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Anti-inflammatory drugs. IX.[1] Hydrated diethylammonium [2-(2,6-dichlorophenylamino)phenyl]acetate ($HDEA{\cdot}D{\cdot}H_2O$)

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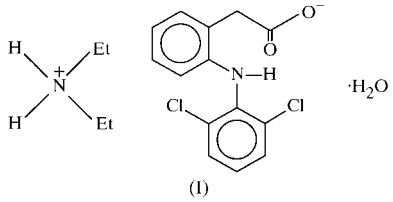
In the solid-state structure of the title compound, $C_4H_{12}N^+{\cdot}C_{14}H_{10}Cl_2NO_2^-{\cdot}H_2O$, the asymmetric unit contains one cation, one anion and a water molecule. A complex network of hydrogen bonds is present. A comparison is made with the structure of the anhydrous salt.

Comment

The present structural work on a diclofenac salt has been performed as part of a study on non-steroidal anti-inflammatory drugs (Castellari & Sabatino, 1994, 1996; Castellari & Ottani, 1995, 1996, 1997*a*,*b*, 1998; Castellari, Feroci & Ottani, 1999; Castellari, Comelli & Ottani, 1999). We have also redetermined the crystalline structure of diethylammonium [2-(2,6-dichlorophenylamino)phenyl]acetate (HDEA·D), which has been published previously (Pomes-Hernandez *et al.*, 1997). Crystallographic data (excluding structure factors) for the structure of HDEA·D (Castellari *et al.*, 2000) have been deposited with the Cambridge Structural Database (Allen & Kennard, 1993).



(I)

A comparison between the structures of HDEA·D and $HDEA{\cdot}D{\cdot}H_2O$ allows the evaluation of the effects of the incorporation of a water molecule in the structure. Such a comparison has relevant pharmaceutical implications, since drug bio-availability is influenced by the presence of water. The asymmetric unit of the title compound, (I), is shown in Fig. 1. The bond lengths and angles of the anion and cation are in good agreement with the corresponding values found in the anhydrous salt. However, the presence of the water molecule in the asymmetric unit influences the network of hydrogen bonds. In HDEA·D, two intramolecular hydrogen bonds and two normal intermolecular hydrogen bonds are detected between carboxylic acid groups and ammoniun ions, with the anions and cations linked in a chain running along [001]. The following intramolecular hydrogen-bond geometry was found: H1···O1 2.08 (2), N1···O1 2.8834 (2) Å and N1—H1···O1 153 (2)°; H1···Cl1 2.60 (2), N1···Cl1 2.9811 (2) Å and N1—H1···Cl1 107 (2)°. In contrast, in $HDEA{\cdot}D{\cdot}H_2O$ (see Table 2), there is only one normal (charge-assisted and resonance-assisted) hydrogen bond between cations and anions, but in this case the water molecule is involved in the hydrogen-bond network. The O3*W* atom acts as a donor towards both the carboxylate O atoms, O1 and O2. As a result, in $HDEA{\cdot}D{\cdot}H_2O$, the polymeric structure consists of a two-dimensional network with base vectors [010] and [100]. The diclofenac anion is stabilized, as usual, by two intramolecular hydrogen bonds between the amino group and the O1 and Cl1 atoms. The C5—H4···Cl2 bond is much weaker, but may still have some influence on the molecular packing.

Finally, in the anhydrous compound, the two torsion angles C7—N1—C1—C6 and C1—N1—C7—C12 are 16.7 (3) and 58.3 (3)°, respectively. Thus, in $HDEA{\cdot}D{\cdot}H_2O$, the dihedral angle between the two phenyl rings, 72.4 (2)°, is larger than that found in the anhydrous form of the salt, 66.9 (8)°. This work confirms the importance of solid-state characterization in pharmaceutical hydrates (Khankari & Grant, 1995), since the anti-inflammatory power of the drug seems to depend strongly on the reciprocal orientation of the phenyl rings (Moser *et al.*, 1990).

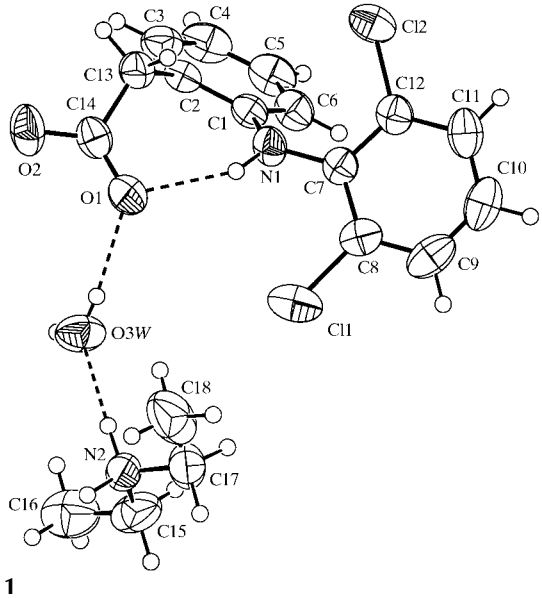


Figure 1
PLATON (Spek, 2001) diagram of $HDEA{\cdot}D{\cdot}H_2O$ showing the asymmetric unit. Dashed lined indicate hydrogen bonds. Non-H atoms are represented by displacement ellipsoids of 50% probability and H atoms by spheres of arbitrary size.

[1] Part VIII: Castellari, Comelli & Ottani (1999).

Experimental

Crystalline HDEA·D·H_2O was prepared by mixing equivalent molar amounts of diclofenac acid and diethylamine. Crystals were obtained from a water solution.

Crystal data

$C_4H_{12}N^+·C_{14}H_{10}Cl_2NO_2^-·H_2O$
M_r = 387.29
Monoclinic, $P2_1/a$
a = 11.7490 (10) Å
b = 12.2960 (10) Å
c = 14.5910 (10) Å
β = 107.544 (3)°
V = 2009.9 (3) Å^3
Z = 4
D_x = 1.280 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 5166 reflections
θ = 2.45–26.08°
μ = 0.341 mm^{-1}
T = 293 (2) K
Block, colourless
0.5 × 0.4 × 0.3 mm

Data collection

Bruker SMART 2000 CDD diffractometer
ω scans
26 140 measured reflections
5884 independent reflections
3025 reflections with $I > 2\sigma(I)$
R_{int} = 0.084
θ_{max} = 30.08°
$h = -16 \rightarrow 16$
$k = -17 \rightarrow 17$
$l = -20 \rightarrow 20$
112 standard reflections
every 20 reflections
intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.121
S = 1.055
5882 reflections
250 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0776P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.001$
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.36 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N2—C17	1.485 (3)	C14—O1	1.242 (2)
N2—C15	1.502 (3)	C14—O2	1.261 (2)
O1—C14—O2	125.4 (2)		
C7—N1—C1—C6	16.8 (3)	C1—N1—C7—C12	63.4 (2)

The H atom bound to N1 was located from a difference synthesis and was refined isotropically. The H atoms on the N2 and O3*W* atoms were located experimentally and were refined isotropically with distance restraints. The starting positions of H atoms of the methyl groups were found from a difference electron-density synthesis. The remaining H atoms were placed in calculated positions (C—H = 0.93–0.97 Å) and refined riding on their parent atoms.

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···Cl1	0.85 (2)	2.69 (2)	2.990 (2)	102 (2)
N1—H1···O1	0.85 (2)	2.08 (2)	2.853 (2)	151 (2)
O3*W*—H1*W*···O1	0.78 (2)	2.00 (2)	2.773 (2)	172 (2)
O3*W*—H2*W*···O2^{i}	0.81 (2)	1.98 (2)	2.788 (2)	175 (3)
N2—H11···O2^{ii}	0.93 (2)	1.79 (2)	2.713 (2)	170 (2)
N2—H12···O3*W*	0.95 (2)	1.84 (2)	2.786 (2)	176 (2)
C5—H4···Cl2^{iii}	0.93	2.93	3.851 (2)	173

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

Data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT-Plus* (Bruker, 1999); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *PLATON* (Spek, 2001).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1485). Services for accessing these data are described at the back of the journal.

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