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Article

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Anhydrous Polymorphs of Theophylline: The stable Form IV consists of dimer pairs, and the metastable Form I consists of H-bonded chains

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Abstract

The structure of a previously unreported polymorph of anhydrous theophylline (1,3-dimethyl-7H-purine-2,6-dione), $C_7H_8N_4O_2$, at 100K has monoclinic symmetry. The structure is named Form IV and experimental observation indicates that this is the stable form of the material. The molecular packing consists of discrete hydrogen-bonded dimers similar to that observed in the monohydrate structure. The structure of Form I has also been determined and consists of hydrogen bonded chains.

Comment

Theophylline, (I), is a bronchodilator used to treat asthma in an oral dosage form. Its hydration behaviour and solid state chemistry has been studied (Wikstroem *et al.*, 2008; Amado *et al.*, 2007) and it is known to exist as a monohydrate form (Sun *et al.* 2002), and three anhydrous polymorphs, Forms I, II and III are reported (Ebisuzaki *et al.* 1997; Suzuki *et al.*,1989; Matsuo & Matsuoka 2007). Theophylline has been shown to convert between the monohydrate and anhydrous Form II dependent on the humidity or water activity of the solvent environment (Zhu *et al.*,1996). The pharmaceutical properties of anhydrous and monohydrate material have been studied and shown to differ (Phadnis & Suryanarayanan 1997).

The monohydrate, Form M, has a channel hydrate structure which has been shown to lose water to produce Form II anhydrous material (Zhu *et al.*,1996; Ticehurst *et al.*, 2002). The monohydrate packing (Sun *et al.*,2002) [Cambridge Structural Database (Allen 2002) refcode THEOPH01] consists of hydrogen bonded dimer pairs which link via further H-bonding with water molecules to form chains.

Form II occurs when the monohydrate loses water, either in low humidity or at temperatures above 80°C. The Form II structure has been determined (Ebisuzaki *et al.*, 1997) [CSD refcode BAPLOT01] and consists of two bifurcated C–H···O hydrogen bonds and one N–H···N hydrogen bond. The molecules join via these bonds to form chains. Unlike the monohydrate, there are no discrete dimers present in the crystal structure of Form II.

Form I is reported to be the stable form at higher temperatures. Its powder pattern has been presented in the literature (Suzuki *et al.*,1989), but its structure has not been previously reported.

Form III, is a highly metastable form and rapidly converts to Form II. Its powder pattern has been reported (Matsuo & Matsuoka 2007) but its structure has not been obtained due to its metastable nature.

Recently, a fourth anhydrous polymorph of theophylline was identified (Seton *et al.* 2010).

Form IV occurs as a result of slow, solvent mediated conversion from Form II or Form I, and is therefore identified as the most thermodynamically stable anhydrous polymorph of theophylline. Form IV can be identified from its plate-like hexagonal morphology, distinct from the elongated needles observed in particles of Form I, II and monohydrate. This paper presents the structure of this previously unreported anhydrous polymorph of theophylline, and the structure of the high temperature anhydrous polymorph, Form I.

The structure of Form IV is monoclinic and consists of hydrogen bonded, dimer pairs formed by hydrogen bond contacts between N7 (donator) and C=O13 (acceptor) as shown in Figure 1. Short contacts link the dimers into chains, and further contacts link the chains to each other as displayed in Figure 2. The individual molecules of the dimer have distinct patterns of short contacts: molecule 1 of the dimer pair donates from C8 to O11 of a third molecule, and accepts via N9 a contact from C8 of a fourth molecule. Molecule 2 of the dimer has a single contact which it donates from C8 to N9 of a neighbouring molecule. The nitrogen at the N9 position is a good acceptor (Etter 1990) but due to insufficient donors, only one of the N9 atoms of the two molecules which make up the dimer is involved in a hydrogen bond contact.

This dimerisation is similar to the packing motif observed in the monohydrate structure and in a number of co-crystals of theophylline (Trask *et al.*, 2006) and may account for the thermodynamic stability of the structure compared with the chain motif of Form II. Both Form I and Form II are known to immediately convert to the monohydrate on contact with water (Suzuki *et al.*, 1989) and therefore the monohydrate structure is considered to be the most thermodynamically stable structure for the theophylline molecule in an aqueous environment. It makes sense then, that the dimer-based structure of Form IV, containing the same dimer pair motif as the monohydrate, is the most thermodynamically stable of the observed anhydrous forms. It has been observed that, like Form I and II, Form IV will convert to the monohydrate on contact with water, further stability being conferred by the hydrogen bonding of the dimer pairs with the water molecules.

The assymetric unit of the high temperature polymorph, Form I, is shown in Figure 3. The structure consists of extended chains made by hydrogen bonding between O11 and N7 as shown in Figure 4. Chains are parallel to each other and are stacked with a π-π interaction. The chains are discrete with no close contacts between them. This might explain the metastable nature of this structure compared with Forms II and IV which both have extended networks of close contacts.

The common form, Form II, consists of chains of molecules formed by strong hydrogen bonding interactions between N7 and N9. This interaction is unique to Form II, and may be stronger than the other hydrogen bond motifs observed in the other anhydrous forms This be the reason for the propensity of the material to crystallise as Form II.

Figure 1

The crystal structures of the two molecues int he assymetric unit of Form IV(I) showing hydrogen bonding to form dimer pair. The displacement ellipsoids are drawn at the 50% probablility level and h atoms are shown as spheres of arbitrary radii.

Figure 2

The structure of Form IV is built from hydrogen bonded dimers (visible top) which are linked via close contacts to form extended chains. The chains form close contacts with each other to form an extended network structure. The rings of the molecule also stack in a π -π fashion (bottom).

Figure 3

The assymetric unit of Form I. The displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as spheres with arbitrary radii.

Figure 4

Projection of Form I down the c axis (top) and the b axis (bottom) showing chain motif parallel to the a axis. Hydrogen bonds are indicated by broken lines. The chains are discrete and have no hydrogen bonds joining individual chains.

Anhydrous theophylline purchased from Sigma Aldrich UK was identified as Form II and used as received. Form I was prepared by heating Form II in glass vials at 265-268°C for 2 h. To prepare Form IV, a saturated solution of theophylline was prepared by suspending excess Form II in a 9:1, methanol (HPLC gradient grade): water solvent mixture for 1 h at 45°C and then filtering with a syringe filter of 0.45μm size. The filtered solution was cooled to room temperature. After 1 h, needle-like crystals were observed which were held in contact with the mother liquor for 2 months. Over this period, the morphology of the crystals was observed to change, with hexagonal plates being observed after several days, indicating the solvent mediated transformation to Form IV.

(Form_IV)

Crystal data

$C_7H_8N_4O_2$

$M_r = 180.17$

Monoclinic, $P2_1/c$

$a = 7.7055$ (1) Å

$b = 13.0010$ (2) Å

$c = 15.7794$ (3) Å

$\beta = 103.224$ (1)°

$V = 1538.85$ (4) Å^3

$Z = 8$

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

$\mu = 0.12$ mm^{-1}

$T = 100$ K

0.25 × 0.2 × 0.08 mm

Data collection

KappaCCD diffractometer

Absorption correction: multi-scan Blessing, R. H. (1989). *J. Appl. Cryst.* **22**, 396–397.

$T_{\min} = 0.971$, $T_{\max} = 0.991$

35162 measured reflections

3023 independent reflections

2275 reflections with $I > 2\sigma(I)$

$R_{\rm int} = 0.075$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.050$

$wR(F^2) = 0.138$

$S = 1.07$

3023 reflections

300 parameters

0 restraints

All H-atom parameters refined

$\Delta\rho_{\max} = 0.25$ e Å^{-3}

$\Delta\rho_{\min} = -0.31$ e Å^{-3}

(Form_I)

Crystal data

$C_7H_8N_4O_2$

$M_r = 180.17$

$V = 792.6$ (3) Å^3

$Z = 4$

Orthorhombic, *Pna*2_1	Mo *K*α radiation, λ = 0.71073 Å
a = 13.158 (2) Å	μ = 0.12 mm^{-1}
b = 15.630 (3) Å	T = 100 K
c = 3.854 (1) Å	0.25 × 0.06 × 0.03 mm

Data collection

KappaCCD diffractometer	462 reflections with $I > 2\sigma(I)$
1246 measured reflections	R_{int} = 0.040
764 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.088	H-atom parameters constrained
$wR(F^2)$ = 0.202	$\Delta\rho_{max}$ = 0.34 e $Å^{-3}$
S = 0.98	$\Delta\rho_{min}$ = −0.30 e $Å^{-3}$
764 reflections	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
120 parameters	Flack parameter: −10 (10)
1 restraint	

Table 1

Table 1

Form IV hydrogen-bonding geometry (Å, °)

D*–H—*A	***D*–H**	**H—*A***	***D*—*A***	***D*–H—*A***
N(7)–H(7)*A*—O(13)*B*	0.978	1.793	2.759	168.45
C(8)–H(8)*A*—O(11)*D*^{i}	0.991	2.386	3.222	141.56
N(7)–H(7)*B*—O(13)*A*	0.937	1.826	2.736	163.21
C(8)–H(8)*C*—N(9)*A*^{ii}	1.017	2.274	3.266	164.87

Symmetry codes: (i) -x, y-1/2, -z+1/2; (ii) x, -y-1/2,z+1/2

Table 2

Table 2

Form I hydrogen-bonding geometry (Å, °)

D*–H—*A	***D*–H**	**H—*A***	***D*—*A***	***D*–H—*A***
N(7) –H(7)—O(11)	0.881	1.919	2.741	154.67

Symmetry code: x-1/2, -y+1/2, z-1

For both structures H atoms were constrained to chemically reasonable positions.

For both compounds, data collection: Collect (Nonius BV, 1997-2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor 1997); data reduction: *HKL DENZO* and *SCALEPACK* (Otwinowski & Minor 1997); program(s) used to solve structure: *SIR92* (Giacovazzo *et al.*, 1993); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* publication routines (Farrugia, 1999).

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supplementary materials

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(Form_IV)

Crystal data

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$a = 7.7055$ (1) Å
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$\beta = 103.224$ (1)°
$V = 1538.85$ (4) Å^3
$Z = 8$

$F(000) = 752$
$D_x = 1.555$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 3844 reflections
$\theta = 2–26°$
$\mu = 0.12$ mm^{-1}
$T = 100$ K
Plate, colourless
0.25 × 0.2 × 0.08 mm

Data collection

KappaCCD diffractometer
Radiation source: Enraf Nonius FR590
graphite
Detector resolution: 9 pixels mm^{-1}
CCD rotation images, thick slices scans
Absorption correction: multi-scan Blessing, R. H. (1989). *J. Appl. Cryst.* **22**, 396–397.
$T_{min} = 0.971$, $T_{max} = 0.991$
35162 measured reflections

3023 independent reflections
2275 reflections with $I > 2\sigma(I)$
$R_{int} = 0.075$
$\theta_{max} = 26°$, $\theta_{min} = 3.1°$
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 16$
$l = -19 \rightarrow 18$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.138$
$S = 1.07$
3023 reflections
300 parameters
0 restraints
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
$w = 1/[\sigma^2(F_o^2) + (0.0683P)^2 + 1.0567P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.25$ e Å^{-3}
$\Delta\rho_{min} = -0.31$ e Å^{-3}
Extinction correction: *SHELXL*, $Fc^* = kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Extinction coefficient: 0.0035 (14)

Special details

Geometry. All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell s.u.'s are taken into account individually in the estimation of s.u.'s in distances, angles and torsion angles; correlations between s.u.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell s.u.'s is used for estimating s.u.'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 $F^2 > 2\sigma(F^2)$ 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	$U_{\rm iso}$*/$U_{\rm eq}$
C1	0.3212 (3)	0.50420 (17)	0.63506 (14)	0.0266 (5)
C2	0.2328 (3)	0.52543 (15)	0.49470 (13)	0.0215 (4)
C3	0.1953 (3)	0.52080 (16)	0.40273 (14)	0.0234 (5)
C4	0.0124 (3)	0.67913 (15)	0.40692 (13)	0.0218 (4)
C5	0.1655 (3)	0.59992 (15)	0.53948 (13)	0.0217 (4)
C6	0.0417 (3)	0.6053 (2)	0.26781 (14)	0.0309 (5)
C7	−0.0217 (3)	0.75327 (19)	0.54468 (16)	0.0288 (5)
C11	0.4273 (3)	0.22393 (17)	0.29313 (14)	0.0255 (5)
C12	0.5243 (3)	0.20659 (15)	0.43310 (13)	0.0212 (4)
C13	0.5653 (3)	0.21345 (16)	0.52510 (13)	0.0227 (5)
C14	0.7217 (3)	0.04496 (16)	0.52199 (13)	0.0227 (5)
C15	0.5764 (3)	0.12563 (15)	0.38935 (13)	0.0216 (4)
C16	0.7207 (3)	0.12615 (18)	0.66041 (14)	0.0266 (5)
C17	0.7376 (3)	−0.03938 (17)	0.38541 (15)	0.0262 (5)
N1	0.2190 (2)	0.58844 (14)	0.62739 (12)	0.0258 (4)
N2	0.3339 (2)	0.46310 (14)	0.55842 (11)	0.0250 (4)
N3	0.0856 (2)	0.60140 (13)	0.36367 (11)	0.0232 (4)
N4	0.0553 (2)	0.67640 (13)	0.49658 (11)	0.0226 (4)
N11	0.5177 (2)	0.13552 (14)	0.30143 (11)	0.0260 (4)
N12	0.4254 (2)	0.26962 (14)	0.36910 (11)	0.0235 (4)
N13	0.6660 (2)	0.12947 (13)	0.56479 (11)	0.0227 (4)
N14	0.6739 (2)	0.04496 (13)	0.43192 (11)	0.0233 (4)
O1	0.2495 (2)	0.45574 (12)	0.35749 (10)	0.0286 (4)
O2	−0.08478 (19)	0.74583 (11)	0.36696 (10)	0.0277 (4)
O11	0.5225 (2)	0.28330 (11)	0.56969 (9)	0.0282 (4)
O12	0.8084 (2)	−0.02497 (11)	0.56285 (10)	0.0284 (4)
H1	0.381 (3)	0.4730 (17)	0.6924 (15)	0.021 (5)*
H2	0.401 (4)	0.402 (2)	0.5508 (19)	0.055 (9)*
H6A	−0.006 (5)	0.537 (3)	0.245 (2)	0.081 (11)*
H6B	0.152 (5)	0.618 (2)	0.246 (2)	0.064 (9)*
H6C	−0.041 (5)	0.664 (3)	0.247 (3)	0.094 (13)*
H7A	0.007 (4)	0.740 (2)	0.606 (2)	0.053 (8)*
H7B	0.017 (4)	0.822 (3)	0.5344 (19)	0.057 (9)*
H7C	−0.149 (5)	0.752 (2)	0.523 (2)	0.061 (9)*
H11	0.364 (3)	0.2532 (19)	0.2357 (17)	0.036 (7)*
H12	0.374 (4)	0.338 (2)	0.373 (2)	0.056 (9)*
H16A	0.682 (4)	0.062 (2)	0.6818 (18)	0.042 (7)*

H16B	0.848 (4)	0.130 (2)	0.6808 (18)	0.046 (8)*
H16C	0.667 (4)	0.191 (2)	0.6834 (17)	0.041 (7)*
H17A	0.688 (3)	−0.0299 (17)	0.3207 (16)	0.024 (6)*
H17B	0.866 (4)	−0.039 (2)	0.3948 (18)	0.043 (7)*
H17C	0.701 (3)	−0.108 (2)	0.4056 (16)	0.038 (7)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0278 (11)	0.0261 (11)	0.0249 (11)	0.0002 (9)	0.0039 (9)	0.0019 (9)
C2	0.0198 (10)	0.0200 (10)	0.0240 (10)	−0.0005 (8)	0.0037 (8)	0.0011 (8)
C3	0.0194 (9)	0.0226 (11)	0.0272 (11)	−0.0008 (8)	0.0035 (8)	0.0000 (8)
C4	0.0198 (10)	0.0217 (10)	0.0237 (10)	−0.0010 (8)	0.0044 (8)	−0.0002 (8)
C5	0.0207 (10)	0.0202 (10)	0.0233 (10)	−0.0027 (8)	0.0033 (8)	0.0010 (8)
C6	0.0362 (13)	0.0348 (13)	0.0207 (11)	0.0079 (11)	0.0042 (9)	−0.0006 (10)
C7	0.0325 (13)	0.0268 (12)	0.0273 (12)	0.0075 (10)	0.0075 (10)	−0.0033 (9)
C11	0.0264 (11)	0.0266 (11)	0.0220 (11)	−0.0010 (9)	0.0027 (9)	−0.0003 (9)
C12	0.0209 (10)	0.0197 (10)	0.0219 (10)	−0.0008 (8)	0.0027 (8)	0.0016 (8)
C13	0.0195 (10)	0.0224 (10)	0.0262 (11)	−0.0011 (8)	0.0050 (8)	0.0010 (8)
C14	0.0216 (10)	0.0207 (10)	0.0255 (11)	−0.0023 (8)	0.0046 (8)	0.0001 (8)
C15	0.0225 (10)	0.0198 (10)	0.0216 (10)	−0.0030 (8)	0.0028 (8)	0.0008 (8)
C16	0.0298 (12)	0.0279 (12)	0.0211 (11)	0.0028 (10)	0.0040 (9)	0.0027 (9)
C17	0.0289 (12)	0.0228 (11)	0.0276 (12)	0.0035 (9)	0.0079 (9)	−0.0028 (9)
N1	0.0276 (9)	0.0248 (9)	0.0239 (9)	0.0004 (8)	0.0032 (7)	0.0021 (7)
N2	0.0255 (9)	0.0226 (9)	0.0253 (10)	0.0025 (8)	0.0024 (7)	0.0032 (7)
N3	0.0245 (9)	0.0225 (9)	0.0213 (9)	0.0026 (7)	0.0026 (7)	0.0011 (7)
N4	0.0250 (9)	0.0188 (9)	0.0239 (9)	0.0021 (7)	0.0052 (7)	−0.0002 (7)
N11	0.0266 (9)	0.0257 (10)	0.0241 (9)	0.0015 (8)	0.0022 (7)	−0.0002 (7)
N12	0.0233 (9)	0.0219 (9)	0.0235 (9)	0.0010 (7)	0.0019 (7)	0.0010 (7)
N13	0.0248 (9)	0.0220 (9)	0.0215 (9)	0.0025 (7)	0.0054 (7)	0.0015 (7)
N14	0.0253 (9)	0.0220 (9)	0.0219 (9)	0.0015 (7)	0.0040 (7)	−0.0013 (7)
O1	0.0301 (8)	0.0273 (8)	0.0273 (8)	0.0055 (6)	0.0045 (6)	−0.0031 (6)
O2	0.0270 (8)	0.0252 (8)	0.0287 (8)	0.0050 (6)	0.0017 (6)	0.0024 (6)
O11	0.0349 (8)	0.0245 (8)	0.0247 (8)	0.0051 (6)	0.0060 (6)	−0.0027 (6)
O12	0.0307 (8)	0.0239 (8)	0.0294 (8)	0.0051 (6)	0.0045 (7)	0.0036 (6)

Geometric parameters (Å, º)

C1—N1	1.338 (3)	C11—N12	1.341 (3)
C1—N2	1.346 (3)	C11—H11	1.00 (3)
C1—H1	1.00 (2)	C12—C15	1.368 (3)
C2—C5	1.369 (3)	C12—N12	1.386 (3)
C2—N2	1.384 (3)	C12—C13	1.416 (3)
C2—C3	1.415 (3)	C13—O11	1.239 (3)
C3—O1	1.239 (3)	C13—N13	1.401 (3)
C3—N3	1.398 (3)	C14—O12	1.221 (2)
C4—O2	1.222 (2)	C14—N14	1.384 (3)
C4—N4	1.378 (3)	C14—N13	1.407 (3)
C4—N3	1.408 (3)	C15—N11	1.363 (3)
C5—N1	1.362 (3)	C15—N14	1.373 (3)
C5—N4	1.380 (3)	C16—N13	1.471 (3)
C6—N3	1.473 (3)	C16—H16A	0.97 (3)
C6—H6A	1.00 (4)	C16—H16B	0.96 (3)
C6—H6B	1.00 (3)	C16—H16C	1.04 (3)
C6—H6C	1.00 (4)	C17—N14	1.465 (3)

C7—N4	1.460 (3)	C17—H17A	1.01 (2)
C7—H7A	0.96 (3)	C17—H17B	0.96 (3)
C7—H7B	0.97 (3)	C17—H17C	1.01 (3)
C7—H7C	0.96 (4)	N2—H2	0.97 (3)
C11—N11	1.334 (3)	N12—H12	0.98 (3)

N1—C1—N2	113.95 (19)	O12—C14—N13	121.20 (19)
N1—C1—H1	123.6 (12)	N14—C14—N13	117.01 (18)
N2—C1—H1	122.5 (12)	N11—C15—C12	111.93 (18)
C5—C2—N2	104.83 (18)	N11—C15—N14	125.94 (18)
C5—C2—C3	123.17 (19)	C12—C15—N14	122.12 (18)
N2—C2—C3	131.99 (19)	N13—C16—H16A	110.1 (16)
O1—C3—N3	120.46 (18)	N13—C16—H16B	111.8 (16)
O1—C3—C2	127.12 (19)	H16A—C16—H16B	107 (2)
N3—C3—C2	112.41 (18)	N13—C16—H16C	107.0 (15)
O2—C4—N4	121.51 (18)	H16A—C16—H16C	113 (2)
O2—C4—N3	121.70 (18)	H16B—C16—H16C	107 (2)
N4—C4—N3	116.79 (17)	N14—C17—H17A	108.8 (13)
N1—C5—C2	112.71 (18)	N14—C17—H17B	111.7 (16)
N1—C5—N4	125.97 (19)	H17A—C17—H17B	107 (2)
C2—C5—N4	121.32 (18)	N14—C17—H17C	110.7 (15)
N3—C6—H6A	108 (2)	H17A—C17—H17C	111.1 (19)
N3—C6—H6B	110.4 (18)	H17B—C17—H17C	108 (2)
H6A—C6—H6B	107 (3)	C1—N1—C5	102.51 (18)
N3—C6—H6C	110 (2)	C1—N2—C2	105.99 (18)
H6A—C6—H6C	114 (3)	C1—N2—H2	125.9 (18)
H6B—C6—H6C	107 (3)	C2—N2—H2	128.1 (18)
N4—C7—H7A	112.0 (18)	C3—N3—C4	126.40 (17)
N4—C7—H7B	111.7 (19)	C3—N3—C6	116.89 (17)
H7A—C7—H7B	109 (2)	C4—N3—C6	116.71 (17)
N4—C7—H7C	107.7 (19)	C4—N4—C5	119.88 (17)
H7A—C7—H7C	110 (2)	C4—N4—C7	119.05 (17)
H7B—C7—H7C	107 (3)	C5—N4—C7	121.04 (18)
N11—C11—N12	113.96 (19)	C11—N11—C15	103.02 (17)
N11—C11—H11	123.5 (15)	C11—N12—C12	105.83 (18)
N12—C11—H11	122.5 (15)	C11—N12—H12	122.9 (18)
C15—C12—N12	105.25 (17)	C12—N12—H12	130.9 (18)
C15—C12—C13	122.90 (18)	C13—N13—C14	126.32 (17)
N12—C12—C13	131.80 (19)	C13—N13—C16	118.72 (17)
O11—C13—N13	120.63 (18)	C14—N13—C16	114.96 (17)
O11—C13—C12	127.04 (19)	C15—N14—C14	119.31 (17)
N13—C13—C12	112.33 (18)	C15—N14—C17	122.36 (17)
O12—C14—N14	121.79 (19)	C14—N14—C17	118.26 (17)

(Form_I)

Crystal data

$C_7H_8N_4O_2$

$M_r = 180.17$

Orthorhombic, $Pna2_1$

Hall symbol: P 2c -2n

$a = 13.158$ (2) Å

$b = 15.630$ (3) Å

$c = 3.854$ (1) Å

$V = 792.6$ (3) Å^3

$F(000) = 376$

$D_x = 1.51$ Mg m^{-3}

Mo *K*α radiation, λ = 0.71073 Å

Cell parameters from 817 reflections

θ = 2–26°

μ = 0.12 mm^{-1}

$T = 100$ K

Prism, colourless

$Z = 4$

0.25 × 0.06 × 0.03 mm

Data collection

KappaCCD diffractometer

Radiation source: Enraf Nonius FR590

graphite

Detector resolution: 9 pixels mm^{-1}

CCD rotation images, thick slices scans

1246 measured reflections

764 independent reflections

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

$R_{\text{int}} = 0.040$

$\theta_{\text{max}} = 25.4°$, $\theta_{\text{min}} = 3.1°$

$h = -15 \rightarrow 15$

$k = -18 \rightarrow 18$

$l = -4 \rightarrow 4$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.088$

$wR(F^2) = 0.202$

$S = 0.98$

764 reflections

120 parameters

1 restraint

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.010P)^2 + 3.5P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\text{max}} = 0.005$

$\Delta\rho_{\text{max}} = 0.34$ e Å^{-3}

$\Delta\rho_{\text{min}} = -0.30$ e Å^{-3}

Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881

Flack parameter: −10 (10)

Special details

Geometry. All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell s.u.'s are taken into account individually in the estimation of s.u.'s in distances, angles and torsion angles; correlations between s.u.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell s.u.'s is used for estimating s.u.'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 $F^2 > 2\sigma(F^2)$ 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}
C1	−0.0241 (7)	0.4035 (6)	0.658 (3)	0.064 (3)
H1	−0.0622	0.4514	0.5809	0.077*
C2	0.0194 (6)	0.2682 (5)	0.772 (3)	0.052 (2)
C3	0.0271 (6)	0.1808 (6)	0.807 (4)	0.061 (3)
C4	0.1886 (6)	0.2116 (5)	1.116 (3)	0.055 (3)
C5	0.0913 (6)	0.3256 (6)	0.895 (3)	0.052 (2)
C6	0.1345 (7)	0.0626 (5)	1.058 (3)	0.069 (3)

H6A	0.2063	0.0537	1.1142	0.104*
H6B	0.1171	0.0296	0.8497	0.104*
H6C	0.0923	0.0435	1.2523	0.104*
C7	0.2524 (6)	0.3593 (5)	1.190 (3)	0.061 (3)
H7A	0.2713	0.3464	1.4305	0.091*
H7B	0.2232	0.4169	1.1783	0.091*
H7C	0.313	0.3565	1.0426	0.091*
N1	0.0697 (5)	0.4080 (5)	0.828 (2)	0.060 (2)
N2	−0.0530 (5)	0.3202 (4)	0.621 (2)	0.062 (2)
H2	−0.1087	0.3025	0.5166	0.074*
N3	0.1159 (5)	0.1552 (5)	0.992 (3)	0.062 (2)
N4	0.1776 (5)	0.2970 (5)	1.070 (2)	0.057 (2)
O1	−0.0350 (4)	0.1251 (4)	0.705 (2)	0.067 (2)
O2	0.2641 (4)	0.1825 (4)	1.281 (3)	0.070 (2)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.060 (5)	0.065 (6)	0.069 (9)	0.001 (4)	0.000 (6)	−0.003 (6)
C2	0.040 (4)	0.061 (5)	0.056 (7)	0.002 (4)	−0.008 (5)	−0.005 (5)
C3	0.048 (5)	0.071 (6)	0.064 (8)	0.004 (5)	0.003 (6)	0.001 (6)
C4	0.047 (5)	0.058 (5)	0.059 (8)	−0.004 (4)	0.005 (5)	0.002 (5)
C5	0.049 (5)	0.067 (5)	0.042 (7)	−0.004 (4)	−0.003 (4)	−0.002 (5)
C6	0.081 (6)	0.058 (5)	0.069 (9)	0.008 (5)	0.002 (7)	0.001 (6)
C7	0.056 (5)	0.063 (5)	0.062 (8)	−0.010 (4)	−0.003 (5)	−0.004 (5)
N1	0.058 (4)	0.064 (5)	0.058 (6)	0.004 (4)	0.009 (4)	0.001 (4)
N2	0.062 (4)	0.064 (4)	0.059 (6)	−0.002 (4)	−0.001 (5)	−0.002 (5)
N3	0.054 (4)	0.066 (5)	0.068 (7)	−0.001 (4)	0.004 (5)	0.000 (5)
N4	0.049 (4)	0.070 (5)	0.053 (6)	0.002 (4)	0.001 (4)	0.007 (5)
O1	0.056 (3)	0.070 (4)	0.077 (6)	−0.008 (3)	−0.003 (4)	−0.010 (4)
O2	0.052 (3)	0.080 (4)	0.079 (6)	0.004 (3)	−0.015 (4)	0.006 (5)

Geometric parameters (Å, º)

C1—N2	1.364 (10)	C5—N1	1.345 (11)
C1—N1	1.399 (11)	C5—N4	1.393 (10)
C1—H1	0.95	C6—N3	1.489 (10)
C2—C3	1.376 (12)	C6—H6A	0.98
C2—N2	1.381 (11)	C6—H6B	0.98
C2—C5	1.388 (11)	C6—H6C	0.98
C3—O1	1.257 (10)	C7—N4	1.460 (10)
C3—N3	1.426 (13)	C7—H7A	0.98
C4—O2	1.265 (11)	C7—H7B	0.98
C4—N4	1.354 (10)	C7—H7C	0.98
C4—N3	1.387 (11)	N2—H2	0.88

N2—C1—N1	110.1 (8)	H6A—C6—H6C	109.5
N2—C1—H1	124.9	H6B—C6—H6C	109.5
N1—C1—H1	124.9	N4—C7—H7A	109.5
C3—C2—N2	132.6 (8)	N4—C7—H7B	109.5
C3—C2—C5	123.9 (9)	H7A—C7—H7B	109.5
N2—C2—C5	103.5 (7)	N4—C7—H7C	109.5
O1—C3—C2	127.6 (9)	H7A—C7—H7C	109.5
O1—C3—N3	119.6 (8)	H7B—C7—H7C	109.5
C2—C3—N3	112.8 (8)	C5—N1—C1	103.2 (7)

O2—C4—N4	120.4 (8)	C1—N2—C2	109.0 (8)
O2—C4—N3	119.1 (8)	C1—N2—H2	125.5
N4—C4—N3	120.5 (8)	C2—N2—H2	125.5
N1—C5—C2	114.2 (8)	C4—N3—C3	124.0 (8)
N1—C5—N4	124.9 (8)	C4—N3—C6	116.5 (8)
C2—C5—N4	120.9 (8)	C3—N3—C6	119.5 (8)
N3—C6—H6A	109.5	C4—N4—C5	117.8 (8)
N3—C6—H6B	109.5	C4—N4—C7	122.9 (8)
H6A—C6—H6B	109.5	C5—N4—C7	119.3 (7)
N3—C6—H6C	109.5		