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Acemetacin monohydrate

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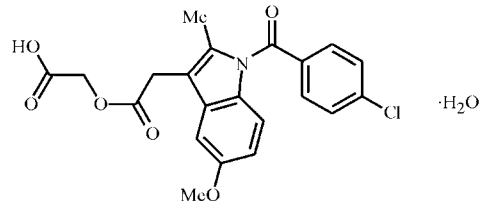
The structure of the title compound (systematic name: 2-{2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetoxy}acetic acid monohydrate, $C_{21}H_{18}ClNO_6\cdot H_2O$) contains one-dimensional infinite hydrogen-bonded chains. Molecules of acemetacin, a nonsteroidal anti-inflammatory drug, and water are linked by three independent O—H···O bonds. The central unit in each chain consists of a sequence of alternating centrosymmetric $R_4^4(12)$ and $R_4^4(18)$ rings, which are edge-fused. Each ring links two acemetacin and two water molecules. A comparison with seven related structures reveals that molecules of acemetacin, indomethacin and their analogues can adopt two principal conformations.

Comment

Acemetacin is a prodrug of indomethacin. It is a nonsteroidal anti-inflammatory drug used for the treatment of osteoarthritis, rheumatoid arthritis, low back pain, and post-operative inflammation and post-operative pain. Yoneda *et al.* (1981) described four polymorphic forms and two hydrates of acemetacin. Burger & Lettenbichler (1993) investigated five polymorphic forms, one monohydrate and the relatively stable amorphous form of acemetacin, and characterized these phases by means of thermomicroscopy, differential scanning calorimetry, thermogravimetry, IR spectroscopy, X-ray powder diffraction and pycnometry. Crystals of the monohydrate, (I), can be obtained from solutions with aqueous solvents. The existence of a second hydrate of acemetacin (Yoneda *et al.*, 1981) was firmly rejected by Burger & Lettenbichler (1993). These authors explained the underlying observations as a consequence of an unusual melting behaviour of the monohydrate. Auer *et al.* (2003) investigated the FT–Raman spectra of six solid phases of acemetacin, and another account of the monohydrate was given by Kim *et al.* (1993). To date, no structural information relating to any of the six characterized crystalline phases of acemetacin is available in the Cambridge Structural Database (Version 5.28, November 2006; Allen, 2002).

A comparison of the powder pattern calculated from the structural model of the title compound discussed here with that reported by Burger & Lettenbichler (1993) for their monohydrate confirms that both studies were carried out on



(I)

the same phase. The structure of the acemetacin molecule is shown in Fig. 1. Bond lengths and angles are unexceptional. The indole unit makes an angle of 69.03 (5)° with the chlorobenzyl fragment and an angle of 69.08 (6)° with the mean plane through the CCOO unit attached to atom C9.

The acemetacin molecule has one potential hydrogen-bond donor and the water molecule has two. These are engaged in three independent O—H···O hydrogen bonds linking the two types of molecule. The OH group of (I) acts as a hydrogen-bond donor to one water molecule (O5—H1O···O7), and two water H atoms are linked to carbonyl atoms O2 and O4 [O7—H2O···O2($x-1, y, z$) and O7—H3O···O4($-x-1, -y, -z+1$); Table 1]. These acceptor atoms are located in the respective oxyacetic acid units of two different acemetacin molecules. The latter two molecules are related *via* a centre of inversion. Each water molecule bridges between three

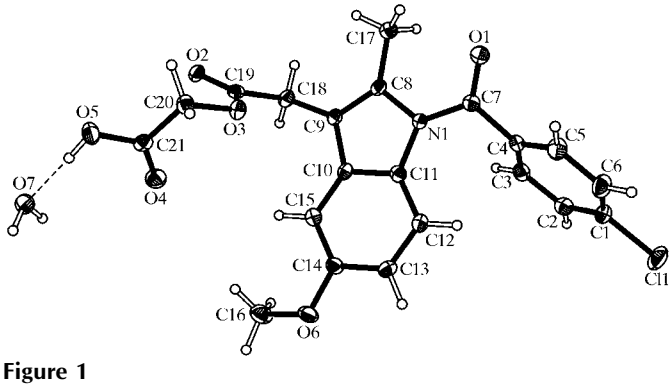


Figure 1
The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

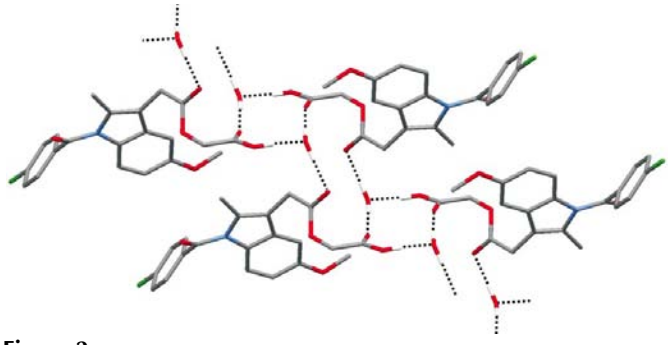


Figure 2
Part of a hydrogen-bonded chain composed of edge-fused $R_4^4(12)$ and $R_4^4(18)$ rings.

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acemetacin molecules. In turn, each acemetacin molecule is hydrogen bonded to three water molecules. The described connections generate two fundamentally different centrosymmetric rings. The first ring can be characterized by the graph-set notation $R_4^4(12)$ (Bernstein *et al.*, 1995) and the other is an $R_4^4(18)$ ring. Rings of different types are edge-fused in such a way that $C_2^2(9)$ fragments are formed. Thus, infinite chains (Fig. 2) are generated, whose central unit consists of alternating $R_4^4(12)$ and $R_4^4(18)$ rings. These one-dimensional hydrogen-bonded chains are centrosymmetric and propagate parallel to the *a* axis. The water molecules lie at the centre of each chain and all acemetacin molecules are oriented with their oxyacetic acid units towards the central unit, while their 4-chlorobenzoyl fragments point in the opposite direction. The stacking of the chains in the crystal structure is such that the central unit of a given chain is adjacent to the tail units of four neighbouring chains that are related to the former by a translation along [010], [0$\bar{1}$0], [011], [0$\bar{1}$0] and [0$\bar{1}\bar{1}$].

The closest intermolecular C—H···O intra-chain contacts are C17—H17*A*···O4($x+1, y, z$) and C3—H3···O6($x+1, y, z$). The shortest C—H···O contacts between acemetacin molecules belonging to different O—H···O bonded chains are C18—H18*A*···O2($-x, -y, -z+1$) and C20—H20*A*···O1($-x+1, -y+1, -z+1$).

The Cambridge Structural Database currently holds records for seven structures that contain the indomethacin molecule (α form: Chen *et al.*, 2002; γ form: Cox & Manson, 2003*a*; MeOH solvate: Stowell *et al.*, 2002; *t*-ButOH solvate: Cox & Manson, 2003*b*) or other close analogues of acemetacin (Loll *et al.*, 1996; Trask *et al.*, 2004; Bis & Zaworotko, 2005). The molecular conformations in these structures can be characterized in terms of two torsion angles, T_1 (C—C—N—C) and T_2 (C—C—C—N), which are indicated in Fig. 3 and tabulated in Table 2. Analysis of this list reveals that only two principal conformations exist. Type I and type II are associated with T_1 values of approximately 150 and −30°, respectively, while T_2 lies between −30 and −55° for both types. Thus, the main difference between the alternative principal conformations is a rotation by 180° about the C—N bond. As a consequence, the C═O bond and the methyl substituent of the indole unit point either in the same direction (type I) or in opposite directions (type II). The conformation adopted by the acemetacin molecule in the title structure is of type I. It is noteworthy that the type I conformation is also adopted by the γ form and the *t*-BuOH solvate of indomethacin, and also by two of the three independent molecules of the α form, while the conformation of the third molecule in this modification is of type II.

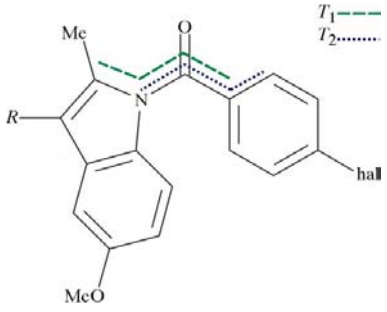

Figure 3
The common structural unit of the compounds listed in Table 1 and definition of the torsion angles T_1 and T_2 for acemetacin [R = –CH_2-C(═O)OCH_2COOH and hal = Cl], indomethacin (R = –CH_2COOH and hal = Cl), iodoindomethacin (R = –CH_2COOH and hal = I) and indomethacin methyl ester (R = –CH_2COOMe and hal = Cl).

The hydrogen bonding in the MeOH and *t*-BuOH solvates of indomethacin is such that molecules of different types are linked by hydrogen bonds. The COOH group of indomethacin is employed in these interactions in the same fashion as the COOH units are engaged in hydrogen bonding between acemetacin and water molecules in Fig. 2. Thus, the indomethacin solvates form a very similar kind of $R_4^4(12)$ ring, where the OH group of the solvent replaces the water molecule. However, the lack of additional OH donors in the indomethacin molecules prevents further aggregation of these rings *via* classical hydrogen bonds, so that the hydrogen-bonded structure in these solvates is dimeric.

Experimental

Acemetacin was supplied by Bayer. Colourless prismatic crystals of the title compound were formed by slow evaporation of an acetone/water solution at room temperature.

Crystal data

$C_{21}H_{18}ClNO_6·H_2O$
M_r = 433.83
Triclinic, $P\bar{1}$
a = 7.7257 (3) Å
b = 10.2208 (3) Å
c = 13.4225 (4) Å
α = 96.879 (2)°
β = 96.354 (2)°
γ = 107.158 (2)°
V = 993.44 (6) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.24 mm^{-1}
T = 120 (2) K
0.25 × 0.15 × 0.10 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.943, T_{max} = 0.977
12459 measured reflections
3877 independent reflections
3065 reflections with $I > 2\sigma(I)$
R_{int} = 0.072

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.127
S = 1.09
3877 reflections
285 parameters
3 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O5—H1O···O7	0.828 (10)	1.760 (10)	2.587 (2)	176 (2)
O7—H2O···O2^{i}	0.872 (10)	1.950 (12)	2.7980 (19)	164 (2)
O7—H3O···O4^{ii}	0.875 (10)	1.891 (10)	2.7649 (19)	177 (2)
C20—H20*A*···O1^{iii}	0.99	2.67	3.424 (3)	133
C18—H18*A*···O2^{iv}	0.99	2.61	3.371 (2)	134
C17—H17*A*···O4^{v}	0.98	2.48	3.381 (2)	153
C3—H3···O6^{v}	0.95	2.67	3.417 (2)	136

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

Table 2
Solid-state conformation types I and II of acemetacin and related molecules indicated by torsion angles T_1 and T_2 (see Fig. 3).

Crystal structure	Molecule	T_1 (°)	T_2 (°)	Conformation	Reference
Acemetacin monohydrate	*A*	154.3	−48.7	I	This work
Indomethacin *t*-BuOH solvate	*A*	147.8	−38.4	I	Cox & Manson (2003*b*)
2-Amino-5-picolinium indomethacin	*A*	146.9	−29.7	I	Bis & Zaworotko (2005)
	B	148.9	−30.6	I	
γ-Indomethacin	*A*	150.8	−40.7	I	Cox & Manson (2003*a*)
α-Indomethacin	*A*	153.6	−53.3	I	Chen *et al.* (2002)
	C	154.4	−52.9	I	
	B	−22.7	−54.5	II	
Indomethacin MeOH solvate	*A*	−36.9	−44.9	II	Stowell *et al.* (2002)
Iodoindomethacin	*A*	−35.0	−44.3	II	Loll *et al.* (1996)
Indomethacin methyl ester	*A*	−33.0	−51.4	II	Trask *et al.* (2004)

Methyl H atoms were located in difference syntheses, idealized and included as rigid groups allowed to rotate but not tip. Other C-bonded H atoms were positioned geometrically and refined using a riding model, with U_{iso}(H) values of $1.2U_{eq}$(C) for CH and CH_2 or $1.5U_{eq}$(C) for CH_3 H atoms. The C—H bond lengths were set at 0.95 (aromatic), 0.99 (CH_2) or 0.98 Å (CH_3). H atoms attached to O atoms were refined using geometrical restraints [O—H = 0.82 (2) Å and U_{iso}(H) = $1.2U_{eq}$(O) for OH, and O—H = 0.88 (2) Å and U_{iso}(H) = $1.5U_{eq}$(O) for H_2O].

Data collection: *COLLECT* (Hooft, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* (Bruker, 1998) and *Mercury* (Bruno *et al.*, 2002); software used to prepare material for publication: *publCIF* (Westrip, 2007).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ3078). Services for accessing these data are described at the back of the journal.

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