Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

A monoclinic polymorph of theophylline

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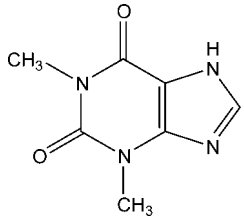
Received 20 October 2011; accepted 9 November 2011

Key indicators: single-crystal X-ray study; T = 299 K; mean σ(C–C) = 0.003 Å; R factor = 0.048; wR factor = 0.129; data-to-parameter ratio = 12.9.

A monoclinic polymorph of theophylline, $C_7H_8N_4O_2$, has been obtained from a chloroform/methanol mixture by evaporation under ambient conditions. The new polymorph crystallizes with two molecules in the asymmetric unit. The structure features intermolecular N—H···O hydrogen bonds, resulting in the formation of dimers between two crystallographically different molecules; each molecule acts as both donor and acceptor.

Related literature

For the orthorhombic polymorph of anhydrous theophylline, see: Ebisuzaki *et al.* (1997).



Experimental

Crystal data

$C_7H_8N_4O_2$
M_r = 180.17
Monoclinic, $P2_1/c$
a = 7.8935 (6) Å
b = 12.9087 (7) Å
c = 15.9055 (8) Å
β = 104.214 (5)°
V = 1571.07 (17) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.12 mm^{-1}
T = 299 K
0.35 × 0.29 × 0.04 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.863, T_{max} = 0.995
19027 measured reflections
3074 independent reflections
1972 reflections with $I > 2\sigma(I)$
R_{int} = 0.058

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.129
S = 1.05
3074 reflections
239 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···O3^{i}	0.86	1.92	2.753 (2)	163
N8—H8···O1^{i}	0.86	1.94	2.782 (2)	165

Symmetry code: (i) $-x, -y, -z+1$.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *DIRAX* (Duisenberg, 1992); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg, 2007); software used to prepare material for publication: *publCIF* (Westrip, 2010).

The Swedish Research Council (VR) is acknowledged for providing funding for the single-crystal diffractometer.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: WN2455).

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supporting information

Acta Cryst. (2011). E**67**, o3357 [https://doi.org/10.1107/S1600536811047532]

A monoclinic polymorph of theophylline

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S1. Comment

Theophylline,1,3-dimethyl-7*H*-purine-2,6-dione, is an FDA-approved compound for the treatment of respiratory diseases such as asthma, as are other related compounds, such as caffeine and theobromine.

Thus far, only one crystal structure of anhydrous theophylline has been reported (Ebisuzaki *et al.*, 1997). This orthorhombic structure has one molecule per asymmetric unit and is characterized by N—H···N hydrogen bonds, yielding infinite chains.

The polymorph of theophylline in this work was found during a solubility study using a 4:1 mixture ofchloroform and methanol as solvent. This monoclinic polymorph has been found to be thermodynamically stable at room temperature. Solubility data and a discussion of thermodynamic stability relationships will be presented elsewhere. (Zhang & Rasmuson, manuscript in preparation).

The title compound features two molecules in the asymmetric unit (Fig. 1). They are almost coplanar with a dihedral angle of 5.31 (3)°. Each molecule acts as N—H···O bond donor and acceptor, yielding dimers of two crystallographically different molecules (Fig. 2).

The major difference between the structures of the two polymorphs is their hydrogen bonding pattern.

S2. Experimental

Commercial theophylline was dissolved in a mixture of chloroform and methanol (ratio 4:1 *v*/*v*). Evaporation at ambient temperature and pressure over a period of five weeks yielded the title compound. Powder X-ray diffraction confirmed that the bulk material was identical with the single-crystal from which the crystal structure was obtained.

S3. Refinement

H atoms were placed at calculated positions and refined as riding, with N—H = 0.86 Å, C(methyl)—H = 0.96 Å and Csp^2—H = 0.93 Å. U_{iso}(H) = xU_{eq}(C,N), where x = 1.5 for methyl H and 1.2 for all other H atoms.

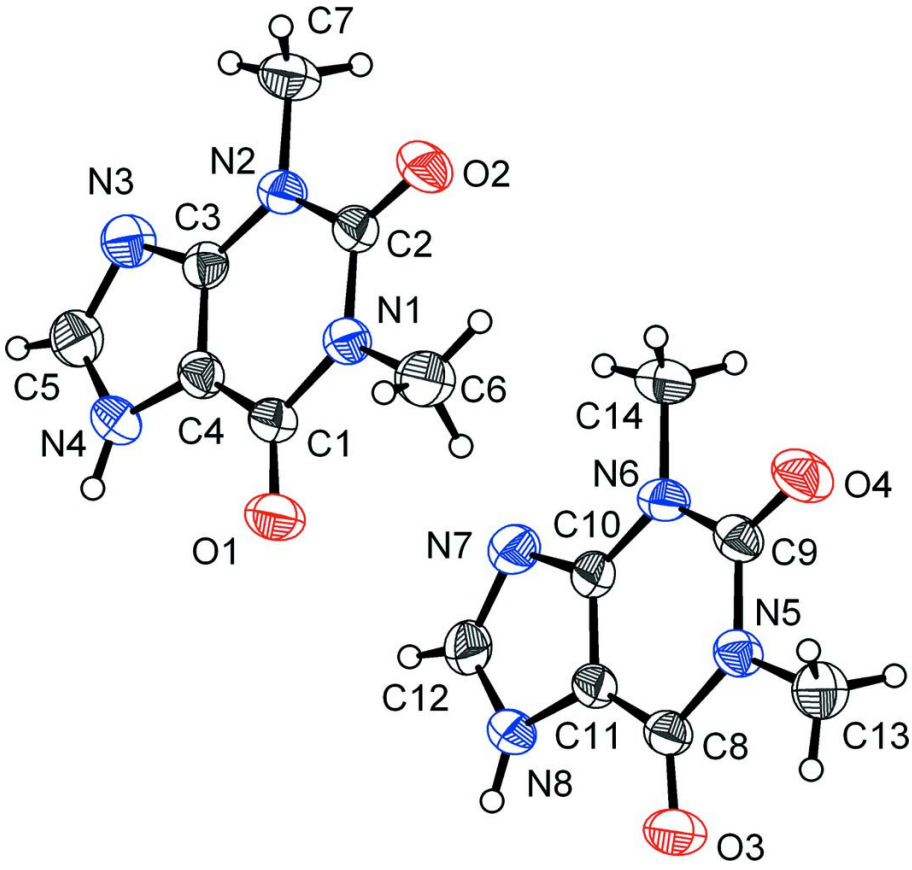

Figure 1

The asymmetric unit of the title compound. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary radius.

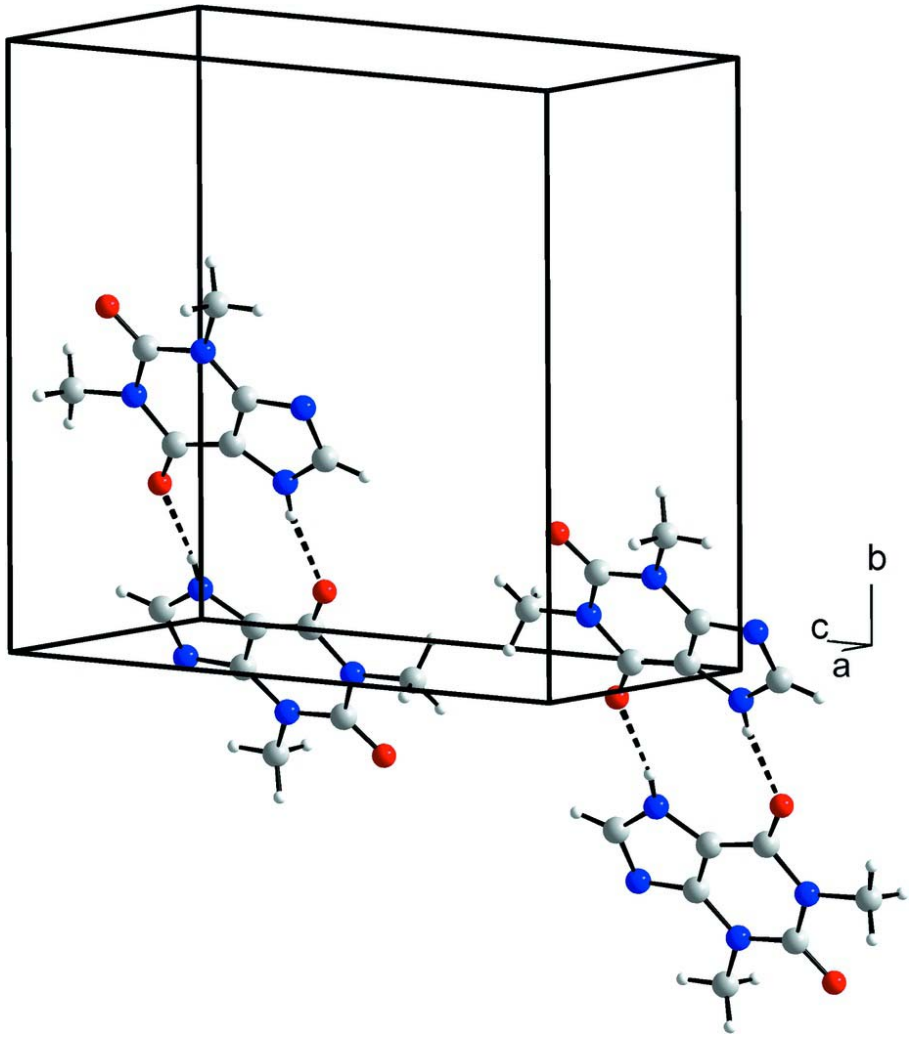

Figure 2

The hydrogen bonding pattern in the title compound, yielding dimers. Hydrogen bonds are indicated as dashed lines.

1,3-dimethyl-7*H*-purine-2,6-dione

Crystal data

$C_7H_8N_4O_2$
$M_r = 180.17$
Monoclinic, $P2_1/c$
Hall symbol: -P 2ybc
$a = 7.8935\ (6)$ Å
$b = 12.9087\ (7)$ Å
$c = 15.9055\ (8)$ Å
$\beta = 104.214\ (5)°$
$V = 1571.07\ (17)$ Å^3
$Z = 8$

$F(000) = 752$
$D_x = 1.523$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 82 reflections
$\theta = 4.2–20.8°$
$\mu = 0.12$ mm^{-1}
$T = 299$ K
Plate, colourless
0.35 × 0.29 × 0.04 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Radiation source: fine-focus sealed tube
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.863, T_{max} = 0.995
19027 measured reflections
3074 independent reflections
1972 reflections with $I > 2\sigma(I)$
R_{int} = 0.058
θ_{max} = 26.0°, θ_{min} = 4.5°
h = −9→8
k = −15→15
l = −19→19

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.129
S = 1.05
3074 reflections
239 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0593P)^2 + 0.4941P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

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 $F^2 > \sigma(F^2)$ 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	0.3056 (3)	0.02115 (17)	0.09461 (14)	0.0352 (5)
C2	0.4877 (3)	0.17786 (17)	0.09060 (14)	0.0342 (5)
C3	0.3328 (3)	0.09963 (17)	−0.04057 (13)	0.0316 (5)
C4	0.2672 (3)	0.02566 (17)	0.00340 (14)	0.0336 (5)
C5	0.1763 (3)	0.0045 (2)	−0.13534 (15)	0.0435 (6)
C6	0.4624 (4)	0.1056 (2)	0.22819 (15)	0.0554 (7)
C7	0.5185 (3)	0.2516 (2)	−0.04623 (16)	0.0489 (6)
C8	0.0635 (3)	0.28631 (17)	1.02459 (14)	0.0337 (5)
C9	0.2209 (3)	0.45280 (17)	1.02194 (14)	0.0351 (5)
C10	0.0752 (3)	0.37253 (17)	0.89022 (13)	0.0324 (5)
C11	0.0220 (3)	0.29279 (16)	0.93328 (13)	0.0314 (5)
C12	−0.0732 (3)	0.27496 (19)	0.79473 (14)	0.0425 (6)
C13	0.2196 (3)	0.3724 (2)	1.15919 (14)	0.0475 (6)
C14	0.2368 (3)	0.53625 (19)	0.88634 (16)	0.0471 (6)
N1	0.4160 (2)	0.10126 (14)	0.13328 (11)	0.0361 (5)
N2	0.4434 (2)	0.17564 (14)	0.00173 (11)	0.0346 (4)
N3	0.2779 (3)	0.08774 (15)	−0.12768 (12)	0.0418 (5)

N4	0.1653 (2)	−0.03563 (15)	−0.05995 (12)	0.0391 (5)
N5	0.1646 (2)	0.36962 (14)	1.06438 (11)	0.0345 (4)
N6	0.1742 (2)	0.45278 (14)	0.93298 (12)	0.0366 (5)
N7	0.0172 (3)	0.36232 (15)	0.80311 (12)	0.0433 (5)
N8	−0.0753 (2)	0.23019 (15)	0.86970 (11)	0.0366 (5)
O1	0.2529 (2)	−0.04282 (13)	0.13937 (10)	0.0497 (5)
O2	0.5851 (2)	0.24386 (13)	0.13070 (10)	0.0484 (4)
O3	0.0208 (2)	0.21730 (13)	1.06858 (10)	0.0496 (5)
O4	0.3076 (2)	0.52232 (13)	1.06289 (11)	0.0514 (5)
H5	0.1181	−0.0232	−0.1886	0.052*
H6A	0.5544	0.1552	0.2475	0.083*
H6B	0.5013	0.0386	0.2512	0.083*
H6C	0.3619	0.1259	0.2481	0.083*
H7A	0.4913	0.3201	−0.0300	0.073*
H7B	0.4707	0.2419	−0.1073	0.073*
H7C	0.6430	0.2429	−0.0330	0.073*
H12	−0.1301	0.2474	0.7412	0.051*
H13A	0.3448	0.3691	1.1774	0.071*
H13B	0.1704	0.3143	1.1825	0.071*
H13C	0.1797	0.4355	1.1798	0.071*
H14A	0.2042	0.6019	0.9061	0.071*
H14B	0.1856	0.5293	0.8253	0.071*
H14C	0.3617	0.5324	0.8970	0.071*
H4	0.1062	−0.0893	−0.0523	0.047*
H8	−0.1272	0.1735	0.8769	0.044*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0348 (11)	0.0294 (13)	0.0408 (12)	−0.0032 (10)	0.0079 (10)	0.0011 (10)
C2	0.0323 (12)	0.0308 (12)	0.0378 (12)	−0.0009 (10)	0.0052 (9)	−0.0005 (10)
C3	0.0316 (11)	0.0286 (12)	0.0336 (11)	0.0031 (9)	0.0061 (9)	−0.0018 (9)
C4	0.0315 (11)	0.0301 (13)	0.0378 (12)	−0.0008 (9)	0.0059 (9)	−0.0033 (10)
C5	0.0490 (14)	0.0433 (15)	0.0358 (13)	−0.0034 (12)	0.0054 (10)	−0.0076 (11)
C6	0.0696 (18)	0.0563 (18)	0.0351 (13)	−0.0173 (14)	0.0034 (12)	0.0011 (12)
C7	0.0568 (15)	0.0423 (15)	0.0501 (14)	−0.0130 (12)	0.0182 (12)	0.0037 (12)
C8	0.0329 (11)	0.0294 (12)	0.0391 (12)	−0.0022 (9)	0.0093 (9)	−0.0004 (10)
C9	0.0343 (11)	0.0301 (13)	0.0412 (13)	−0.0035 (10)	0.0098 (10)	−0.0047 (10)
C10	0.0298 (11)	0.0312 (12)	0.0347 (11)	0.0018 (9)	0.0049 (9)	0.0014 (10)
C11	0.0309 (11)	0.0268 (12)	0.0348 (12)	−0.0019 (9)	0.0046 (9)	−0.0016 (9)
C12	0.0443 (13)	0.0419 (15)	0.0354 (13)	−0.0028 (11)	−0.0018 (10)	−0.0015 (11)
C13	0.0569 (15)	0.0482 (16)	0.0349 (12)	−0.0065 (13)	0.0063 (11)	−0.0055 (11)
C14	0.0518 (15)	0.0378 (15)	0.0526 (15)	−0.0097 (11)	0.0147 (12)	0.0067 (11)
N1	0.0400 (10)	0.0336 (11)	0.0318 (10)	−0.0063 (8)	0.0030 (8)	−0.0002 (8)
N2	0.0377 (10)	0.0297 (10)	0.0356 (10)	−0.0049 (8)	0.0074 (8)	0.0007 (8)
N3	0.0493 (11)	0.0394 (12)	0.0359 (10)	−0.0039 (9)	0.0088 (9)	−0.0042 (9)
N4	0.0390 (10)	0.0334 (11)	0.0428 (11)	−0.0084 (8)	0.0060 (9)	−0.0048 (9)
N5	0.0386 (10)	0.0321 (11)	0.0321 (9)	−0.0047 (8)	0.0073 (8)	−0.0038 (8)

N6	0.0413 (11)	0.0280 (10)	0.0404 (11)	−0.0055 (8)	0.0096 (8)	0.0020 (8)
N7	0.0495 (12)	0.0381 (12)	0.0377 (11)	−0.0044 (10)	0.0021 (9)	0.0034 (9)
N8	0.0385 (10)	0.0301 (11)	0.0384 (10)	−0.0073 (8)	0.0040 (8)	−0.0013 (8)
O1	0.0596 (11)	0.0450 (11)	0.0429 (10)	−0.0183 (8)	0.0099 (8)	0.0047 (8)
O2	0.0516 (10)	0.0408 (10)	0.0483 (10)	−0.0171 (8)	0.0034 (8)	−0.0057 (8)
O3	0.0661 (11)	0.0410 (10)	0.0410 (9)	−0.0177 (9)	0.0116 (8)	0.0023 (8)
O4	0.0599 (11)	0.0405 (10)	0.0518 (10)	−0.0173 (9)	0.0098 (8)	−0.0104 (8)

Geometric parameters (Å, º)

C1—O1	1.228 (3)	C10—N6	1.373 (3)
C1—N1	1.394 (3)	C11—N8	1.373 (3)
C1—C4	1.409 (3)	C12—N7	1.324 (3)
C2—O2	1.218 (3)	C12—N8	1.329 (3)
C2—N2	1.370 (3)	C13—N5	1.464 (3)
C2—N1	1.396 (3)	C14—N6	1.461 (3)
C3—N3	1.355 (3)	C5—H5	0.9300
C3—C4	1.359 (3)	C6—H6A	0.9600
C3—N2	1.374 (3)	C6—H6B	0.9600
C4—N4	1.375 (3)	C6—H6C	0.9600
C5—N4	1.328 (3)	C7—H7A	0.9600
C5—N3	1.329 (3)	C7—H7B	0.9600
C6—N1	1.465 (3)	C7—H7C	0.9600
C7—N2	1.455 (3)	C12—H12	0.9300
C8—O3	1.230 (3)	C13—H13A	0.9600
C8—N5	1.395 (3)	C13—H13B	0.9600
C8—C11	1.411 (3)	C13—H13C	0.9600
C9—O4	1.216 (3)	C14—H14A	0.9600
C9—N6	1.372 (3)	C14—H14B	0.9600
C9—N5	1.398 (3)	C14—H14C	0.9600
C10—N7	1.355 (3)	N4—H4	0.8600
C10—C11	1.359 (3)	N8—H8	0.8600
O1—C1—N1	120.46 (19)	C9—N6—C10	119.16 (18)
O1—C1—C4	127.4 (2)	C9—N6—C14	118.99 (19)
N1—C1—C4	112.14 (19)	C10—N6—C14	121.81 (19)
O2—C2—N2	121.5 (2)	C12—N7—C10	102.95 (19)
O2—C2—N1	121.4 (2)	C12—N8—C11	106.07 (19)
N2—C2—N1	117.11 (19)	N4—C5—H5	123.1
N3—C3—C4	112.32 (19)	N3—C5—H5	123.1
N3—C3—N2	125.9 (2)	N1—C6—H6A	109.5
C4—C3—N2	121.75 (19)	N1—C6—H6B	109.5
C3—C4—N4	104.81 (18)	H6A—C6—H6B	109.5
C3—C4—C1	123.1 (2)	N1—C6—H6C	109.5
N4—C4—C1	132.1 (2)	H6A—C6—H6C	109.5
N4—C5—N3	113.8 (2)	H6B—C6—H6C	109.5
O3—C8—N5	120.43 (19)	N2—C7—H7A	109.5
O3—C8—C11	127.0 (2)	N2—C7—H7B	109.5

N5—C8—C11	112.55 (19)	H7A—C7—H7B	109.5
O4—C9—N6	121.7 (2)	N2—C7—H7C	109.5
O4—C9—N5	120.8 (2)	H7A—C7—H7C	109.5
N6—C9—N5	117.47 (19)	H7B—C7—H7C	109.5
N7—C10—C11	111.92 (19)	N7—C12—H12	123.0
N7—C10—N6	126.0 (2)	N8—C12—H12	123.0
C11—C10—N6	122.04 (19)	N5—C13—H13A	109.5
C10—C11—N8	105.13 (18)	N5—C13—H13B	109.5
C10—C11—C8	122.8 (2)	H13A—C13—H13B	109.5
N8—C11—C8	132.1 (2)	N5—C13—H13C	109.5
N7—C12—N8	113.9 (2)	H13A—C13—H13C	109.5
C1—N1—C2	126.52 (17)	H13B—C13—H13C	109.5
C1—N1—C6	117.04 (18)	N6—C14—H14A	109.5
C2—N1—C6	116.44 (18)	N6—C14—H14B	109.5
C2—N2—C3	119.36 (18)	H14A—C14—H14B	109.5
C2—N2—C7	119.55 (19)	N6—C14—H14C	109.5
C3—N2—C7	121.06 (18)	H14A—C14—H14C	109.5
C5—N3—C3	102.70 (19)	H14B—C14—H14C	109.5
C5—N4—C4	106.34 (19)	C5—N4—H4	126.8
C8—N5—C9	125.98 (18)	C4—N4—H4	126.8
C8—N5—C13	118.55 (18)	C12—N8—H8	127.0
C9—N5—C13	115.47 (18)	C11—N8—H8	127.0

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4—H4···O3^{i}	0.86	1.92	2.753 (2)	163
N8—H8···O1^{i}	0.86	1.94	2.782 (2)	165

Symmetry code: (i) −*x*, −*y*, −*z*+1.