

7,7-Dimethyl-5*H*-dibenzo[*e,i*][1,4,8]-  
triazacycloundecine-6,9,15-  
(7*H*,8*H*,14*H*)-trione pyridine solvateJames C. Morris,<sup>a\*</sup> Scott W. Gordon-Wylie<sup>b</sup> and  
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Received 26 July 2006

Accepted 6 October 2006

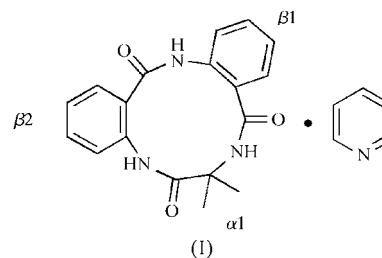
Online 10 November 2006

The X-ray crystal structure and hydrogen-bonding patterns of the title compound, C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>·C<sub>5</sub>H<sub>5</sub>N, a non-*N*-alkylated cyclotripeptide containing one  $\alpha$ - and two  $\beta$ -amino acids, are reported. The amides in the 11-membered ring have an unprecedented all-*transoid* configuration. The torsion angles and Dunitz parameters describing non-planarity of the amides contained in the cyclotripeptide are discussed.

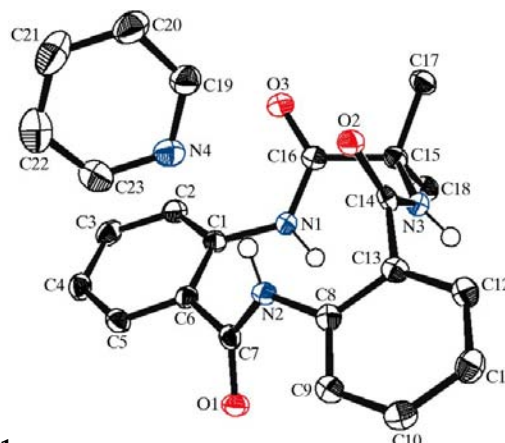
## Comment

*N*-Alkylated cyclotripeptides have often been synthesized as structural models for  $\beta$ - and  $\gamma$ -turn mimetics (Wels *et al.*, 2002; Schumann *et al.*, 2000), for their interesting antibacterial effects (Hamuro *et al.*, 1999), and for solution *versus* solid phase comparisons (Bats & Fuess, 1980). Synthesis of non-*N*-alkylated cyclotripeptides is extremely difficult, as the preferred *transoid* conformation of amide bonds prevents unassisted ring closure. Most reported cyclotripeptides contain proline residues, which lower the energy difference between the *cisoid* and *transoid* conformations. Crystallographically characterized examples of cyclotripeptide ten-membered rings (2 $\alpha$  and 1 $\beta$ ; Cerrini *et al.*, 1988; Rothe *et al.*, 1973; Wels *et al.*, 2002) and 12-membered rings (3 $\beta$ ) are all *N*-alkylated (Ollis & Stoddart, 1984). We are not aware of any reported examples of cyclotripeptide 11-membered rings. Incorporation of  $\alpha$ - and  $\beta$ -amino acids into a single medium-sized ring gives unique qualities that may not occur in cyclotripeptides containing solely  $\alpha$ - or  $\beta$ -amino acids. Syntheses of non-*N*-alkylated cyclotripeptides have only been reported twice (Imagawa *et al.*, 1987; Villalgordo & Heimgartner, 1997); however, the compounds were never characterized crystallographically. These results do not exclude the possibility that the peptide precursors may have dimerized before cyclization, thus forming cyclohexapeptides (Schröder & Lübke, 1965).

In this communication, we report the first crystal structure determination of a non-*N*-alkylated cyclotripeptide containing all-*transoid* amides, (I) (Fig. 1). Two of the amides are significantly non-planar. This contrasts with previously reported crystal structures of *N*-alkylated cyclotripeptides, where at least one of the amides is in a *cisoid* configuration. The all-*transoid* configuration in (I) could make it a good candidate for studies in  $\beta$ -turn mimetics (Wels *et al.*, 2002). However, the torsion angles for the  $\alpha$ -amino acid (Table 2) are closer to those of an  $\alpha$ -helix than a  $\beta$ -sheet on a Ramachandran plot. Hence, this particular *transoid* cyclotripeptide is not the most suitable candidate for  $\beta$ -turn mimetic studies. The torsion angles ( $\varphi$  and  $\psi$ ) of the  $\beta$ -amino acids (Table 2) do show similarities to the calculated preferred minimum energy conformations for  $\beta$ -peptides in a H12-helix configuration (Günther & Hofmann, 2001). The  $\theta$  torsion angles for the  $\beta$ -peptides differ from the normally preferred minimums because the aromatic ring constrains this angle to be close to zero (Günther & Hofmann, 2001). The fixed torsion angles inside the 11-membered ring may allow such rings to be used as possible scaffolds in drug development (Ro *et al.*, 2002). This approach has been attempted using other peptide systems whose torsion angles mimic those of bioactive molecules (Ro *et al.*, 2002).



The primary hydrogen-bonding motif (Fig. 2 and Table 1) consists of hydrogen-bonded dimers using the N1—H1...O1 links between adjacent molecules. Atom H3, attached to atom N3, is potentially available for an intermolecular hydrogen bond; however, it is not sterically accessible, with the geminal dimethyl group and aromatic rings on both macrocycles

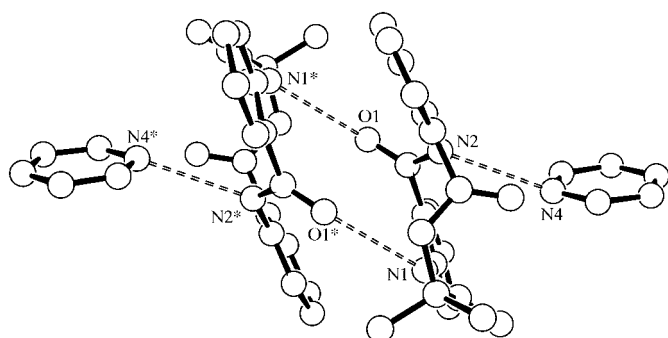


**Figure 1**  
ORTEP (Burnett & Johnson, 1996) diagram of the X-ray crystal structure of (I). Displacement ellipsoids are drawn at the 50% probability level and non-amide H atoms have been omitted for clarity.

prohibiting approach from this side of the molecule. It seems possible that the pyridine solvent molecule prevents the formation of a hydrogen-bonded supramolecular structure by binding (Table 1) a H atom (H2) that is internal to the ring. This would not normally be available for hydrogen bonding to another neighboring ring.

The  $\omega$  angles (Winkler & Dunitz, 1971) (Table 2) of the amide residues show that the H atoms of amides 2 and 3 lie out of their plane. Specifically, atom H2 is 0.229 (1) Å from the N2/C7/O1 plane and atom H3 is 0.207 (1) Å from the N3/C14/O2 plane. Amide non-planarity can arise from one of two possible distortions in the amide bond, which cannot be identified by the  $\omega$  angle. The first distortion is from pyramidalization of the amide N atom or carbonyl C atom. The second distortion is from a twist of the amide C—N bond. A Dunitz analysis of amide non-planarity (Table 3) relates amide non-planarity to the precise distortion causing the non-planarity [ $\tau$  is the non-planarity of the amide; for a planar *trans*-amide, this value should be close to 180°;  $\chi_N$  and  $\chi_C$  measure the angular pyramidalization of the amide N atom and carbonyl C atom, respectively]. The values of  $\chi_N$  and  $\chi_C$  suggest that the observed non-planarity for amide 2 (H2/N2/C7/O1) and amide 3 (H3/N3/C14/O2) is due to a twist in the amide bond, rather than pyramidalization of the N or carbonyl C atoms. Amide 1 (H1/N1/C16/O3) is relatively planar, with atom H1 0.079 (2) Å from the N1/C16/O3 plane.

Modeling (*Spartan'04 Mechanics PC/x86 RB3LYP/6-311 G\**; Hehre, 2003; Kong *et al.*, 2000) does predict that the all-*trans* system is favored as the monomer by 22.5 kJ mol<sup>-1</sup>, and by 93.7 kJ mol<sup>-1</sup> in the hydrogen-bonded dimer as the pyridine solvate. In the crystallographically determined hydrogen-bonded dimer (Fig. 2), the rings are equivalent because of a center of symmetry. In the theoretical model for an isolated pyridine hydrogen-bonded dimer such as the one in Fig. 2, the two tripeptide rings contain different sets of torsion angles and different sources of amide non-planarity (Table 3). Dunitz analysis of the theoretical dimer system predicts amide non-planarity to be a combination of pyramidalization of the atoms and a twist of the amide bonds; this is in contrast to (I), which exhibits almost exclusive twisting of the amide bond. The (solid-state) hydrogen bonding (Table 1) here may also be affecting this distortion from planarity.



**Figure 2**

Hydrogen bonding in (I). H atoms have been omitted for clarity. The two halves of the dimer are related by a crystallographic center of symmetry [symmetry code: (\*)  $-x + 1, -y + 2, -z$ ].

Amide non-planarity in (I) must help reduce the strain caused by having three rigorously *transoid* amides in the medium-sized ring. Relieving ring strain through amide non-planarity has been seen in cyclotetrapeptides (with a 12-membered ring), such as dihydrochlamydocin, which also exhibits an all *trans*-configuration (Flippen & Karle, 1976). Dunitz analysis of dihydrochlamydocin indicates that there is a significant contribution from pyramidalization of the amide C or N atoms to the non-planarity, as opposed to a twist of the amide bond. To our knowledge, no other cyclotriptide containing  $\alpha$ -amino acids exhibits the all-*trans* configuration reported here. This leads us to believe that further study of this unusual structural type is warranted.

## Experimental

Compound (I) was synthesized using methods carried forward from Ollis & Stoddart (1984) and Imagawa *et al.* (1987). Dimethyl sulfoxide and dimethylformamide solvent systems were also attempted, but did not yield X-ray quality crystals. Methyl 2-[2-(2-aminobenzoyl-amino)benzoylamino]-2-methylpropionate (0.996 g, 0.0028 mol) was dissolved in freshly distilled tetrahydrofuran (THF, 25 ml) and sodium hydride 60% in mineral oil was added. The solution was refluxed for 3 d and then quenched in 150 ml of ice-cold water. The THF was distilled out of the solution at ambient pressure. The resulting cloudy solution was cooled and filtered. The isolated solid (0.600 g after air drying) is the macrocyclic product with 95–98% purity (crystallization from hot/cold pyridine). For other spectroscopic data, see the supplementary CIF.

### Crystal data

C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>·C<sub>5</sub>H<sub>5</sub>N  
 $M_r = 402.45$   
 Monoclinic,  $P2_1/c$   
 $a = 12.107$  (2) Å  
 $b = 11.050$  (2) Å  
 $c = 14.627$  (3) Å  
 $\beta = 92.42$  (3)°  
 $V = 1955.1$  (7) Å<sup>3</sup>

$Z = 4$   
 $D_x = 1.373$  Mg m<sup>-3</sup>  
 Mo  $K\alpha$  radiation  
 $\mu = 0.09$  mm<sup>-1</sup>  
 $T = 85$  (2) K  
 Plate, colorless  
 $0.28 \times 0.24 \times 0.20$  mm

### Data collection

Siemens SMART CCD area-detector diffractometer  
 $\omega$  scans  
 Absorption correction: multi-scan (SADABS; Sheldrick, 1997)  
 $T_{\min} = 0.757$ ,  $T_{\max} = 0.978$

11782 measured reflections  
 4001 independent reflections  
 3360 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.023$   
 $\theta_{\max} = 26.4^\circ$

### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.039$   
 $wR(F^2) = 0.100$   
 $S = 1.03$   
 4001 reflections  
 273 parameters  
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0409P)^2 + 1.2338P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} < 0.001$   
 $\Delta\rho_{\max} = 0.53$  e Å<sup>-3</sup>  
 $\Delta\rho_{\min} = -0.52$  e Å<sup>-3</sup>

**Table 1**

Hydrogen-bond geometries (Å, °) for (I).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1—H1 $\cdots$ O1*	0.86	2.11	2.9705 (17)	174
N2—H2 $\cdots$ N4	0.86	2.17	2.9932 (19)	160

Symmetry code: (\*)  $-x + 1, -y + 2, -z$ .

**Table 2**

Torsion angles (°) for amino acids in (I).

Angles are as defined by Winkler & Dunitz (1971).

Torsion angles	$\varphi$	$\psi$	$\theta$	$\omega$
$\beta 1$	−137.37 (15)	51.62 (19)	5.03 (19)	−162.12 (12)
$\beta 2$	128.95 (15)	−102.10 (15)	1.90 (19)	159.46 (12)
$\alpha 1$	−49.99 (17)	−47.82 (16)	—	176.19 (13)

**Table 3**

Dunitz parameters (°) for the amide bonds in (I) and for theoretical calculations (see *Comment*).

Angles are as defined by Winkler & Dunitz (1971) and H atoms are in calculated positions.

Bond	Crystal data <sup>1</sup>			Theoretical data <sup>2</sup>					
	N1	N2	N3	N1a	N2a	N3a	N1b	N2b	N3b
$\tau$	175.3	−162.3	161.7	−170.9	174.3	178.4	−164.0	180.2	168.4
$\chi_N$	0.0	0.0	0.0	−15.8	5.8	26.0	8.0	10.7	8.7
$\chi_C$	1.7	0.4	−4.5	−0.9	1.5	5.9	3.0	3.9	−0.9

Notes: (1) both halves of the hydrogen-bonded dimer are crystallographically equivalent; (2) theory predicts non-equivalent halves of the hydrogen-bonded dimer and these are labeled *a* and *b*, respectively.

H atoms were placed in calculated positions and refined using a riding model (C—H = 0.93 and 0.96 Å, and N—H = 0.86 Å), with  $U_{iso}(H)$  values of 1.2 or 1.5 times  $U_{eq}(C,N)$ .

Data collection: *SMART* (Siemens, 1995); cell refinement: *SAINT* (Siemens, 1995); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXTL* (Siemens, 1995).

This work was supported by NSF Vermont-EPSCoR (cooperative agreement #9874685) and ACS-PRF (grant #36567-G3).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3020). Services for accessing these data are described at the back of the journal.

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