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Low-temperature determination of theophylline dimethyl sulfoxide solvate

Christine Cardin,[a] Yu Gan[a] and Thomas Lewis[b]*

[a]School of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, England, and [b]Pharmaterials Ltd, Earley Gate, Whiteknights Road, Reading RG6 6AD, England
Correspondence e-mail: thomas.lewis@pharmaterials.co.uk

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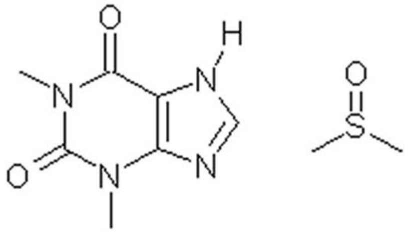
Key indicators: single-crystal X-ray study; *T* = 150 K; mean σ(C–C) = 0.002 Å; *R* factor = 0.039; *wR* factor = 0.103; data-to-parameter ratio = 16.1.

The title solvate, $C_7H_8N_4O_2\cdot C_2H_6OS$, was obtained unintentionally from a cocrystal screen involving theophylline and isophthalic acid. One molecule each of theophylline and dimethyl sulfoxide is present in the asymmetric unit. The packing consists of molecular sheets lying parallel to the (040) series of lattice planes, in which each theophylline molecule is hydrogen bonded to one dimethyl sulfoxide molecule through an N—H···O [2.7658 (15) Å] hydrogen bond. This particular hydrogen-bond donor was found to be used in this type of interaction in a variety of other crystal structures of theophylline.

Related literature

For related literature, see: Ebisuzaki *et al.* (1997); Sun *et al.* (2002); Sutor (1958); Trask *et al.* (2006); Wiedenfeld & Knoch (1986); Nakao *et al.* (1977); Spek (2003).



Experimental

Crystal data

$C_7H_8N_4O_2\cdot C_2H_6OS$
$M_r = 258.30$
Monoclinic, $P2_1/c$
$a = 10.1078$ (4) Å
$b = 6.6686$ (2) Å
$c = 17.3716$ (6) Å
$\beta = 94.000$ (3)°

$V = 1168.08$ (7) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.28$ mm^{-1}
$T = 150$ (2) K
0.30 × 0.20 × 0.10 mm

Data collection

Oxford Diffraction Xcalibur System diffractometer
Absorption correction: multi-scan (*ABSPACK*; Oxford Diffraction, 2005)
$T_{min} = 0.909$, $T_{max} = 1.000$

7829 measured reflections
3389 independent reflections
2954 reflections with $I > 2\sigma(I)$
$R_{int} = 0.018$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.039$
$wR(F^2) = 0.103$
$S = 1.14$
3389 reflections

210 parameters
All H-atom parameters refined
$\Delta\rho_{max} = 0.48$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N7—H1···O01	0.90 (2)	1.87 (2)	2.7658 (15)	172.8 (19)

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2005); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2005); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *Mercury* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

The authors acknowledge Dr Mark Saunders and Dr David Churchley for useful discussions during this study.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: EZ2079).

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supplementary materials

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Low-temperature determination of theophylline dimethyl sulfoxide solvate

C. Cardin, Y. Gan and **T. Lewis**

Comment

Theophylline is a pharmaceutically active compound for the treatment of asthma, and is currently known to have two anhydrous and one monohydrate crystal modifications (Sun *et al.*, 2002; Sutor, 1958; Ebisuzaki *et al.*, 1997). A variety of molecular complexes of theophylline have been determined, including with urea (Wiedenfeld & Knoch, 1986), and phenobarbital (Nakao *et al.*, 1977). In addition, a recent co-crystal study on theophylline has also been performed (Trask *et al.*, 2006). In this paper we report the dimethyl sulfoxide solvate of theophylline (I).

(I) has one molecule each of theophylline and dimethyl sulfoxide in the asymmetric unit, with the C—N and C—C bond lengths in (I) ranging from 1.3470 (17) to 1.4702 (16) Å, and 1.3720 (16) to 1.4251 (17) Å, respectively. The packing consists of molecular sheets (Fig 2), lying parallel to the (040) series of lattice planes. Within the molecular sheets each theophylline molecule is hydrogen bonded to one dimethyl sulfoxide molecule through a N—H···O -(2.7658 (15) Å) hydrogen bond (Fig 1). This particular hydrogen bond donor (N7—H1) was found to undergo hydrogen bonding within a variety of theophylline crystal structures, including the anhydrous (Sutor, 1958; Ebisuzaki *et al.*, 1997) and monohydrate (Sun *et al.*, 2002) forms, and in a variety of theophylline cocrystals (Trask *et al.*, 2006).

Experimental

As part of a cocrystal study on theophylline, (I) was obtained from a solution of theophylline in dimethyl sulfoxide to which an equimolar amount of isophthalic acid was added. The solution was allowed to evaporate at room temperature, forming long plate-like crystals.

Refinement

All non-hydrogen atoms were refined with anisotropic displacement parameters, while the hydrogen atoms were freely refined with an isotropic model.

Figures

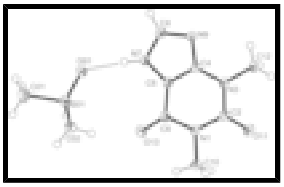

Fig. 1. View of (I) showing the atom labelling scheme. Displacement ellipsoids are drawn at 50% level. The N7—H1···O01 hydrogen bond is also shown.

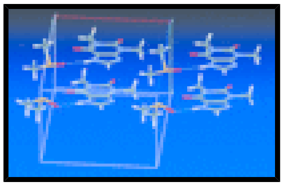

Fig. 2. The crystal packing in (I) showing the molecular sheets parallel to the (040) series of lattice planes.

Theophylline dimethyl sulfoxide solvate

Crystal data

$C_7H_8N_4O_2 \cdot C_2H_6OS$

$M_r = 258.30$

Monoclinic, $P2_1/c$

$a = 10.1078\ (4)$ Å

$b = 6.6686\ (2)$ Å

$c = 17.3716\ (6)$ Å

$\beta = 94.000\ (3)^\circ$

$V = 1168.08\ (7)$ Å^3

$Z = 4$

$F_{000} = 544$

$D_x = 1.469$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å

Cell parameters from 7829 reflections

$\theta = 3.0–30.1^\circ$

$\mu = 0.28$ mm^{-1}

$T = 150\ (2)$ K

Plate, colourless

0.30 × 0.20 × 0.10 mm

Data collection

Oxford Diffraction Xcalibur System diffractometer

Radiation source: Enhance (Mo) X-ray Source

Monochromator: graphite

$T = 150(2)$ K

321 frames, counting time 10 s. scans

Absorption correction: multi-scan
(ABSPACK; Oxford Diffraction, 2005)

$T_{min} = 0.909$, $T_{max} = 1.000$

7829 measured reflections

3389 independent reflections

2954 reflections with $I > 2\sigma(I)$

$R_{int} = 0.018$

$\theta_{max} = 30.1^\circ$

$\theta_{min} = 3.0^\circ$

$h = -14 \rightarrow 13$

$k = -9 \rightarrow 4$

$l = -24 \rightarrow 23$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.039$

$wR(F^2) = 0.103$

$S = 1.14$

3389 reflections

210 parameters

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites

All H-atom parameters refined

$w = 1/[\sigma^2(F_o^2) + (0.0448P)^2 + 0.4489P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0.001$

$\Delta\rho_{max} = 0.48$ e Å^{-3}

$\Delta\rho_{min} = -0.32$ e Å^{-3}

Extinction correction: none

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit S are based on F^2, conventional *R*-factors *R* are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on F, and R– factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	*y*	*z*	U_{iso}*/U_{eq}
S01	0.99246 (3)	0.27513 (6)	0.39406 (2)	0.02725 (10)
O01	0.86611 (10)	0.21464 (19)	0.43009 (6)	0.0339 (3)
O13	0.80020 (10)	0.20643 (18)	0.22207 (6)	0.0324 (2)
C12	0.25006 (13)	0.2289 (3)	0.17748 (8)	0.0280 (3)
N3	0.39458 (10)	0.21980 (16)	0.18986 (6)	0.0185 (2)
O11	0.41996 (10)	0.22404 (15)	0.06081 (5)	0.0259 (2)
N7	0.61561 (11)	0.21610 (16)	0.35505 (6)	0.0196 (2)
N1	0.60823 (11)	0.21461 (16)	0.14185 (6)	0.0197 (2)
N9	0.39424 (11)	0.21847 (17)	0.33061 (6)	0.0210 (2)
C10	0.68505 (15)	0.2138 (2)	0.07304 (8)	0.0285 (3)
C02	1.04433 (15)	0.0636 (3)	0.34142 (9)	0.0341 (3)
C4	0.45550 (12)	0.21723 (17)	0.26335 (7)	0.0165 (2)
C8	0.49588 (13)	0.21820 (19)	0.38458 (7)	0.0208 (2)
C6	0.67877 (13)	0.21158 (19)	0.21484 (7)	0.0206 (2)
C5	0.59106 (12)	0.21525 (17)	0.27559 (6)	0.0171 (2)
C2	0.47051 (12)	0.21983 (18)	0.12719 (7)	0.0186 (2)
C01	1.12025 (16)	0.2617 (3)	0.47024 (10)	0.0364 (4)
H2	0.4860 (17)	0.220 (2)	0.4387 (10)	0.024 (4)*
H6	0.6500 (17)	0.105 (3)	0.0372 (10)	0.033 (4)*
H1	0.694 (2)	0.220 (3)	0.3829 (12)	0.038 (5)*
H7	0.7726 (19)	0.191 (3)	0.0903 (11)	0.033 (5)*
H11	1.1159 (19)	0.130 (3)	0.4954 (11)	0.043 (5)*
H8	0.6760 (18)	0.344 (3)	0.0467 (11)	0.038 (5)*
H13	1.039 (2)	−0.057 (3)	0.3756 (12)	0.050 (6)*
H5	0.222 (2)	0.309 (4)	0.1328 (14)	0.056 (6)*
H12	1.134 (2)	0.086 (3)	0.3285 (11)	0.044 (5)*
H14	0.986 (2)	0.051 (3)	0.2967 (12)	0.049 (6)*
H3	0.220 (2)	0.294 (3)	0.2224 (14)	0.054 (6)*
H9	1.106 (2)	0.364 (3)	0.5073 (12)	0.046 (5)*
H4	0.215 (2)	0.103 (4)	0.1702 (14)	0.065 (7)*
H10	1.204 (3)	0.280 (3)	0.4482 (16)	0.064 (7)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S01	0.01938 (16)	0.03553 (19)	0.02636 (17)	0.00271 (12)	−0.00191 (12)	0.00318 (13)
O01	0.0160 (4)	0.0631 (7)	0.0226 (5)	0.0054 (4)	0.0019 (3)	−0.0009 (5)
O13	0.0174 (5)	0.0550 (7)	0.0245 (5)	−0.0004 (4)	0.0007 (4)	0.0054 (4)
C12	0.0171 (6)	0.0443 (8)	0.0218 (6)	−0.0008 (5)	−0.0038 (5)	0.0000 (6)
N3	0.0163 (5)	0.0248 (5)	0.0141 (4)	−0.0004 (4)	−0.0021 (3)	−0.0002 (4)
O11	0.0256 (5)	0.0369 (5)	0.0145 (4)	−0.0007 (4)	−0.0025 (3)	−0.0007 (4)
N7	0.0196 (5)	0.0238 (5)	0.0149 (4)	−0.0004 (4)	−0.0027 (4)	0.0005 (4)
N1	0.0196 (5)	0.0253 (5)	0.0143 (4)	−0.0003 (4)	0.0015 (4)	0.0001 (4)
N9	0.0197 (5)	0.0278 (5)	0.0154 (4)	0.0001 (4)	0.0011 (4)	−0.0003 (4)
C10	0.0245 (7)	0.0431 (8)	0.0185 (6)	−0.0004 (6)	0.0062 (5)	−0.0018 (5)
C02	0.0215 (7)	0.0530 (10)	0.0281 (7)	0.0041 (6)	0.0030 (5)	−0.0064 (7)
C4	0.0183 (5)	0.0163 (5)	0.0146 (5)	−0.0004 (4)	−0.0013 (4)	−0.0001 (4)
C8	0.0229 (6)	0.0245 (6)	0.0149 (5)	0.0005 (5)	0.0000 (4)	0.0000 (4)
C6	0.0193 (6)	0.0241 (6)	0.0180 (5)	−0.0009 (4)	−0.0010 (4)	0.0017 (4)
C5	0.0177 (5)	0.0191 (5)	0.0143 (5)	−0.0004 (4)	−0.0016 (4)	0.0008 (4)
C2	0.0214 (6)	0.0184 (5)	0.0156 (5)	−0.0004 (4)	−0.0007 (4)	−0.0005 (4)
C01	0.0254 (7)	0.0438 (9)	0.0382 (8)	0.0013 (6)	−0.0106 (6)	−0.0062 (7)

Geometric parameters (Å, °)

S01—O01	1.5156 (11)	N1—C10	1.4702 (16)
S01—C02	1.7797 (17)	N9—C8	1.3417 (16)
S01—C01	1.7859 (16)	N9—C4	1.3601 (15)
O13—C6	1.2256 (16)	C10—H6	1.003 (18)
C12—N3	1.4628 (16)	C10—H7	0.927 (19)
C12—H5	0.97 (2)	C10—H8	0.98 (2)
C12—H3	0.96 (2)	C02—H13	1.01 (2)
C12—H4	0.91 (3)	C02—H12	0.96 (2)
N3—C2	1.3751 (16)	C02—H14	0.94 (2)
N3—C4	1.3781 (14)	C4—C5	1.3720 (16)
O11—C2	1.2286 (15)	C8—H2	0.952 (17)
N7—C8	1.3470 (17)	C6—C5	1.4251 (17)
N7—C5	1.3854 (15)	C01—H11	0.98 (2)
N7—H1	0.90 (2)	C01—H9	0.96 (2)
N1—C2	1.3980 (16)	C01—H10	0.96 (3)
N1—C6	1.4108 (15)		

O01—S01—C02	106.75 (7)	S01—C02—H12	108.2 (12)
O01—S01—C01	105.50 (8)	H13—C02—H12	110.5 (17)
C02—S01—C01	96.73 (8)	S01—C02—H14	107.5 (13)
N3—C12—H5	112.3 (13)	H13—C02—H14	111.2 (17)
N3—C12—H3	105.7 (14)	H12—C02—H14	111.4 (17)
H5—C12—H3	107.8 (19)	N9—C4—C5	112.12 (10)
N3—C12—H4	110.7 (15)	N9—C4—N3	126.50 (11)
H5—C12—H4	107.8 (19)	C5—C4—N3	121.37 (11)

H3—C12—H4	112.6 (19)	N9—C8—N7	113.49 (11)
C2—N3—C4	119.69 (10)	N9—C8—H2	124.2 (11)
C2—N3—C12	119.36 (10)	N7—C8—H2	122.3 (11)
C4—N3—C12	120.92 (11)	O13—C6—N1	122.16 (12)
C8—N7—C5	106.03 (10)	O13—C6—C5	126.50 (12)
C8—N7—H1	125.1 (13)	N1—C6—C5	111.33 (11)
C5—N7—H1	128.8 (13)	C4—C5—N7	105.19 (10)
C2—N1—C6	126.76 (10)	C4—C5—C6	123.47 (11)
C2—N1—C10	115.32 (10)	N7—C5—C6	131.34 (11)
C6—N1—C10	117.92 (11)	O11—C2—N3	121.64 (12)
C8—N9—C4	103.18 (10)	O11—C2—N1	121.01 (11)
N1—C10—H6	108.9 (10)	N3—C2—N1	117.35 (10)
N1—C10—H7	106.5 (12)	S01—C01—H11	108.8 (12)
H6—C10—H7	111.7 (15)	S01—C01—H9	109.1 (12)
N1—C10—H8	109.7 (11)	H11—C01—H9	108.9 (18)
H6—C10—H8	109.4 (15)	S01—C01—H10	108.1 (16)
H7—C10—H8	110.6 (16)	H11—C01—H10	111.0 (18)
S01—C02—H13	107.8 (12)	H9—C01—H10	110.9 (19)

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N7—H1···O01	0.90 (2)	1.87 (2)	2.7658 (15)	172.8 (19)

Fig. 1

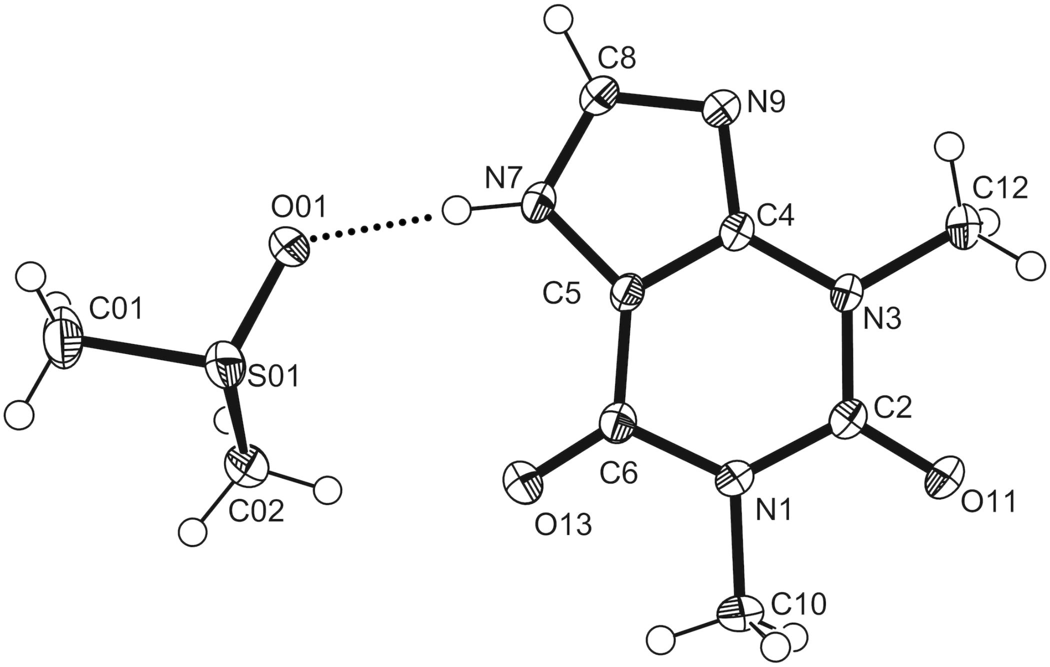

Fig. 2