organic compounds

5-(3,4-Dimethoxybenzyl)-7-isopropyl-1,3,5-triazepane-2,6-dione acetonitrile solvate refined using a multipolar atom model

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The crystal structure of the title compound, $C_{16}H_{23}N_3O_4$·CH_3CN, was refined using a multipolar atom model transferred from an experimental electron-density database. The refinement showed some improvement in crystallographic statistical indices compared with the independent atom model. The triazepane ring adopts a twist-boat conformation. In the crystal structure, the molecule forms intermolecular contacts with 14 different neighbours. There are two N—H···O and one C—H···O intermolecular hydrogen bond.

Comment

1,3,5-Triazepane-2,6-diones are a novel class of dipeptidomimetics (Lena *et al.* 2006; Lena & Guichard, 2008) whose skeleton can be readily prepared starting from N-protected dipeptides. All five points of diversity can be manipulated using either solution-phase or solid-phase synthesis. Our interest in 1,3,5-triazepane-2,6-diones stems from the identification of several inhibitors of group V and X of secreted phospholipase A2 (Muller *et al.*, 2006). With the aim of improving the potency of the first reported inhibitors, we have started structure–activity relationship studies by systematically varying the nature of the substituents on the ring, and at the amide N3 position in particular. Interestingly, the nature and the number of substitutents on the ring can dramatically affect the overall geometry, with the side chain at C7 adopting a pseudo-equatorial or pseudo-axial orientation. Moreover, 1,3,5-triazepane-2,6-diones can be used in crystal engineering to create helical molecular tapes that can self-assemble to form channel-type structures (Schaffner *et al.*, 2006). We

report here the structure of the title compound, (I), an analogue of cyclo(L-Val-gSar-CO) (Aubert *et al.*, 2007) in which the methyl group at N3 is replaced by the much bulkier 3,4-dimethoxybenzyl group. This structure has been refined using a multipolar atom model.
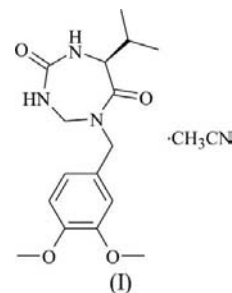
Initially, in the independent atom model (IAM) refinement, a conventional spherical neutral atom model was applied. Scale factors, atomic positions and displacement parameters for all atoms were refined using the *MoPro* program (Guillot *et al.*, 2001; Jelsch *et al.*, 2005) until convergence. In the experimental library multipolar atom model (ELMAM; Pichon-Pesme *et al.*, 2004; Zarychta *et al.*, 2007) refinement, the same parameters were varied but a multipolar charged atom model was applied. The electron-density parameters were transferred from the ELMAM library and subsequently kept fixed. Riding constraints on H-atom isotropic displacement parameters were applied similarly in both refinements, which were carried out with the same diffraction data using all reflections.

The ELMAM refinement shows a slight improvement in statistical indexes when compared with the IAM refinement. The $I > 2\sigma(I)$ crystallographic factors are reduced from 5.18 to 3.59% for $R(F)$ and from 3.86 to 2.53% for $wR_2(F)$. The minimum and maximum peaks in the residual electron density are −0.050862 and 0.062570 e Å^{-3} after the IAM refinement, and −0.042279 and 0.053564 e Å^{-3} after the ELMAM refinement. The largest effect of the multipole transfer on the crystallographic structure is observed on the atomic displacements. The average value of U_{eq} (geometric mean of eigenvalues U_i) derived from the IAM refinement is 0.0214 Å^2, which is slightly higher than the value of 0.0182 Å^2 from the ELMAM refinement. With the IAM spherical atom model, the displacement parameters are incorrect as they incorporate some significant deformation electron density, due to improper deconvolution between these two features (Jelsch *et al.*, 1998).

The molecular structure of (I), with the atomic numbering scheme, is presented in Fig. 1. All bond distances and angles are normal (Table 1) and are in good agreement with the geometry of similar 1,3,5-triazepane-2,6-diones (Lena *et al.*, 2006; Lena & Guichard, 2008). The S configuration of the C atom at the 2-position of the seven-membered ring was assumed from the precursor Boc-L-Tic OH compound. The triazepane ring adopts a twist-boat conformation, TB (Boessenkool & Boyens, 1980), similar to those observed in the crystal structures of carbazepine (Hempel *et al.*, 2005; Lisgarten *et al.*, 1989). The seven-membered ring consists of
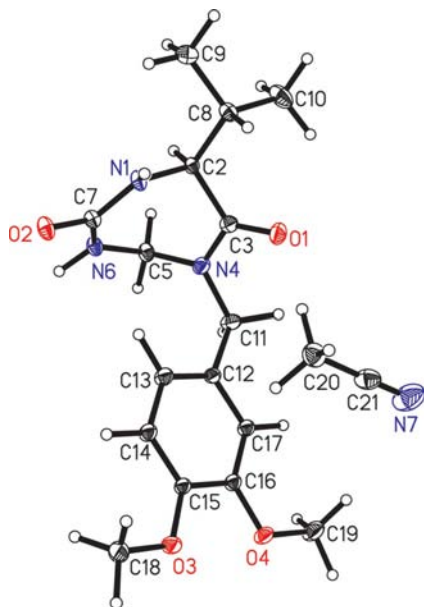
Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.
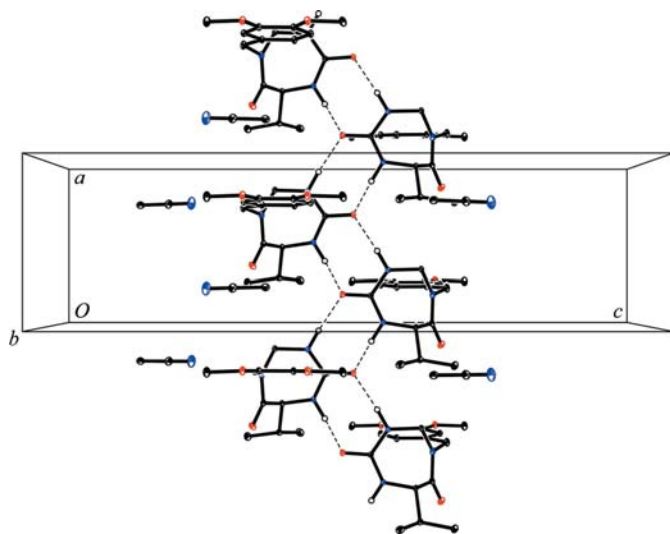

Figure 2
A packing diagram for (I). Dashed lines indicate hydrogen bonds.

two nearly planar halves. The first is defined by atoms C2/C3/N4/C5, with the largest deviation from this plane not exceeding 0.025 (2) Å. The second half of the ring is composed of atoms C2/N1/C7/N6/C5 and only atom N6 is displaced from the mean plane, by 0.115 (2) Å; for the other atoms, the deviation does not exceed 0.063 (2) Å. The dihedral angle between the two halves is 64.7 (1)° and is almost in the range of values found for this group of compounds (57.74–63.93°; Aubert *et al.*, 2007; Lena *et al.*, 2006; Lena & Guichard, 2008; Schaffner *et al.*, 2006). The plane of the benzene ring makes angles of 82.1 (1) and 66.9 (1)° with these planes, respectively. Amide atom N4 is almost exactly in the plane defined by the three neighbouring C atoms (C3, C5 and C11), at a distance

not exceeding 0.03 Å. Therefore, the sum of the valence angles around the N atom is 359.8 (2)°, which identifies very clear sp^2 hybridization (328° for sp^3 and 360° for sp^2).

In the crystal structure of (I), molecules are linked by two C=O···H—N hydrogen bonds (Table 2 and Fig. 2), which consecutively generate the graph-set motif $C_2^1(6)$ (Bernstein *et al.*, 1995) and form chains of molecules running along the [100] direction. Adjacent molecules in these chains are also double-bridged by the hydrogen bonds, so that an $R_2^2(8)$ ring motif can additionally be discerned. The planes of parallel benzene rings of neighbouring molecules are separated from each other by 7.01 Å. The acetonitrile solvent molecules are in the space between these planes. The distance from the centre of the benzene ring to the nearest H atom of the methyl group of acetonitrile is about 2.6 Å. The third H atom of this group takes part in a weak C20—H20C···O1 hydrogen bond (Table 2). Atom N7 of the acetonitrile solvent molecule does not participate in hydrogen bonds, but forms a significant interaction with amide atom N4 (3.36 Å), the N7···N4 direction being nearly perpendicular to the amide sp^2 plane.

Experimental

The title compound was prepared starting from benzyl bromoacetate. Reaction with veratrylamine gave the corresponding *N*-alkylated aminobenzyl ester in 71% yield. Coupling with Boc-L-Tic-OH followed by hydrogenolysis afforded the corresponding *N*-Boc-protected dipeptide in 90% yield. The dipeptide was then used in a four-step procedure as described previously (Lena *et al.*, 2006), to give the title triazepanedione in 50% yield. Compound (I) was recrystallized by slow evaporation of a 1:1 mixture of methanol and acetonitrile.

Crystal data

$C_{16}H_{23}N_3O_4 \cdot C_2H_3N$	$V = 1881.9\ (1)$ Å^3
$M_r = 362.41$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation
$a = 7.0090\ (2)$ Å	$\mu = 0.09$ mm^{-1}
$b = 10.5040\ (3)$ Å	$T = 100$ K
$c = 25.5620\ (9)$ Å	$0.3 \times 0.1 \times 0.1$ mm

Data collection

Oxford Xcalibur diffractometer	2881 reflections with $I > 2\sigma(I)$
6144 measured reflections	$R_{int} = 0.013$
3421 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.036$	235 parameters
$wR(F) = 0.027$	H-atom parameters constrained
$S = 1.65$	$\Delta\rho_{max} = 0.05$ e Å^{-3}
3421 reflections	$\Delta\rho_{min} = -0.04$ e Å^{-3}

Least-squares refinements, based on |*F*|, were carried out with the program *MoPro* (Guillot *et al.*, 2001; Jelsch *et al.*, 2005) using the ELMAM electron-density database (Zarychta *et al.*, 2007). According to Wilson (1976), a refinement *versus F* is equivalent to obtaining a least-squares fit between the calculated electron density and that obtained from a Fourier series based on the observed structure factors. A refinement *versus I* is equivalent to obtaining a least-squares fit for the Patterson syntheses. Both refinements *versus F* and *I* are valid, and are very close for good quality structures. The

Table 1
Selected geometric parameters (Å, °).

N1—C7	1.351 (2)	N4—C5	1.462 (2)
N1—C2	1.463 (2)	N6—C7	1.357 (2)
C3—N4	1.359 (2)		
C3—N4—C11	119.5 (1)	C5—N4—C11	119.4 (1)
C3—N4—C5	120.9 (1)		
N1—C7—N6—C5	17.1 (1)	C3—N4—C5—N6	−68.64 (9)
N1—C2—C3—N4	71.15 (9)	C3—C2—N1—C7	−67.4 (1)
C2—N1—C7—N6	0.5 (1)	N4—C5—N6—C7	38.6 (1)
C2—C3—N4—C5	4.8 (1)		

Table 2
Hydrogen-bond geometry (Å, °).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N1—H1$\cdots$O2[i]	1.01	1.79	2.792 (1)	172
C2—H2$\cdots$O4[ii]	1.10	2.41	3.485 (2)	165
N6—H6$\cdots$O2[iii]	1.01	1.93	2.917 (1)	166

Symmetry codes: (i) $x - \frac{1}{2}, -y + \frac{1}{2}, -z + 1$; (ii) $x, y - 1, z$; (iii) $x + \frac{1}{2}, -y + \frac{1}{2}, -z + 1$.

diffraction data set had no negative intensity and the refinement versus $|F|$ was carried out using all reflections. The weighted R factor wR and goodness-of-fit S are based on F, and conventional R factors are based on F. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R factors and is not relevant to the choice of reflections for refinement. The reflection weights were set equal to $7.29/\sigma^2(F_o)$. The riding was defined with $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl groups and $U_{iso}(H) = 1.2U_{eq}(X)$ for all other chemical groups. The H—X distances were constrained to standard values from neutron diffraction studies (Allen, 1986) in the IAM and ELMAM refinements. The target distances were 1.059 Å for C—CH₃, 1.066 Å for O—CH₃, 1.009 Å for amide N—H, 1.083 Å for aromatic >C—H, 1.092 Å for >CH₂ groups and 1.099 Å for sp^3 C—H groups.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *MoPro* (Guillot *et al.*, 2001; Jelsch *et al.*, 2005); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *MoPro*.

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