Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Theophylline monohydrate

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.003 Å
Disorder in main residue
R factor = 0.045
wR factor = 0.125
Data-to-parameter ratio = 11.2

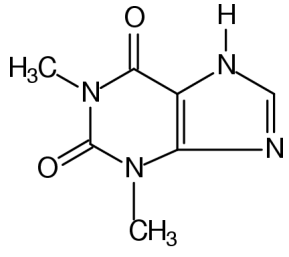
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 25 January 2002
Accepted 12 February 2002
Online 8 March 2002

The crystal structure of the title compound, 3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione monohydrate, $C_7H_8N_4O_2\cdot H_2O$, was determined by single-crystal X-ray diffractometry using direct methods. Water molecules in the crystals form infinite chains, through hydrogen-bonded chains running through tunnels formed by surrounding theophylline molecules along the *a* axis. The water chains are also crosslinked through hydrogen bonds by hydrogen-bonded theophylline dimers, and form a two-dimensional hydrogen-bonded structure parallel to the *ab* plane. The previously reported structure [Suctor (1958), *Acta Cryst.* **11**, 83–87] in space group $P2_1$, with Z = 4, appears to be incorrect.

Comment

Theophylline, (I), is a common therapeutic agent for the treatment of asthma. It exists as two polymorphic anhydrates and as a monohydrate.



(I)

The change in the crystal structure of a drug, as a result of its solid-state hydration, alters many pharmaceutically important properties, such as solubility and tableting behavior (Khankari & Grant, 1995). The differences between the physical properties of theophylline anhydrate and monohydrate have been the subject of numerous studies (Rodríguez-Hornedo *et al.*, 1992; Zhu *et al.*, 1996; Phadnis & Suryanarayanan, 1997). Differences between the structures of crystals may provide an important fundamental understanding of the differences in the thermodynamic activities, mechanical behavior, and other important physicochemical properties of the different solid phases containing the same molecule (Payne *et al.*, 1996; Nichols & Frampton, 1998; Sun & Grant, 2001). For these purposes, an accurate determination of the structure of a crystal is critical. The crystal structure of theophylline monohydrate has been reported previously (Suctor, 1958), with the reference code THEOPH in the Cambridge Structural Database (CSD; Allen & Kennard, 1993). However, this published crystal structure appears to be

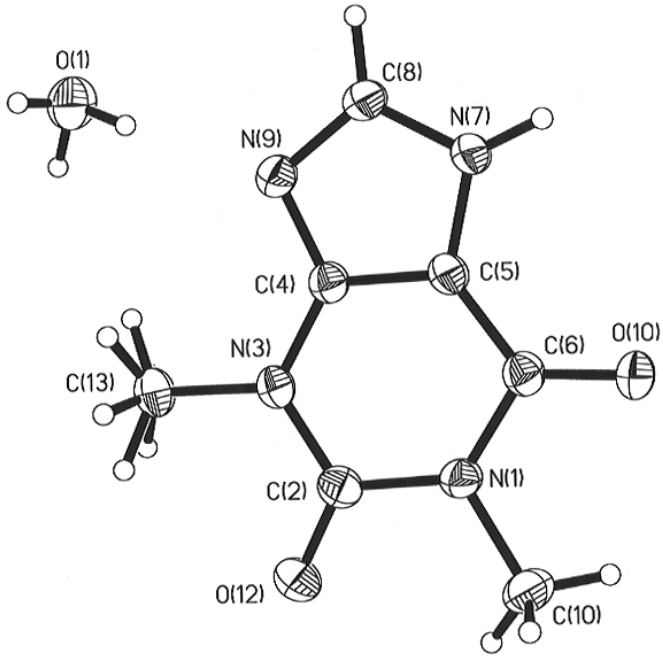


Figure 1
The atomic numbering scheme of theophylline monohydrate, with displacement ellipsoids drawn at the 50% probability level. H atoms are drawn as spheres with arbitrary radii.

incorrect (CSD, error message, April 2000; x and y coordinates of N7 and C8 should be $x-\frac{1}{2}$ and $y-\frac{1}{2}$, respectively; similarly for its H atoms and H10 of the water molecules). The present work shows that the space group of the previous crystal structure is not $P2_1$ (Sutor, 1958) but $P2_1/n$ (Table 1).

In the present structure, one H atom of the water molecule has two disordered sites with 50:50 occupancy (Fig. 1). The O1—H1*B* bond points in the direction of the inversion center. This H atom is found at the correct distance to form a hydrogen bond with the water molecule related by the inversion center, which means that the H atom can not have full occupancy. The other half occupancy is found with H1*C* which forms a hydrogen bond with another symmetry-related water molecule (Table 2). The H atoms on C13 are disordered by a rotation of 60° and the occupancy of the two sets is 64:36 (Table 2).

Two centrosymmetrically related theophylline molecules form a dimer through two hydrogen bonds in the crystal of theophylline monohydrate. The water molecules in the crystal form infinite hydrogen-bonded chains, running through tunnels along the *a* axis (Fig. 2). These chains are parallel and are crosslinked, through hydrogen bonds, by theophylline dimers (Fig. 2). Consequently, two-dimensional hydrogen-bonded layers, parallel to the *ab* plane, are formed.

Experimental

Theophylline anhydrate powder (95 mg, Sigma Chemical Co., St. Louis, MO) was suspended in 10 ml of distilled water contained in a 20 ml glass vial. The vial was heated gradually until a clear solution was obtained. The solution was filtered through a 0.2 mm pore membrane filter to remove residual particles. The filtrate was transferred to another 20 ml glass vial. The vial was covered with aluminum foil with a circular hole of diameter 1.5 mm and was left undisturbed in a fume hood. Transparent needle-shaped crystals were obtained after slow evaporation of water for one month.

Crystal data

$C_7H_8N_4O_2\cdot H_2O$
$M_r = 198.19$
Monoclinic, $P2_1/n$
$a = 4.468\ (2)$ Å
$b = 15.355\ (5)$ Å
$c = 13.121\ (5)$ Å
$\beta = 97.792\ (7)^\circ$
$V = 891.9\ (6)$ Å^3
$Z = 4$
$D_x = 1.476$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 514 reflections
$\theta = 2.1$–25.0°
$\mu = 0.12$ mm^{-1}
$T = 173\ (2)$ K
Needle, light yellow
$0.50 \times 0.11 \times 0.09$ mm

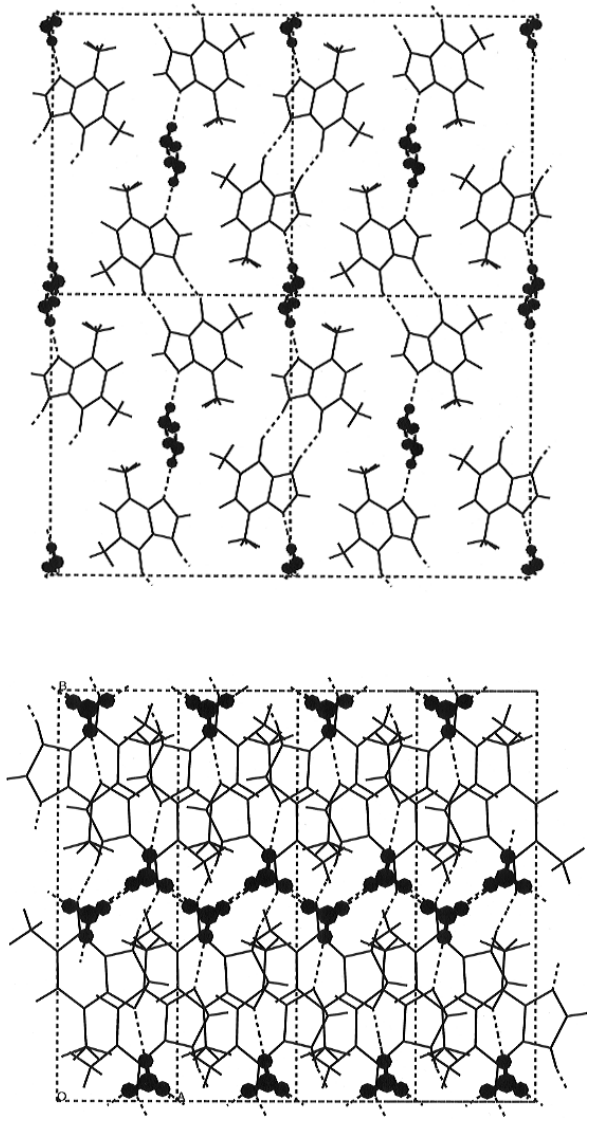


Figure 2
Projection of the molecules on the 100 plane (top), showing dimers bound by two hydrogen bonds, and on the 001 planes (bottom), showing the infinite chain of water molecules attached, by hydrogen bonds, to the theophylline molecules in the theophylline monohydrate crystal. The water molecules are shown as sticks and balls. The hydrogen bonds are indicated by the broken lines.

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Blessing, 1995; Sheldrick, 2000)
T_{min} = 0.985, T_{max} = 0.989
5481 measured reflections
1554 independent reflections
1285 reflections with $I > 2\sigma(I)$
R_{int} = 0.031
θ_{max} = 25.0°
$h = -5 \rightarrow 5$
$k = -18 \rightarrow 18$
$l = -15 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.125
S = 1.01
1554 reflections
139 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.063P)^2 + 0.7841P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 1
Crystal data of theophylline monohydrate.

	The present work	Sutor (1958)[a]
Experimental temperature	173 (2) K	295 K
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1$
a	4.468 (2)	4.50
b	15.355 (5)	15.3
c	13.121 (5)	13.3
β	97.792 (7)	99.5
Volume	891.9 (6)	903.15
Z	4	4
Density	1.476	1.456

Notes: (*a*) the *a* and *c* axes of this earlier crystal structure (Sutor, 1958) were assigned differently and have now been interchanged to match the assignment in the present work.

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

D—H···A	D—H	H···A	D···A	D—H···A
N7—H7A···O10^{i}	0.88	1.90	2.763 (2)	168
O1—H1A···N9	0.86 (2)	2.05 (3)	2.901 (3)	171 (3)
O1—H1B···O1^{ii}	0.86 (3)	1.92 (3)	2.726 (4)	156 (6)
O1—H1C···O1^{iii}	0.85 (3)	2.01 (4)	2.744 (4)	143 (5)

Symmetry codes: (i) $-x, 2-y, 1-z$; (ii) $-x, 1-y, 1-z$; (iii) $-1-x, 1-y, 1-z$.

Most H atoms were placed in ideal positions and refined as riding atoms with individual isotropic displacement parameters. Water H atoms were refined isotropically with O—H distance restraints and individual isotropic displacement parameters

Data collection: *SMART* (Bruker, 2000); cell refinement: *SAINT* (Bruker, 2000); data reduction: SAINT; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Bruker, 1997); software used to prepare material for publication: *SHELXTL/PC*.

References

Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 1, 31–37.
Blessing, R. (1995). *Acta Cryst.* A**51**, 33–38.
Bruker (1997). *SHELXTL/PC*. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2000). *SMART* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Khankari, R. K. & Grant, D. J. W. (1995). *Thermochim. Acta*, **248**, 61–79.
Nichols, G. & Frampton, C. S. (1998). *J. Pharm. Sci.* **87**, 684–693.
Payne, R. S., Roberts, R. J., Rowe, R. C., McPartlin, M. & Bashal, A. (1996). *Int. J. Pharm.* **145**, 165–173.
Phadnis, N. V. & Suryanarayanan, R. (1997). *J. Pharm. Sci.* **86**, 1256.
Rodríguez-Hornedo, N., Lechuga-Ballesteros, D. & Wu, H.-J. (1992). *Int. J. Pharm.* **85**, 149–162.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Sheldrick, G. M. (2000). *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
Sutor, D. J. (1958). *Acta Cryst.* **11**, 83–87.
Sun, C. & Grant, D. J. W. (2001). *Pharm. Res.* **18**, 274–280.
Zhu, H., Yuen, C. & Grant, D. J. W. (1996). *Int. J. Pharm.* **135**, 151–160.