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A synchrotron study of (2*R*,5′*S*)-5′-benzyl-5-bromo-6-methoxyspiro[indane-2,2′-piperazine]-3′,6′-dione dimethylformamide solvate

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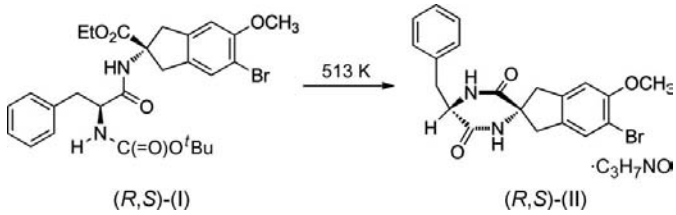
Synchrotron radiation was used to study the structure of the title compound, $C_{20}H_{19}BrN_2O_3\cdot C_3H_7NO$, which was obtained as fine fragile needle-shaped crystals by recrystallization from dimethylformamide (DMF), one molecule of which is incorporated per asymmetric unit into the crystal. The compound adopts a compact closed conformation with the orientation of the benzyl group such that the aryl ring is positioned over the piperazinedione ring, resulting in a $C_{spiro}\cdots C_{trans}-C-C_{Ph}$ pseudo-torsion angle of −3.3 (3)°. The five-membered ring is present in an expected envelope conformation and the six-membered piperazinedione ring adopts a less puckered boat-like conformation. Reciprocal amide-to-amide hydrogen bonding between adjacent piperazinedione rings and C—H···O interactions involving DMF molecules propagate in the crystal as a thick ribbon in the *a*-axis direction.

Comment

In the course of studies on the properties of piperazinediones (Jagadish *et al.*, 2003; Ntirampebura *et al.*, 2008; Weatherhead-Kloster *et al.*, 2005), we recently prepared the enantiomers of 2-amino-5-hydroxyindane-2-carboxylic acid, a conformationally constrained tyrosine analog (Murigi *et al.*, 2010). Resolution of this acid was achieved by a process that passed through dipeptides (*R,S*)-(I) (see scheme) and (*S,S*)-(I) (not shown). Separation of these diastereomers by silica-gel column chromatography was difficult, and so separation was deferred until a later step in the synthesis. However, enough pure (*R,S*)-(I) was available to carry out a thermolysis to produce (2*R*,5′*S*)-5′-benzyl-5-bromo-6-methoxyspiro[indane-2,2′-piperazine]-3′,6′-dione dimethylformamide solvate, *i.e.* (*R,S*)-(II).

Crystallization of (*R,S*)-(II) from dimethylformamide (DMF) yielded a mass of very fine fragile colorless needle-shaped crystals. Single-crystal diffraction analysis was carried out using synchrotron radiation (λ = 0.7749 Å) and yielded reasonable measurable diffraction to a resolution of approximately 0.8 Å with an exposure time of 7 s per frame. The asymmetric unit of (*R,S*)-(II) is shown in Fig. 1 and one fully ordered DMF solvent molecule per spiro[indane-2,2′-piperazine]-3′,6′-dione molecule has been incorporated into the structure. The title compound, for which molecular dimensions are generally unexceptional, has a compact closed



conformation, similar to that found in the related compound (*R,S*)-*cyclo*[phenylalanyl-(2-amino-4-bromo-7-methoxyindan-2-carboxylic acid)] as reported by Williams *et al.* (1999). The benzyl group adopts an orientation such that the aryl ring is positioned over the piperazinedione ring, resulting in a C2···C4—C14—C15 pseudo-torsion angle of −3.3 (3)°. As a consequence of this orientation, atom H122 (bonded to C12) points towards the centroid of the phenyl ring, with an H···*Cg* distance of approximately 2.80 Å. However, the driving force behind this molecular conformation is more likely to be crystal-packing stability rather than the attractive effect of a single C—H···*Cg* interaction between an aryl ring and an unactivated H atom. The methoxy group is coplanar with the aryl ring to which it is bonded and a mean plane fitted through atoms Br1, O3 and C5 to C13 has an r.m.s. deviation of 0.082 Å. The ring defined by atoms C2, C5, C6, C11 and C12 is present in an envelope conformation with C2 as the 'flap atom' and Cremer–Pople puckering parameters (CPPPs) Q = 0.377 (3) Å and φ = 357.5 (5)° (Cremer & Pople, 1975). Similarly, the central piperazinedione ring adopts a less puckered boat-like conformation, with atoms C2 and C4 as the 'bowsprit atoms' and CPPPs Q = 0.201 (3) Å, θ = 86.5 (9)° and φ = 219.5 (9)°.

Hydrogen bonding dominates the crystal packing. Reciprocal amide-to-amide hydrogen bonding is commonly [but not exclusively; see, for example, Jagadish *et al.* (2008)] found

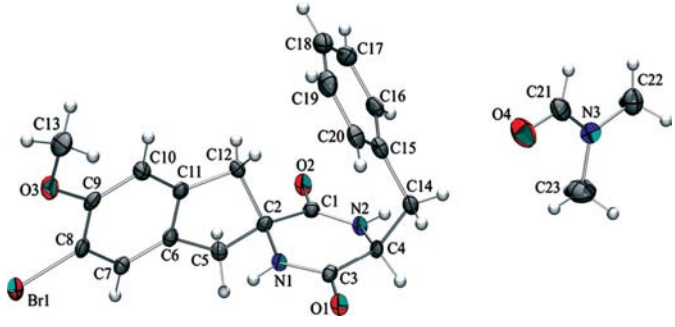


Figure 1
The asymmetric unit of (*R,S*)-(II), with displacement ellipsoids drawn at the 50% probability level.

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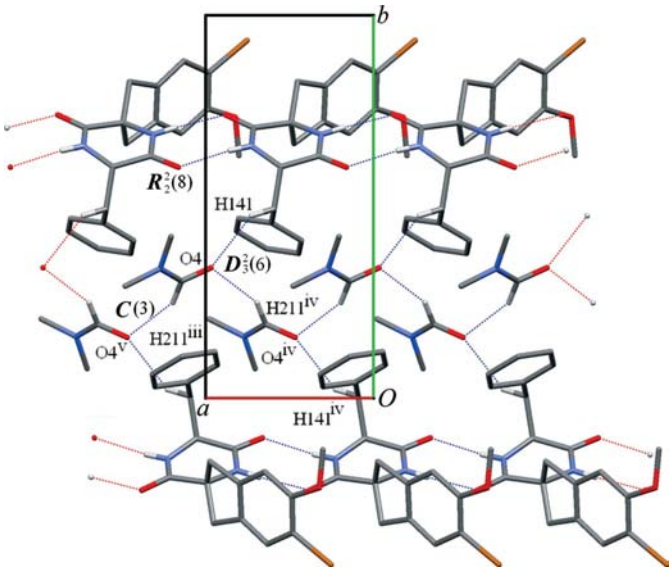

Figure 2
Part of the crystal packing in (*R,S*)-(II), projected along the *c* axis. [Symmetry codes: (iii) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iv) $x-\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (v) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$.]

between adjacent piperazinedione rings in compounds of this type. In this structure, adjacent molecules of (*R,S*)-(II) are connected *via* an $R_2^2(8)$ motif (Bernstein *et al.*, 1995) composed of two N—H···O interactions to form an infinite tape parallel to the *a* axis (Fig. 2). Similarly, adjacent DMF molecules are connected *via* a *C*(3) motif formed by C21^{iii}—H211^{iii}···O4^{v} (atoms used as an example in Fig. 2) into a chain which propagates along the *a* axis. The DMF O atom acts as a bifurcated acceptor, participating in a further motif which is shown in Fig. 2 by a combination of C14—H141···O4, C21^{iv}—H211^{iv}···O4 and C14^{iv}—H141^{iv}···O4^{iv} and is probably most appropriately described as $D_3^2(6)$ since it does not propagate beyond H141 or H141^{iv}. Overall the combination of all hydrogen-bonding interactions results in a one-dimensional ribbon, which propagates in the *a*-axis direction, with molecules of (*R,S*)-(II) forming the outermost parts and DMF molecules forming the innermost part of the ribbon.

Experimental

The synthesis of (*R,S*)-(I) has been reported previously (Murigi *et al.*, 2010). Neat (*R,S*)-(I) (105 mg, 0.19 mmol) was heated in a sealed evacuated tube in an oil bath at 513 K for 20 min, which produced a yellow solid. After cooling to room temperature, the tube was opened, the residue was triturated with CH_2Cl_2 (3 ml) to dissolve the yellow impurities, and the remaining solid was collected by filtration, giving (*R,S*)-(II) (45 mg, 0.108 mmol, 58%) as a white solid. The diastereomeric purity of (*R,S*)-(II) was estimated to be 95% by NMR. Crystallization from hot DMF solution with slow cooling gave, after 2–3 d, a white crystalline mass with a diastereomeric purity >99%, as determined by NMR. Characterization data for (*R,S*)-(II): $[\alpha]_D^{24}$ −7.80 [*c* 0.3, dimethyl sulfoxide (DMSO)]; m.p. 563 K; IR (KBr, cm^{-1}): 3434, 3034, 2961, 1672, 1447, 1276, 1044; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.10 (*d*, 1H, *J* = 17.0 Hz), 2.51 (*d*, 1H, *J* = 17.0 Hz), 2.90 (*m*, 2H), 3.14 (*dd*, 1H, *J* = 3.5 Hz, *J* = 13.4 Hz), 3.34 (*d*, 1H, *J* = 16.5 Hz), 3.75 (*s*, 3H), 4.26 (*s*, 1H), 6.65 (*s*, 1H), 7.20 (*d*, 2H, *J* = 6.6 Hz), 7.27 (*s*, 1H), 7.32 (*m*, 3H), 8.22 (*s*, 1H), 8.48 (*s*, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 38.3, 45.5, 46.3, 55.6, 56.2, 63.8, 108.1, 108.6, 126.7, 127.8, 128.1, 130.3, 133.7, 136.1, 141.1, 154.2, 166.0, 169.9; HRMS (ESI) calculated for $C_{20}H_{18}BrN_2O_3$ $(M-H)^-$ 413.0506, found 413.0499.

Crystal data

$C_{20}H_{19}BrN_2O_3\cdot C_3H_7NO$
M_r = 488.38
Orthorhombic, $P2_12_12_1$
a = 6.0741 (7) Å
b = 13.8336 (16) Å
c = 26.076 (3) Å
V = 2191.1 (4) Å^3
Z = 4
Synchrotron radiation
λ = 0.7749 Å
μ = 1.91 mm^{-1}
T = 100 K
1.00 × 0.01 × 0.01 mm

Data collection

Bruker SMART APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.25, T_{max} = 0.98
31454 measured reflections
4493 independent reflections
3882 reflections with $I > 2\sigma(I)$
R_{int} = 0.057

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.073
S = 1.00
4479 reflections
281 parameters
Only H-atom displacement parameters refined
$\Delta\rho_{max}$ = 0.60 e Å^{-3}
$\Delta\rho_{min}$ = −0.67 e Å^{-3}
Absolute structure: Flack (1983), 1890 Friedel pairs
Flack parameter: −0.015 (7)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H11···O2^{i}	0.84	1.98	2.820 (5)	177
N2—H21···O1^{ii}	0.84	2.02	2.854 (5)	171
C14—H141···O4	0.96	2.43	3.257 (5)	143
C21—H211···O4^{iii}	0.96	2.46	3.346 (5)	154

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

H atoms were all located in a difference map, but those attached to C atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H = 0.93–0.98 Å and N—H = 0.86–0.89 Å) and U_{iso}(H) values (1.2–1.5U_{eq} of the parent atom), after which the positions were refined with riding constraints.

Data collection: *APEX2* (Bruker, 2007); cell refinement: *SAINT* (Bruker, 2007); data reduction: *SAINT*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *CRYSTALS*.

Crystallographic data were collected at Beamline 11.3.1 at the Advanced Light Source (ALS), Lawrence Berkeley National Laboratory. The ALS is supported by the US Department of Energy, Office of Energy Sciences, under contract No. DE-AC02-05CH11231. We thank Dr Simon Teat for assistance with the data collection.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: EG3048). Services for accessing these data are described at the back of the journal.

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