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Felbamate: a carbamate-type anticonvulsant

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Key indicators

Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.003 Å
R factor = 0.034
wR factor = 0.093
Data-to-parameter ratio = 9.2

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

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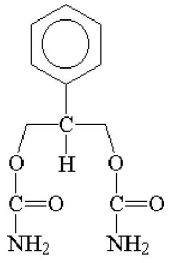
In the crystal structure of 2-phenyl-1,3-propanediol dicarbamate (felbamate), $C_{11}H_{14}N_2O_4$, the molecule is in an extended conformation with respect to the phenyl ring. In the crystal structure, the molecules are connected *via* N—H···O hydrogen bonds to form one-dimensional ribbons running along the *b* axis. Stereochemical and molecular modelling results indicate that the mechanism of the anticonvulsant action of felbamate is likely to differ from that of classical anticonvulsants.

Comment

Felbamate (FBM), chemically related to meprobamate, was first synthesized many years ago for pharmacological central nervous system investigations, and initial reports indicated that the compound possessed anticonvulsant activity (Ludwig *et al.*, 1969). In subsequent controlled clinical trials, FBM has been shown to be a promising anti-epileptic agent, effective in the treatment of partial seizures in adults (Theodore *et al.*, 1991; Ramsay, 1993; Leppik, 1995) and of the Lennox–Gastaut syndrome in children (Bourgeois, 1997). The high expectations for a good therapeutic index for felbamate and its effective anticonvulsant activity were drastically reduced due to high toxicity. Despite this setback, the drug is still administered in many patients, but not necessarily as the first-line treatment (Brown & Aiken, 1998). It is particularly beneficial in some children suffering from the Lennox–Gastaut syndrome and/or Doose Syndrome, where it appears to be the drug of choice (Szczepanik *et al.*, 2000). Recently published data indicate that, when administered in combination, felbamate and carbamazepine can be useful in certain patients (Borowicz *et al.*, 2004). An additive anticonvulsant effect of carbenoxolone in combination with FBM has also been reported (Gareri *et al.*, 2004). These reports prompted us to look for possible structural and stereochemical correlations with structures of well known anti-epileptics, such as diphenylhydantoin (Camerman & Camerman, 1971) and diazepam (Camerman & Camerman, 1972). However, extensive efforts to correlate various structural features of FBM responsible for biological action, such as electron-donating groups, hydrophobic regions and shape, with other anticonvulsants were unsuccessful. This lack of similarities between FBM and its counterparts leads us to believe that the site and mechanism of action of FBM must differ significantly from those of diphenylhydantoin or diazepam. Therefore, it may be worthwhile to look for a derivative of FBM, with its anticonvulsant activity retained and its adverse side effects substantially diminished or entirely removed. The presumably different mechanism of action of FBM may guarantee therapeutic effectivness in patients

showing decreased responses to other anti-epileptics due to prolonged periods of drug administration.



FBM

The structure of FBM is presented in Fig. 1. Bond distances and angles are consistent with normal values. The conformation of the molecule is fully linearly extended, with the two arms of the propanediol dicarbamate in almost total eclipse of each other. In addition, all five atoms of each arm are coplanar: the torsion angles O2—C10—O1—C8 and O4—C11—O3—C9 are −1.6 (2) and −3.9 (2)°, respectively. Throughout the literature on small-molecule crystal structures, this arrangement is the exclusive conformation for this type of side-chain ending, containing amino or methyl groups.

Molecular modelling calculations (*INSIGHT*; Biosym Technologies, 1989) indicated an increase of about 30.0 kcal mol^{-1} (1 kcal mol^{-1} = 4.184 kJ mol^{-1}) for rotation about the O1—C10 bond, due to H···H crowding, making it prohibitive both in solution and, probably, at the biologically active site of a protein receptor.

In the crystal structure, molecules of FBM are hydrogen-bonded (Table 1) in a tail-to-tail fashion, giving rise to distinct hydrophobic and hydrophilic regions. The molecules form ribbons along the *b* direction (Fig. 2). Between the ribbons, there are mainly van der Waals interactions. All the H atoms capable of forming hydrogen bonds are utilized.

Experimental

Crystals of felbamate (Wallace Laboratories) suitable for X-ray crystal structure analysis were obtained by slow crystallization from a methanol–water mixture (1:1). The crystals were colourless transparent needles.

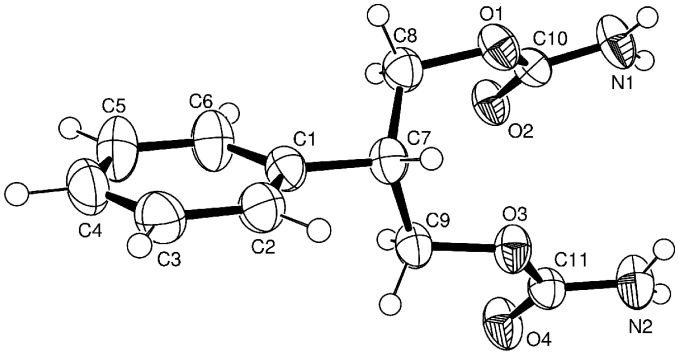


Figure 1
A view of the FBM molecule, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small circles of arbitrary radii.

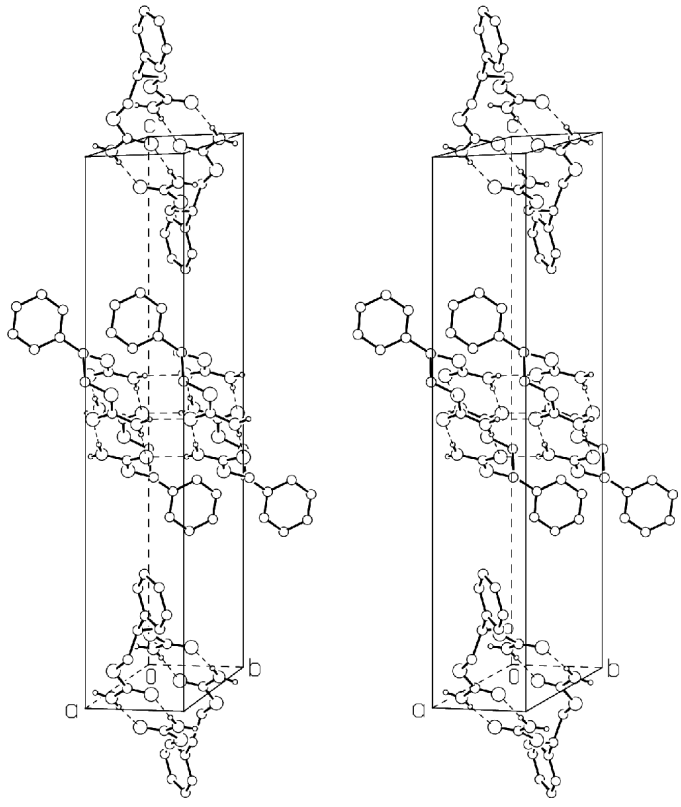


Figure 2
A stereoscpoic view of the FBM crystal packing. For clarity, only H atoms involved in the hydrogen bonding are shown. All the atoms are drawn as circles of arbitrary radii and the dashed lines connecting atoms indicate hydrogen bonds.

Crystal data

$C_{11}H_{14}N_2O_4$
M_r = 238.24
Monoclinic, $P2_1/c$
a = 8.394 (3) Å
b = 5.158 (2) Å
c = 26.972 (6) Å
β = 101.47 (2)°
V = 1144.5 (7) Å^3
Z = 4
D_x = 1.383 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 16 reflections
θ = 20–48°
μ = 0.90 mm^{-1}
T = 294 (2) K
Needle, colourless
0.45 × 0.15 × 0.10 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
1940 measured reflections
1940 independent reflections
1634 reflections with $I > 2\sigma(I)$
θ_{max} = 65.0°
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 6$
$l = -31 \rightarrow 30$
3 standard reflections
every 100 reflections
intensity decay: 0.5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.093
S = 1.01
1940 reflections
211 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0278P)^2 + 0.2981P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0079 (6)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H11···O2^{i}	0.87 (2)	2.14 (2)	2.963 (2)	158 (2)
N1—H12···O4^{ii}	0.92 (2)	2.12 (2)	3.033 (2)	177 (2)
N2—H21···O2^{ii}	0.90 (2)	2.04 (2)	2.943 (2)	180 (2)
N2—H22···O4^{i}	0.89 (2)	2.14 (2)	2.991 (2)	161 (2)

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

All H atoms were found in difference maps and were refined isotropically. The ranges of the bond distances involving H atoms are N—H = 0.87 (2)–0.91 (2) Å and C—H = 0.95 (2)–1.00 (2) Å.

Data collection: *Picker Operating Manual* (Picker, 1967); cell refinement: *Picker Operating Manual*; data reduction: *Picker Operating Manual*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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