

## Anti-inflammatory drugs. X.<sup>1</sup> Hydrated pyrrolidinium {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (HP·D·H<sub>2</sub>O)

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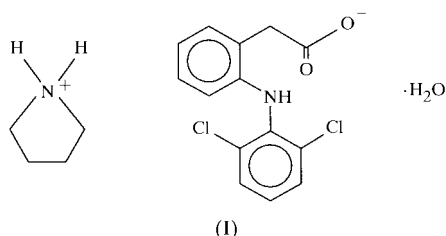
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In the solid-state structure of the title compound, C<sub>4</sub>H<sub>10</sub>N<sup>+</sup>·C<sub>14</sub>H<sub>10</sub>Cl<sub>2</sub>NO<sub>2</sub><sup>-</sup>·H<sub>2</sub>O, the asymmetric unit contains one cation, one anion and a water molecule. There is a network of hydrogen bonds which is similar to that found in the hydrated diethylammonium diclofenac salt. A comparison is made of the molecular conformation of the anions in the two related structures.

### Comment

The systematic structural work being carried out on diclofenac salts, a type of non-steroidal anti-inflammatory drug (Castellari & Sabatino, 1994, 1996; Castellari & Ottani, 1995, 1996, 1997*a,b*, 1998; Castellari, Feroci & Ottani, 1999; Castellari, Comelli & Ottani, 1999; Castellari *et al.*, 2001), has important pharmaceutical implications, since the presence of polymorphic forms and/or hydrates influences the bioavailability of the drug.



As shown in Fig. 1, the asymmetric unit of the title compound, (I), contains one cation, one anion and a water molecule. The bond lengths and angles of the anion are in good agreement with the corresponding values found in previous works. In particular, the carboxylate group shows a marked  $\pi$  delocalization. The diclofenac anion (D) is stabi-

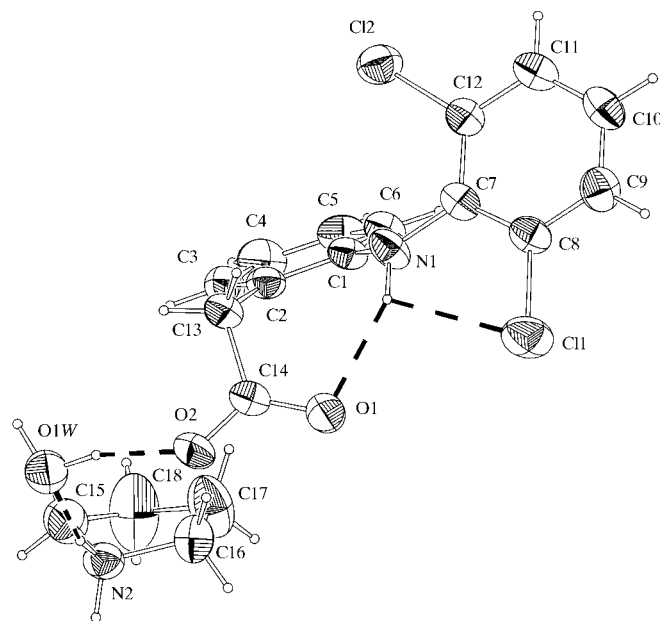
<sup>1</sup> Part IX: Castellari, Comelli & Ottani (2001).

lized, as usual, by two intramolecular hydrogen bonds between the amino group and atoms O1 and C11. In the pyrrolidinium cation, the N atom is shifted out of the plane of the four C atoms by 0.308 (5) Å, and C17 and C18 are out of the C<sub>4</sub> plane by -0.101 (3) and 0.102 (3) Å, respectively

The C—N distances are normal, but the C—C bond lengths are shorter than expected. A similar behaviour in the C—C distances was reported previously for the pyrrolidinium cation (Teske *et al.*, 1996). Since, in both structures, the displacement parameters of the C atoms opposite the N atom are larger than those of the adjacent C atoms, the apparent contraction of the C—C distances could be attributed to the average displacement parameters. Actually, the distances involving C18, the atom affected by the largest thermal motion, are the shortest; C15—C18 = 1.458 (4) Å and C17—C18 = 1.453 (4) Å.

The intermolecular hydrogen-bond network is similar to that reported recently for the hydrated diethylammonium diclofenac salt (HDEA·D·H<sub>2</sub>O; Castellari *et al.*, 2001). In both salts, the anions, cations and water molecules are linked into two-dimensional networks lying in a plane, *i.e.* [001] and [100] for HDEA·D·H<sub>2</sub>O and HP·D·H<sub>2</sub>O, respectively. The intermolecular hydrogen-bond scheme involves four normal hydrogen bonds, one charge-assisted between the anion and the cation, and three involving the water molecule, where the O1W atom acts as a donor towards the two carboxylate O atoms and as an acceptor towards the pyrrolidinium N atom.

A comparison of the molecular conformation of the diclofenac anion in the two structures is of some interest. The degrees of freedom of D can be described by the following dihedral angles between planes, the values being quoted for HDEA·D·H<sub>2</sub>O and HP·D·H<sub>2</sub>O, respectively: C1—C6/C1—



**Figure 1**  
ORTEP (Johnson, 1976) diagram of HP·D·H<sub>2</sub>O. Non-H atoms are represented by displacement ellipsoids of 50% probability and H atoms by spheres of arbitrary size.

N1—C7 = 16.5 (1) and 18.2 (3)°, C7—C12/C1—N1—C7 = 61.6 (1) and 49.5 (2)°, C1—C2—C6/C2—C13—C14 = 77.5 (1) and 79.0 (2)°, and O1—C14—O2/C2—C13—C14 = 56.3 (2) and 52.6 (2)°. Inspection of these values shows that the largest difference in the molecular conformation of the anions occurs in the dihedral angle between the dichlorophenyl ring (C7—C12) and the C1/N1/C7 plane [the difference in torsion angles C1—N1—C7—C12 = 11.0 (2)°]. However, we note that the smaller steric hindrance of the pyrrolidinium cation, compared with that of diethylammonium, influences the crystal packing.

In HP·D·H<sub>2</sub>O, the average H···A distance is 1.84 (1) Å and the density is 1.389 Mg m<sup>-3</sup>. In contrast, the average H···A distance in HDEA·D·H<sub>2</sub>O is 1.90 (1) Å and the density is 1.280 Mg m<sup>-3</sup>. The higher packing efficiency in HP·D·H<sub>2</sub>O compared with HDEA·D·H<sub>2</sub>O most likely results in lower stresses to accommodate the anions in the crystals. This may consequently lead to the smaller twist angle between the two phenyl rings, *viz.* 60.68 (8) versus 72.4 (2)°.

## Experimental

Crystalline HP·D·H<sub>2</sub>O was prepared by mixing equivalent molar amounts of diclofenac acid and pyrrolidine. Crystals were obtained from a water solution.

### Crystal data

C <sub>4</sub> H <sub>10</sub> N <sup>+</sup> ·C <sub>14</sub> H <sub>10</sub> Cl <sub>2</sub> NO <sub>2</sub> <sup>-</sup> ·H <sub>2</sub> O	$D_x = 1.389 \text{ Mg m}^{-3}$
$M_r = 385.28$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 5166 reflections
$a = 18.9631 (7) \text{ \AA}$	$\theta = 2.5\text{--}26.1^\circ$
$b = 9.6845 (3) \text{ \AA}$	$\mu = 0.37 \text{ mm}^{-1}$
$c = 10.0505 (4) \text{ \AA}$	$T = 293 (2) \text{ K}$
$\beta = 93.1340 (10)^\circ$	Block, colourless
$V = 1842.99 (12) \text{ \AA}^3$	$0.5 \times 0.5 \times 0.4 \text{ mm}$
$Z = 4$	

### Data collection

Bruker SMART 2000 CDD diffractometer	$\theta_{\text{max}} = 25.0^\circ$
$\omega$ scans	$h = -22 \rightarrow 22$
17 027 measured reflections	$k = -11 \rightarrow 11$
3244 independent reflections	$l = -11 \rightarrow 11$
2046 reflections with $I > 2\sigma(I)$	112 standard reflections every 20 reflections
$R_{\text{int}} = 0.087$	intensity decay: <2%

**Table 1**

Selected geometric parameters (Å, °).

O1—C14	1.248 (3)	C15—C18	1.458 (4)
O2—C14	1.253 (3)	C16—C17	1.487 (4)
N2—C15	1.483 (3)	C17—C18	1.453 (4)
N2—C16	1.498 (3)		
O1—C14—O2	123.8 (2)	C17—C16—N2	105.9 (2)
C15—N2—C16	106.6 (2)	C18—C17—C16	107.3 (3)
C18—C15—N2	104.7 (2)	C17—C18—C15	108.0 (3)
C7—N1—C1—C6	-18.2 (4)	C1—C2—C13—C14	79.1 (3)
N1—C1—C2—C13	1.3 (3)	C2—C13—C14—O1	-52.6 (3)
C1—N1—C7—C12	-52.4 (4)		

### Refinement

Refinement on $F^2$	$w = 1/[\sigma^2(F_o^2) + (0.0776P)^2]$
$R[F^2 > 2\sigma(F^2)] = 0.041$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.105$	$(\Delta/\sigma)_{\text{max}} = 0.037$
$S = 0.89$	$\Delta\rho_{\text{max}} = 0.29 \text{ e \AA}^{-3}$
3244 reflections	$\Delta\rho_{\text{min}} = -0.30 \text{ e \AA}^{-3}$
247 parameters	Extinction correction: <i>SHELXL97</i>
H atoms treated by a mixture of independent and constrained refinement	Extinction coefficient: 0.0047 (10)

**Table 2**

Hydrogen-bonding geometry (Å, °).

$D\text{---}H\cdots A$	$D\text{---}H$	$H\cdots A$	$D\cdots A$	$D\text{---}H\cdots A$
N1—H1···Cl1	0.92 (2)	2.53 (3)	2.983 (2)	110 (2)
N1—H1···O1	0.92 (2)	2.09 (3)	2.898 (3)	144 (2)
O1W—H1W···O2	0.93 (2)	1.83 (2)	2.733 (3)	164 (4)
O1W—H2W···O1 <sup>i</sup>	0.94 (2)	1.80 (2)	2.730 (3)	170 (3)
N2—H11···O2 <sup>ii</sup>	0.92 (1)	1.85 (1)	2.736 (3)	162 (3)
N2—H12···O1W	0.92 (1)	1.86 (2)	2.758 (2)	164 (3)

Symmetry codes: (i)  $x, \frac{1}{2} - y, z - \frac{1}{2}$ ; (ii)  $1 - x, y - \frac{1}{2}, \frac{3}{2} - z$ .

The H1 atom and the H atoms bonded to the N2 and O1W atoms were located from a difference synthesis and were refined isotropically. The remaining H atoms were placed in calculated positions and refined riding on their parent atoms ( $C\text{---}H = 0.93$  and  $0.97 \text{ \AA}$ ).

Data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT-Plus* (Bruker, 1999); program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993); molecular graphics: *ORTEPII* (Johnson, 1976).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1521). Services for accessing these data are described at the back of the journal.

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