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An Oxidatively Coupled Dimer of Paracetamol

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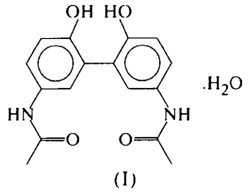
Abstract

The title compound, 5,5′-bis(acetylamino)-2,2′-dihydroxybiphenyl, is a minor oxidation product formed from paracetamol. Its monohydrate, $C_{16}H_{16}N_2O_4.H_2O$, has an extensively hydrogen-bonded crystal structure involving N—H···O(hydroxy), (hydroxy)O—H···O(water) and (water)O—H···O(carbonyl) interactions in a three-dimensional network, with both the oxidation product and the water molecule lying on a twofold axis. The two halves of the molecule have essentially the same geometry as paracetamol in its two known anhydrous polymorphs, except for the variation observed in the dihedral angle between the aromatic ring and its amide substituent.

Comment

As part of an investigation into the processing of pharmaceutical materials, our studies have led to the isolation of crystals of a monohydrate of the title compound, hereafter referred to as 'di-paracetamol', (I). This compound was initially identified by Kaito *et al.* (1974), by non-crystallographic means, as an oxidation product of *p*-hydroxyacetanilide (PHA, alternatively called acetaminophen and commonly known as paracetamol). Di-paracetamol is a dimer of PHA with the loss of two H atoms, connected by a bond between the aromatic rings and having a crystallographic twofold rotation axis bisecting this bond. It crystallizes as a monohydrate, the water molecule also lying on the rotation axis. We investigated it in the expectation that it was a third crystalline form of PHA, which is known to exist as two distinct anhydrous polymorphs, one monoclinic and the other orthorhombic (Haisa *et al.*, 1974; Naumov *et al.*, 1998; Haisa *et al.*, 1976); a third form has previously been postulated (Di Martino *et al.*, 1997).



(I)

The crystal structure is extensively hydrogen bonded (Table 2), the water molecule being involved as both a donor and an acceptor. It donates to the two carbonyl O atoms, forming a 15-atom ring (Fig. 1), and accepts from the hydroxy groups of two other di-paracetamol molecules. Each N—H group also donates to a hydroxy O atom in another molecule, producing a three-dimensional crosslinked network of hydrogen bonds, unlike the two crystalline forms of PHA, which have two-dimensional sheet hydrogen-bonding structures.

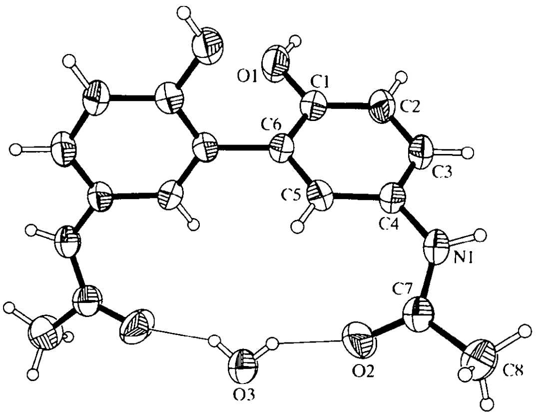


Fig. 1. The molecular structure of the title dimer, including the water molecule, showing the atom labels and with 50% probability ellipsoids for non-H atoms.

The hydrogen bonding apparently has little effect on the internal geometry of the two PHA sub-units of di-paracetamol, which may be compared with the two forms of PHA itself. Bond lengths and angles are very similar in all three structures. The C—C single bond connecting the two sub-units in di-paracetamol has a typical length for this type of bond (Allen *et al.*, 1987). The aromatic rings are planar (r.m.s. deviation = 0.011 Å), with a dihedral angle of 79.3 (1)° (see also the torsion angles in Table 1). Each planar amide group (r.m.s. deviation = 0.012 Å) is inclined at 32.6 (2)° to its adjoining aromatic ring, which represents an increase of twist compared with the two forms of PHA (20.5 and 17.7° for the monoclinic and orthorhombic forms, respectively), this being the main difference between these PHA units.

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Experimental

Crystals of di-paracetamol were obtained by slow evaporation (over two weeks) of an aqueous solution of a commercial sample of PHA, saturated at 338 K. The very small crystals grew simultaneously with large crystals of PHA and were separated manually; their size and weak diffraction necessitated synchrotron data collection.

Crystal data

$C_{16}H_{16}N_2O_4.H_2O$
$M_r = 318.32$
Monoclinic
$C2/c$
$a = 7.617\,(3)$ Å
$b = 15.433\,(6)$ Å
$c = 13.652\,(5)$ Å
$\beta = 90.112\,(10)°$
$V = 1604.8\,(11)$ Å^3
$Z = 4$
$D_x = 1.317$ Mg m^{-3}
D_m not measured

Synchrotron radiation
$\lambda = 0.6874$ Å
Cell parameters from 3307 reflections
$\theta = 2.54$–$26.56°$
$\mu = 0.099$ mm^{-1}
$T = 295\,(2)$ K
Needle
$0.32 \times 0.06 \times 0.04$ mm
Colourless

Data collection

Siemens SMART CCD diffractometer
ω rotation with narrow frames
Absorption correction: none
4688 measured reflections
1705 independent reflections

1186 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.067$
$\theta_{\rm max} = 26.77°$
$h = -9 \rightarrow 9$
$k = -13 \rightarrow 19$
$l = -17 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.062$
$wR(F^2) = 0.158$
$S = 0.933$
1705 reflections
119 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.094P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.297$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.243$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

O1—C1	1.361 (4)	N1—C4	1.416 (4)
O2—C7	1.224 (4)	C6—C6$^{\rm i}$	1.495 (5)
N1—C7	1.336 (4)		
C7—N1—C4	127.3 (3)	O2—C7—N1	123.2 (3)
C7—N1—C4—C3	−151.4 (3)	C1—C6—C6$^{\rm i}$—C1$^{\rm i}$	−83.7 (6)
C7—N1—C4—C5	31.9 (5)	C5—C6—C6$^{\rm i}$—C5$^{\rm i}$	−77.4 (6)

Symmetry code: (i) $1 - x, y, \frac{1}{2} - z$.

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O3—H3O$\cdots$O2	0.79 (4)	1.96 (4)	2.662 (2)	148 (4)
O1—H1O$\cdots$O3$^{\rm i}$	0.87 (3)	1.81 (3)	2.689 (3)	179 (3)
N1—H1N$\cdots$O1$^{\rm ii}$	0.85 (4)	2.19 (4)	3.037 (4)	174 (4)

Symmetry codes: (i) $x - \frac{1}{2}, y - \frac{1}{2}, z$; (ii) $x, 1 - y, \frac{1}{2} + z$.

The data collection nominally covered a hemisphere of reciprocal space by a combination of three sets of exposures; each set had a different φ angle for the crystal and each exposure covered 0.3° in ω. Coverage was essentially complete to $\theta = 25°$. For further information on the synchrotron data collection, see Clegg *et al.* (1998). Decay of the incident beam was corrected by *SADABS* (Sheldrick, 1997). The crystal was found to be twinned, the value of the cell β angle being close to 90°, and was thus pseudo-orthorhombic. Reflections from the two twin components did not overlap precisely, leading to broadening and some minor splitting of profiles. The twin component contributions were refined to 0.502 (3):0.498 (3). C-bound H atoms were placed geometrically and refined with a riding model (including free rotation about C—C bonds), and with $U_{\rm iso}$ constrained to be 1.2 (1.5 for methyl groups) times $U_{\rm eq}$ of the carrier atom. H atoms on N and O atoms were refined freely.

Data collection: *SMART* (Siemens, 1995). Cell refinement: local programs. Data reduction: *SAINT* (Siemens, 1995). Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL*. Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL* and local programs.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1496). Services for accessing these data are described at the back of the journal.

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