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A paracetamol–morpholine adduct

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Key indicators

Single-crystal X-ray study
T = 150 K
Mean σ(C–C) = 0.005 Å
Disorder in solvent or counterion
R factor = 0.054
wR factor = 0.178
Data-to-parameter ratio = 13.9

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

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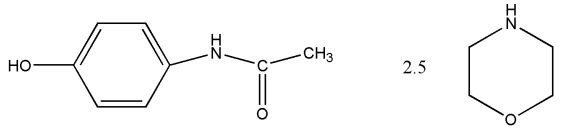
Paracetamol [also known as acetaminophen or *N*-(4-hydroxyphenyl)acetamide] is an important analgesic drug that has recently been cocrystallized with a series of cyclic N- and O-donor compounds. This paper describes the formation of a paracetamol adduct with morpholine, *viz.* paracetamol–morpholine (1/2.5), $C_8H_9NO_2{\cdot}2.5C_4H_9NO$. There are five morpholine molecules and two paracetamol molecules in the unit cell. The paracetamol molecules are held together by hydrogen bonding *via* morpholine molecules, one of which is disordered about an inversion centre.

Comment

Paracetamol (acetaminophen) in its various polymorphic forms has been studied extensively in recent years. It has been shown (Fachaux *et al.*, 1995) that the different polymorphs (monoclinic and orthorhombic) have different compressive properties. This ability for plastic deformation is of great interest to the pharmaceutical industry. The monoclinic form is the thermodynamically more stable form of paracetamol under normal conditions, but shows no plastic deformation. The orthorhombic polymorph is much harder to prepare and, so far, can only be obtained reproducibly from the melt or by seeding a saturated solution (Nichols & Frampton, 1998). This polymorph possesses plastic deformation and, therefore, mass production of this form would facilitate the manufacture of paracetamol for pharmaceutical purposes. In a recent study, our group has explored the use of cocrystals as a means of producing the orthorhombic polymorph. Paracetamol was found to cocrystallize with a number of different solvents (Oswald *et al.*, 2002). Though the majority of the cocrystals formed were hemisolvates, we also produced a 1:2.5 cocrystal, (I), of paracetamol with morpholine.



(I)

There are two and a half morpholine molecules (designated *A*, *B* and *C*; see Fig. 1) present in the asymmetric unit of (I). One of the morpholine molecules (*C*) is disordered over a crystallographic inversion centre, with the N and O atoms sharing an equivalent site. A composite scattering factor [0.5*f*(N) + 0.5*f*(O)] was used for this site. The hydrogen occupancy was fixed at 0.5 in an axial position, which was inferred from a difference map.

The amine function of morpholine is a weak hydrogen-bond acceptor and a moderately strong donor. The ether moiety is a

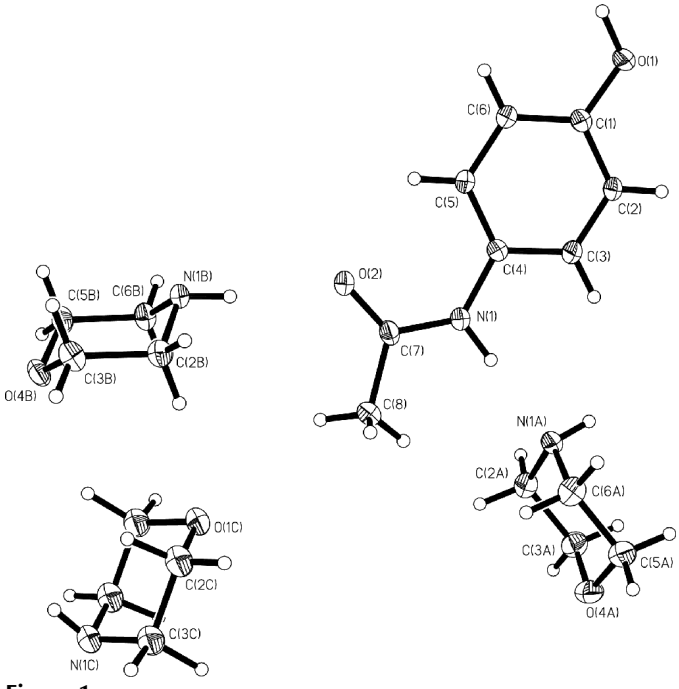


Figure 1
A plot of adduct (I), with ellipsoids at the 30% probability level. Morpholine molecule *C* is disordered about a crystallographic inversion centre, with atoms N1*C* and O1*C* refined as 50% occupied with equal *x,y,z* coordinates and isotropic displacement parameters. All crystallographically independent non-H atoms are labelled.

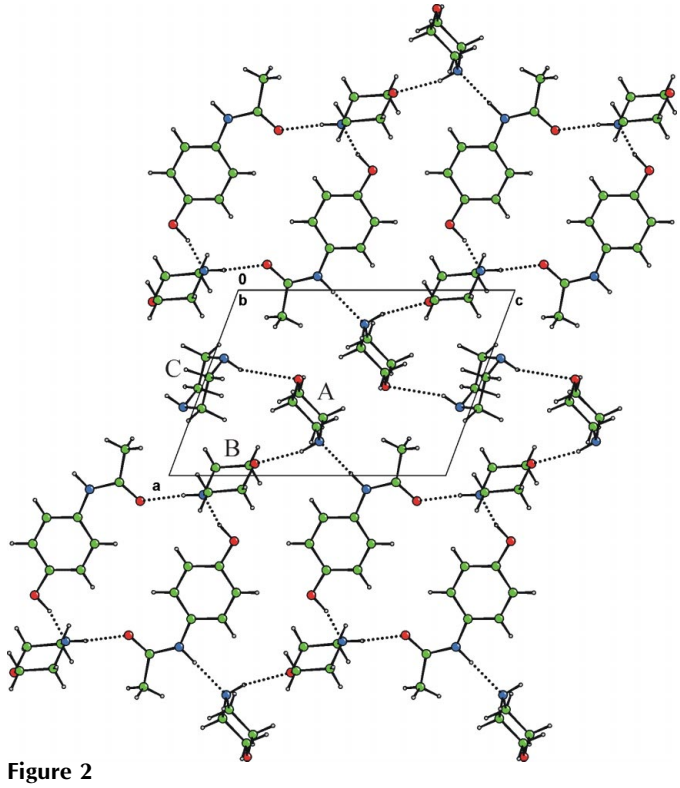


Figure 2
A section of the structure of the title paracetamol–morpholine (1/2.5) adduct. The view is along the *b* axis. O atoms are shown in red, N atoms in blue, C atoms in green and H atoms in grey. Paracetamol molecules within the outlined unit cell are generated from those shown by translation along the (210) direction.

rather weak acceptor. In paracetamol, the amide and hydroxyl groups are strong donors, and the carbonyl group a strong acceptor; the hydroxyl group is a weak acceptor. The structure of adduct (I) is consistent with this hierarchy of interactions. All direct links between paracetamol molecules are absent in the structure of (I) (Fig. 2). Successive paracetamol molecules, related by lattice repeats along *c*, are linked *via* pairs of crystallographically independent morpholine molecules through C═O···H—N, O···H—N and N···H—N interactions. This scheme establishes a chain of molecules in the series paracetamol–morpholine (*B*)–morpholine (*A*)–paracetamol, which can be described with a $C_3^3(11)$ graph at the ternary level (Bernstein *et al.*, 1995). A second chain is related to this *via* a crystallographic inversion centre, and is linked to the first *via* O—H···N hydrogen bonds to morpholine *B*, to form a ribbon-like structure. This scheme satisfies all the hydrogen-bonding characteristics of the paracetamol molecules, with the exception of the weak OH acceptor functionality, although this arguably interacts with an aromatic CH group (O···H = 2.62 Å). The hydrogen-bonding functionality of the morpholine is also satisfied with the exception of the donor character of the ether moiety in molecule *A*. It is notable that, in order to accommodate this scheme, the morpholine molecules *A* and *B* are in different conformations, with the amino H adopting the expected equatorial position in molecule *B*, but the less favourable axial position in molecule *A*.

Neighbouring ribbons are related to each other by inversion centres, which are occupied by a third crystallographically independent molecule of morpholine (*C*). This molecule is disordered about the inversion centre, but forms weak hydrogen bonds [2.59 (5) Å] to one of the ether moieties of the two morpholine A molecules related by the inversion centre. Overall then, the structure of (I) consists of layers formed by weakly connected ribbons. The layers are formed parallel to the ($\bar{1}$20) planes. The distance between the mean paracetamol planes in successive layers alternates between 5.32 and 4.03 Å. The average distance, 4.68 Å, is commensurate with *d*($\bar{1}$20) (4.55 Å). The mean planes of all the morpholine molecules are perpendicular to the plane of the paracetamol molecule. The angles that the mean planes of molecules *A*, *B* and *C* make with the paracetamol plane are 83.73 (10), 79.60 (10) and 75.15 (16)°, respectively. The paracetamol molecules thus form a 'groove' in the layers, which align so that the morpholine molecules lie above and below this 'groove' in successive layers.

The large number of solvent molecules within this structure has resulted in the formation of solvent bridges between the paracetamol molecules, with no paracetamol–paracetamol interactions, as seen in our previous study.

Experimental

Starting materials were obtained from Sigma–Aldrich and were used as received. Paracetamol (0.49 g, 3.24 mmol) was refluxed in 1 ml morpholine (11.42 mmol) and allowed to cool. Pale-yellow crystals were formed on maintaining the solution at 277 K.

Crystal data

$C_8H_9NO_2{\cdot}2.5C_4H_9NO$	$Z = 2$
$M_r = 368.97$	$D_x = 1.260$ Mg m^{-3}
Triclinic, $P\overline{1}$	Cu $K\alpha$ radiation
$a = 8.710$ (4) Å	Cell parameters from 48 reflections
$b = 9.920$ (5) Å	$\theta = 20$–22°
$c = 12.385$ (5) Å	$\mu = 0.74$ mm^{-1}
$\alpha = 102.35$ (3)°	$T = 150$ (2) K
$\beta = 108.33$ (2)°	Plate, colourless
$\gamma = 96.68$ (3)°	0.27 × 0.23 × 0.06 mm
$V = 972.7$ (7) Å^3	

Data collection

Stoe Stadi-4 four-circle diffractometer	1951 reflections with $I > 2\sigma(I)$
ω–θ scans	$R_{int} = 0.028$
Absorption correction: empirical *via* ψ scans [*SHELXTL* (Sheldrick (2001) based on method of North *et al.* (1968)]	$\theta_{max} = 70.3^\circ$
	$h = -10 \rightarrow 10$
	$k = -12 \rightarrow 11$
	$l = -14 \rightarrow 15$
$T_{min} = 0.717$, $T_{max} = 0.889$	3 standard reflections
3596 measured reflections	frequency: 120 min
3416 independent reflections	intensity decay: 5%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0983P)^2 + 0.3346P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.054$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.178$	$\Delta\rho_{max} = 0.35$ e Å^{-3}
$S = 1.03$	$\Delta\rho_{min} = -0.26$ e Å^{-3}
3416 reflections	Extinction correction: *SHELXL*97
246 parameters	Extinction coefficient: 0.0077 (14)
H-atom parameters constrained	

The diffractometer was equipped with an Oxford Cryosystems low-temperature device operating at 150 K. H atoms were placed in calculated positions and allowed to ride on their parent atoms, except for those involved in hydrogen bonding, which were located in a difference map; these were treated with a riding model, following several cycles of refinement in which a C—H distance restraint of 0.9 Å was applied.

Data collection: *DIF*4 (Stoe & Cie, 1990); cell refinement: *DIF*4; data reduction: *REDU*4 (Stoe & Cie, 1990); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Sheldrick, 2001); software used to prepare material for publication: *SHELXTL* and *CAMERON* (Watkin *et al.*, 1996).

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