and attenuation, t_s and t_b are the scan and background times, and I_s, I_b, and I_n are the scan, background, and net intensities, respectively; 1958 reflections with $|F_o| > 3\sigma(F_o)$, representing 64% of the total reflections collected, were considered observed and used in the structure determination and refinement.

Structure determination was first attempted with MULTAN 71[5] without success. Second attempts using 300 reflections with $|E| >$ 5.57 and 2000 phase relationships on MULTAN 74[6] also failed as did attempts using numerous permutations of Debye scattering corrections and normalization by individual parity groups. The structure was finally solved using the same program and data as before but increasing the number of phase relationships to 2500. This could be another example of Lessinger's conclusion on the application of MULTAN to solve complex structures that one should "use only as many E values as necessary but as many Σ_2 relationships as possible".[7] An E map generated from the phase set with the lowest values of both ϕ zero and residual and the highest value of the combined figure of merit revealed 42 nonhydrogen atoms of the peptide and one extra (highest) peak which later was shown to be the sulfur atom in Me_2SO. The entire peptide was found in subsequent electron density maps.

The peptide and sulfur coordinates were refined by block-diagonal

Table III. Bond Lengths (Å) and Bond Angles (deg)

bond	Gly-1	Pro-2	*d*-Phe-3	Gly-4	Pro-5	*d*-Phe-6	av
N_i–C_i^α	1.47 (1)	1.46 (2)	1.41 (2)	1.48 (2)	1.43 (2)	1.45 (2)	1.45
C_i^α–C_i'	1.54 (2)	1.51 (2)	1.56 (2)	1.47 (2)	1.56 (2)	1.54 (2)	1.53
C_i'–O_i	1.18 (2)	1.25 (2)	1.22 (2)	1.24 (2)	1.18 (2)	1.23 (2)	1.22
C_i'–N_{i+1}	1.36 (2)	1.33 (2)	1.31 (2)	1.36 (2)	1.33 (2)	1.33 (1)	1.34
C_i^α–C_i^β		1.52 (2)	1.55 (2)		1.54 (2)	1.54 (2)	
C_i^β–C_i^γ		1.46 (2)	1.50 (2)		1.41 (2)	1.53 (2)	
C_i^γ–C_i^δ		1.50 (2)	1.39 (3)		1.48 (2)	1.37 (2)	
			1.33 (2)			1.32 (2)	
C_i^δ–C_i^ϵ			1.49 (3)			1.40 (2)	
			1.47 (3)			1.36 (2)	
C_i^ϵ–C_i^η			1.30 (3)			1.39 (3)	
			1.35 (4)			1.35 (3)	
C_i^δ–N_i		1.45 (2)			1.45 (2)		
C_{i-1}'–N_i–C_i^α	119.6 (7)	119.4 (10)	123.4 (12)	118.9 (10)	118.7 (10)	121.3 (11)	120.2
N_i–C_i^α–C_i'	107.2 (9)	109.8 (10)	115.4 (10)	108.6 (10)	109.0 (10)	114.7 (10)	110.8
C_i^α–C_i'–N_{i+1}	113.2 (11)	119.1 (12)	117.1 (10)	118.2 (11)	115.7 (10)	116.7 (10)	116.7
C_i^α–C_i'–O_i	125.3 (11)	117.8 (12)	117.5 (11)	122.1 (12)	119.9 (11)	119.7 (11)	120.4
$N_{i+1}C_i'O_i$	121.2 (11)	122.8 (12)	125.3 (12)	119.4 (11)	124.4 (11)	123.1 (10)	122.7
C_i'–C_i^α–C_i^β		114.1 (12)	109.9 (10)		110.8 (11)	112.1 (10)	
N_i–$C_i^\alpha C_i^\beta$		103.9 (10)	108.3 (10)		102.0 (10)	112.7 (11)	
C_i^α–C_i^β–C_i^γ		107.0 (12)	111.2 (12)		106.2 (12)	110.4 (11)	
C_i^β–C_i^γ–C_i^δ		106.6 (13)	120.2 (15)		109.2 (13)	117.8 (14)	
			120.3 (14)			122.4 (14)	
C_i^γ–C_i^δ–C_i^ϵ			121.5 (18)			120.8 (18)	
			118.7 (16)			121.4 (15)	
C_i^δ–C_i^ϵ–C_i^η			118.2 (17)			117.6 (20)	
			120.2 (23)			118.5 (15)	
C_i^ϵ–C_i^η–C_i^ϵ			122.1 (20)			121.3 (17)	
C_i^γ–C_i^δ–N_i		103.7 (12)			101.8 (11)		
C_i^α–N_i–C_i^δ		111.7 (10)			114.5 (10)		
C_{i-1}–N_i–C_i^δ		128.5 (10)			125.3 (10)		
$C_i^{\delta_1}$–C_i^γ–$C_i^{\delta_2}$			118.8 (15)			119.9 (14)	

Table IV. Conformational Angles (deg) for GPF and APF

	1 Gly or *l*-Ala	2 *l*-Pro	3 *d*-Phe	4 Gly or *l*-Ala	5 *l*-Pro	6 *d*-Phe
			GPF			
ϕ	178	−56	100	165	−72	112
ψ	164	134	−9	162	131	−19
ω	170	167	173	177	174	169
			Average GPF (Deviation)			
ϕ	172 (6)	−64 (8)	106 (6)			
ψ	163 (1)	132 (1)	−14 (5)			
ω	173 (3)	170 (4)	171 (2)			
			APF			
ϕ	−157	−60	78			
ψ	172	122	9			
ω	178	171	−169			
			Absolute Difference between the Average GPF and APF			
ϕ	31	4	28			
ψ	9	10	23			
ω	5	1	20			

least squares (minimizing $\Sigma w(\Delta F)^2$).[18] An electron density map in the region of the S atom contained pairs of peaks, ranging from 1 to 3 e/Å^3, which were candidates for the two methyl groups of Me_2SO, as well as a reasonably well-defined oxygen position. Numerous attempts were made to refine the group without great success. Final refinement involved anisotropic temperature factors for the 44 nonhydrogen atoms in the peptide and isotropic temperature factors for the four atoms of Me_2SO. Hydrogen atom coordinates were calculated, based on expected geometry (1.00 Å, 109 or 120°), and their contributions were added to the structure factor calculation with isotropic temperature factors of 4.0, although no attempt was made to refine them. Refinement was considered complete when the shifts in the parameters of the peptide were less than 0.1 times their estimated standard deviations. The final $R = 0.099$ and a final electron density map shows no peaks greater than 0.5 e/Å^3 except in the immediate region of the Me_2SO molecule.

Results and Discussion

The fractional coordinates and estimated standard deviations for the nonhydrogen atoms are listed in Table I and the calculated hydrogen coordinates are listed in Table II. Table III contains the bond angles and bond lengths for the peptide.

The conformational angles for GPF and APF are listed in Table IV. Since for APF the molecule lies on a crystallographic twofold axis, one-half of the molecule is related by C_2 symmetry to the other half. For GPF, the entire molecule is unique

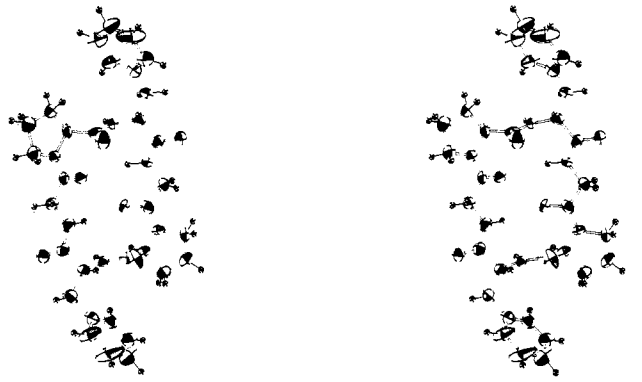


Figure 1. Stereodrawing of GPF.

crystallographically; although the conformational angles between similar residues differ by values larger than experimental error, in solution the molecule probably possesses C_2 symmetry. The maximum difference is 18° between ϕ_2 and ϕ_5, the remaining ϕ angles differ by 12°, and the ψ and ω angles differ by 10° or less. As shown in the stereodrawing (Figure 1), even the orientation of the phenylalanine side chains is similar. χ^1 and χ^2 for Phe_3 are 68.6 and 79.4° and for Phe_6 are 70.3 and 77.1°, respectively.

The molecular configurations of GPF and APF are remarkably similar, especially when one considers their different environments. The largest single difference between backbone conformational angles is 31° for ϕ_{Ala}-ϕ_{Gly}. The region about ϕ, ψ of 172, 163° is a favorable region of the Gly energy map[9] but is unfavorable for Ala. The shift to $\phi, \psi = -157, 172°$ for Ala places that residue in a favorable energy region. Of course, −157, 172 is also favorable for Gly (the energy difference between the two points is negligible for Gly). The major conformational angle differences between GPF and APF are in the angles about Phe, which differ by 20–28°. However, the differences alternate in sign and therefore produce total conformations which are very similar, even in the location of the Phe side chain.

The conformations of both GPF and APF have two type II β turns but are constrained in such a manner that strong 4 → 1 hydrogen bonds are precluded from occurring. In addition, they both have close C=O(1)···O(4)=C contacts, 2.90 Å for APF and 2.84 Å for GPF, which are slightly above the sum of the van der Waals radii. The interaction is shown in detail in Figures 2 and 3. Figures 2a and 3a are views of the 1 and 4 residues in an orientation 90° from that shown in Figure 1 (rotation is about an imaginary line between C_1^d and C_4^d). Figures 2b and 3b show space-filling models[10] (1.2 Å radius spheres on all atoms) in the same orientation as in Figures 2a and 3a. Figures 2c and 3c are in the original orientation of Figure 1. Aside from the closeness of the carbonyl oxygen atoms, it is interesting to note that the methyl groups tilt toward the center of the molecule in APF and the equivalent hydrogen atoms tilt outward in GPF. The opposite conformation would be predicted on steric grounds since the effective radius of the methyl group is larger than the radius of a hydrogen atom. This large a difference is not required by the differences in the Ala and Gly ϕ, ψ maps but rather is probably a result of the nature of the intermolecular forces within the crystal. Since in APF, the regions immediately above and to either side of the Ala residue are occupied by solvent, the methyl groups are attracted inward by their similar hydrophobic character and repelled from the outward orientation by their interaction with the hydrophilic solvent molecules.

As mentioned, strong 4 → 1 hydrogen bonds are not found in either GPF or APF but observed intramolecular geometry does represent a significant hydrophilic interaction. For

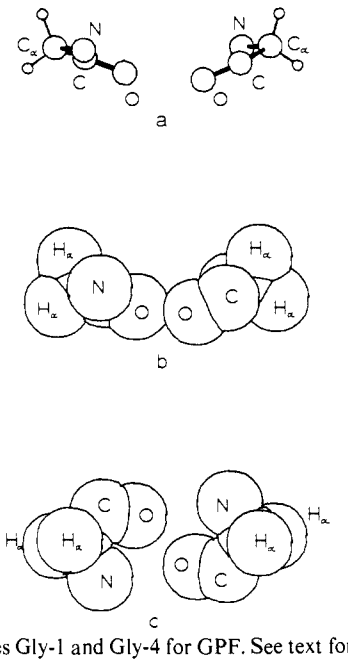


Figure 2. Residues Gly-1 and Gly-4 for GPF. See text for discussion.

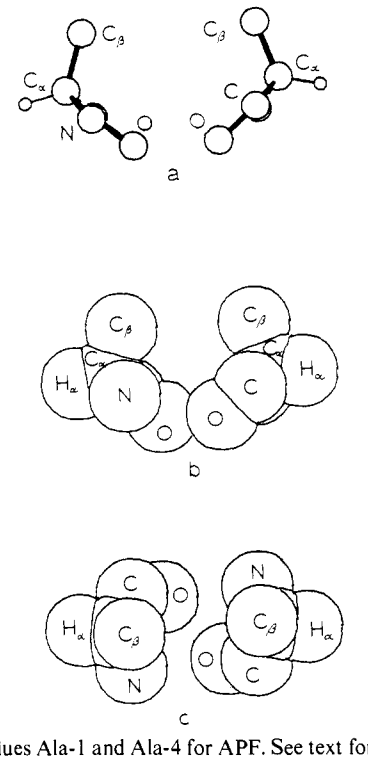


Figure 3. Residues Ala-1 and Ala-4 for APF. See text for discussion.

GPF, the hydrogen bond distance O(1)···H(4) of 2.59 Å and O(4)···H(1) of 2.49 Å corresponds to stabilization energies of −1.5 to −2.0 kcal/mol as compared to a minimum of −3.0 kcal/mol at 2.1 Å.[11] Distances of 3.49 Å for O(4)-N(1) and 3.56 Å for N(4)-O(1) are at the extremes of what is normally considered a hydrogen bond. Indeed, distances in the range of 3.0–3.1 Å have been commonly observed for 4 → 1 type II bonds where geometry permits.

The lack of a strong 4 → 1 interaction in GPF probably cannot be attributed to crystal packing. There are few close contacts between molecules in the structure and these do not appear to interact directly with the β-turn conformation. In addition, in APF, where the peptide is completely surrounded by water, a similar geometry prevails.

In order for a stronger interaction to exist and to increase an already close O(1)-O(4) distance, 2.84 Å, each half of the molecule needs to be shifted in an antiparallel fashion parallel to the extended axis of the molecule. Such a shift will separate the carbonyl oxygens and help to linearize the N-H···O system from the current values of 161° for N(4)-H(4)···O(1) and 167° for N(1)-H(1)···O(4). This antiparallel shift can be accomplished by rotating carbonyl groups for Pro_2 and Pro_5 away from the ring (they point slightly inward). This rotation would decrease the values of ψ_2 and ψ_5 from their current values of 134 and 131°, respectively, by 30-60°. This action is allowed for *trans*-proline systems and results in an insignificant change in energy (a decrease of less than 1 kcal/mol).

Although the resultant geometry will linearize the hydrogen bonds and decrease the carbonyl-carbonyl repulsion, it will not appreciably reduce the H···O distances. To reduce this distance without simultaneously reducing the O-O distance requires a major change in the conformation of the peptide away from the pseudoplanar configuration toward a folded molecule. The major change involves changing ϕ of one of the glycine residues to −130° and ψ to 180°, which are still in allowed regions of a Gly ϕ-ψ energy map. However, only one H···O distance would decrease while the other would significantly increase. We can speculate then that cyclic hexapeptides of the sequence (X-1-Pro-*d*-Y)$_2$ will not form two strong 4 → 1 bonds.

There are no unusual bond distances or bond angles in GPF. Both proline residues have C^γ puckered out of the plane formed by C^δ-N-C^α-C^β as is usually found. The phenyl rings of Phe_3 and Phe_6 are both planar to 0.03 Å. Increased thermal motion of the ϵ and η carbon atoms for the Phe side chains, apparent in Figure 1, is also seen in APF. The six amide planes in GPF show significant deviations from planarity, from 0.03 to 0.06 Å average deviations, which appear to be real since the aromatic rings are planar to one-half that error. Deviations from planarity closely parallel the variations of ω from 180°.

Figure 4 shows the contents of the unit cell as viewed nearly parallel to the 2_1 axis. The plane of the peptide backbone lies parallel to the *ac* lattice plane with the molecules extending nearly one entire unit cell along both *a* and *c*. In contrast, the macrocyclic ring is relatively thin in its third dimension and translationally related molecules are interleaved by Me_2SO molecules in the *b* direction. The S=O···H-N (O-N = 2.85 Å) hydrogen bond and S=O···C_2^α are the only contacts within 3.5 Å between the Me_2SO and the peptide nonhydrogen skeleton. There is one moderately strong hydrogen bond between peptide units which involves N_6-H(N_6)···O_6 ($1 - x$, $y - \frac{1}{2}$, $-z$) (N-O = 2.98 Å, H-O = 2.08 Å, N-H···O angle = 147°).

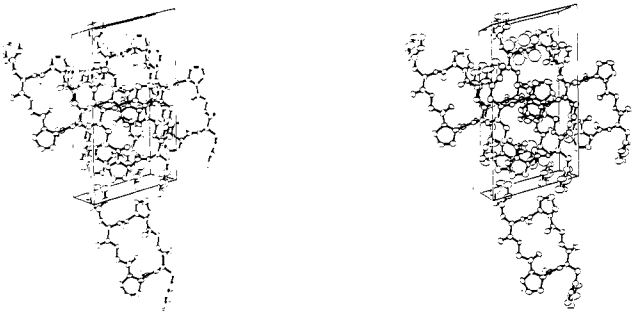


Figure 4. Stereodrawing of the unit cell of GPF.

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Supplementary Material Available: Listing of the structure amplitudes and anisotropic thermal parameters (16 pages). Ordering information is given on any current masthead page.

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