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Lamotrigine dimethylformamide sesquisolvate

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In the title compound, $C_9H_7N_5Cl_2\cdot1.5C_3H_7NO$, the asymmetric unit consists of two crystallographically independent lamotrigine [systematic name: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] and three dimethylformamide molecules. In the crystal structure, N—H···N and N—H···O hydrogen bonds lead to the formation of $R_2^2(8)$ and $R_3^2(8)$ motifs.

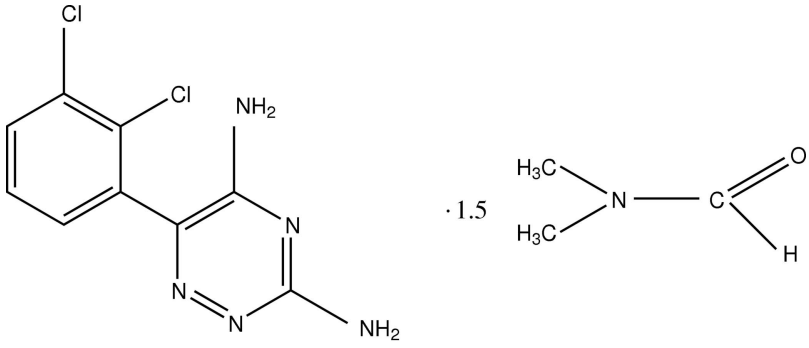
Key indicators

Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.004 Å
Disorder in solvent or counterion
R factor = 0.052
wR factor = 0.172
Data-to-parameter ratio = 14.1

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

Comment

Lamotrigine (marketed as Lamictal by GlaxoSmithKline) is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. Voltage-gated sodium channels are the molecular targets for anticonvulsant compounds, including phenytoin, carbamazepine and lamotrigine (Willow *et al.*, 1984; Xie & Garthwaite, 1996; Kuo & Lu, 1997). Lamotrigine regulates β-adrenergic receptors, a property that has been found to be associated with antidepressant action (Dopheide & Wincor, 1998). Recently, we have reported the crystal structure of lamotriginium benzoate dimethylformamide solvate (Sridhar & Ravikumar, 2005). In continuation of our ongoing programmes on the structural elucidation of drug molecules, we have determined the crystal structure of the title compound, (I).



(I)

The asymmetric unit of (I) contains two independent lamotrigine molecules (unprimed and primed) and three dimethylformamide (DMF) molecules (Fig. 1). The C atoms (C21/C22/C23 and C31/C32/C33) of two DMF solvent molecules are disordered over two sites with occupancies of 0.784 (3) and 0.216 (3). In all essential details, the molecular geometry (Table 1) is in good agreement with that of lamotrigine hydrate (Kubicki & Codding, 2001) and lamotrigine methanol solvate (Janes *et al.*, 1989). Bond distances and angles are similar for both independent molecules; the largest

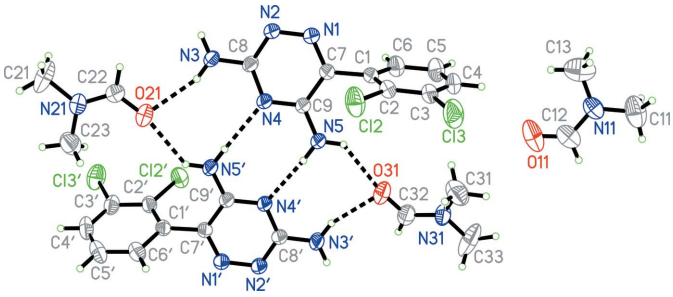


Figure 1
The asymmetric unit of (I), with the atom-numbering scheme. Displacement ellipsoids of non-H atoms are drawn at the 30% probability level. The hydrogen bonds are shown as dashed lines. The disordered atoms of the minor component (C211/C221/C231 and C311/C321/C331) have been omitted for clarity.

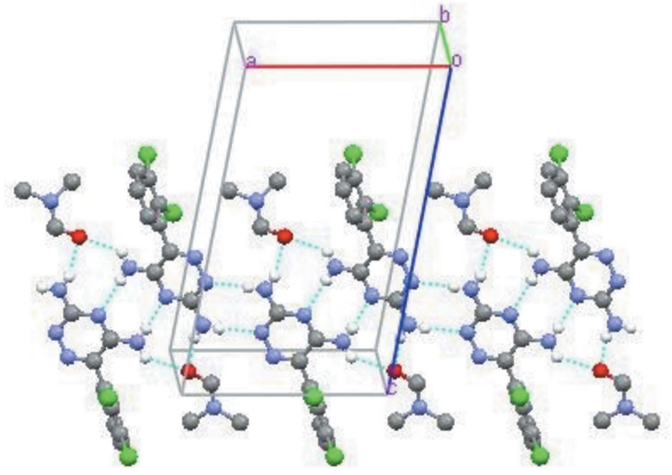


Figure 2
A partial packing diagram of (I), viewed approximately along the *b* axis. Dashed lines indicate N—H···O and N—H···N hydrogen bonds. The disordered atoms of the minor component (C211/C221/C231 and C311/C321/C331), H atoms attached to C atoms and ordered DMF molecules have been omitted for clarity.

differences are 0.018 Å for the bond distances N3—C8, and 1.5 and 1.8° for the angles N1—C7—C1 and C9—C7—C1, respectively.

Both the triazine ring and the dichlorophenyl ring are planar, and the dihedral angles between these rings are 77.5 (1) and 69.2 (1)° for unprimed and primed molecules, respectively. The presence of substituents at the *ortho* position with respect to the central C—C bond may cause these relatively large values. In the absence of such a hindrance, the twist is much smaller [dihedral angle 9.3 (1)°], as observed in the crystal structure of 5-(*p*-chlorophenyl)-1,2,4-triazine (Atwood *et al.*, 1974). The N—N and C—N distances of the triazine rings (Table 1) are intermediate between the expected single- and double-bond distances (N—N = 1.45 Å, C—N = 1.47 Å, N═N = 1.20 Å and C═N = 1.27 Å; Allen *et al.*, 1987). The amino groups (NH_2) are almost coplanar with the attached triazine ring [N3 and N4 are displaced from the plane by 0.021 (2) and 0.009 (2) Å, respectively, for the unprimed molecule and by 0.037 (3) and 0.007 (2) Å, respectively, for the primed molecule].

Two modes of hydrogen-bonding interactions *viz.* lamotrigine–lamotrigine and lamotrigine–DMF solvent, stabilize the molecules in the crystal structure (Table 2 and Fig. 3). The intermolecular N—H···N hydrogen bonds, interconnecting the lamotrigine molecules, lead to the formation of a characteristic dimer of $R_2^2(8)$ motif (Bernstein *et al.*, 1995). The dimers are linked by DMF solvent molecules on both sides through intermolecular N—H···O hydrogen bonds, leading to the formation of an $R_3^2(8)$ motif. It is interesting to note that the ordered DMF solvent molecule does not participate in any hydrogen-bonding interactions. In the crystal packing, the hydrogen-bonding network forms an infinite chain running along the *a* axis.

Experimental

Crystals were grown by slow evaporation of a solution of lamotrigine in dimethylformamide at room temperature.

Crystal data

$C_9H_7Cl_2N_5·1.5C_3H_7NO$
M_r = 365.74
Triclinic, $P\overline{1}$
a = 10.4444 (13) Å
b = 10.9943 (13) Å
c = 16.976 (2) Å
α = 83.637 (2)°
β = 74.850 (2)°
γ = 70.582 (2)°
V = 1773.9 (4) Å^3
Z = 4
D_x = 1.369 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.38 mm^{-1}
T = 273 (2) K
Block, colourless
0.21 × 0.17 × 0.08 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
Absorption correction: none
17267 measured reflections
6231 independent reflections
4575 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 25.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.173
S = 1.03
6231 reflections
443 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.105P)^2 + 0.2266P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C7	1.312 (3)	N1′—C7′	1.309 (3)
N1—N2	1.343 (3)	N1′—N2′	1.338 (3)
N2—C8	1.337 (3)	N2′—C8′	1.342 (3)
N3—C8	1.336 (3)	N3′—C8′	1.318 (3)
N4—C9	1.318 (3)	N4′—C9′	1.321 (3)
N4—C8	1.344 (3)	N4′—C8′	1.342 (3)
N5—C9	1.323 (3)	N5′—C9′	1.327 (3)
N1—C7—C1	117.62 (19)	N1′—C7′—C1′	116.08 (19)
C9—C7—C1	121.92 (19)	C9′—C7′—C1′	123.72 (18)

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3B···O21	0.86	2.16	2.975 (3)	158
N3—H3A···N2′^{i}	0.86	2.09	2.926 (3)	163
N5—H5A···N4′	0.86	2.16	3.015 (3)	171
N5—H5B···O31	0.86	2.20	2.861 (3)	133
N3′—H3′1···N2^{ii}	0.86	2.09	2.944 (3)	175
N3′—H3′2···O31	0.86	2.13	2.952 (3)	161
N5′—H5′2···O21	0.86	2.23	2.884 (3)	133
N5′—H5′1···N4	0.86	2.16	3.011 (3)	169

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

The site occupation factors of the disordered dimethylformamide solvent molecules were refined to 0.784 (3) and 0.216 (3). The geometries about the disordered atoms were restrained, with distances N31—C321 = 1.30 (1) Å, C32—O31 = C321—O31 = C22—O21 = C221—O21 = 1.22 (1) Å. The displacement parameters of the minor components were restrained to isotropic behavior [U_{iso}(minor C) $\simeq U_{eq}$(major C)]. H atoms were positioned geometrically (C—H = 0.93–0.96 and N—H = 0.86 Å) and treated as riding, with U_{iso}(H) = $1.2U_{eq}$(C,N) or $1.5U_{eq}$(methyl C). The methyl groups were allowed to rotate but not to tip.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990) and *MERCURY* (Macrae *et al.*, 2006); software used to prepare material for publication: *SHELXL97*.

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