

References

- Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 31–37.
- Edwards, B. P. E., Harrison, W., Nowell, I. W., Post, M. L., Shearer, H. M. M. & Trotter, J. (1976). *Acta Cryst.* **B32**, 648–649.
- Enraf–Nonius (1994). *CAD-4 Software*. Version 5.1/1.2. Enraf–Nonius, Delft, The Netherlands.
- Fair, C. K. (1990). *MolEN. An Interactive Intelligent System for Crystal Structure Analysis*. Enraf–Nonius, Delft, The Netherlands.
- Ferguson, G., Carroll, C. D., Glidewell, C., Zakaria, C. M. & Lough, A. J. (1995). *Acta Cryst.* **B51**, 367–377.
- Ferguson, G., Gallagher, J. F., Glidewell, C., Low, J. N. & Scrimgeour, S. N. (1992). *Acta Cryst.* **C48**, 1272–1275.
- Ferguson, G., Glidewell, C. & Patterson, I. L. J. (1996). *Acta Cryst.* **C52**, 420–423.
- Immirzi, A., Musco, A. & Mann, B. E. (1977). *Inorg. Chim. Acta*, **21**, L37–L38.
- Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
- Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Universities of York, England, and Louvain, Belgium.
- North, A. C. T., Phillips, D. C., & Mathews, F. S. (1968). *Acta Cryst.* **A24**, 351–359.
- Rudman, R. & Post, B. (1968). *Mol. Cryst.* **5**, 95–110.
- Steiner, T. (1996). *Acta Cryst.* **C52**, 2885–2887.
- Zachariasen, W. H. (1963). *Acta Cryst.* **16**, 1139–1144.

Acta Cryst. (1998). **C54**, 415–417

Stereochemistry of Anti-Inflammatory Drugs. VI. Piperazinium 2-(2,6-Dichlorophenylamino)phenylacetate Dihydrate, $(\text{H}_2\text{PZ})\text{D}_2 \cdot 2\text{H}_2\text{O}$

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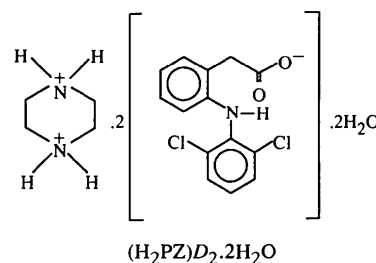
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Abstract

The asymmetric unit of the title compound, $\text{C}_4\text{H}_{12}\text{N}_2^{2+} \cdot 2\text{C}_{14}\text{H}_{10}\text{Cl}_2\text{NO}_2^- \cdot 2\text{H}_2\text{O}$, consists of two piperazinium dications located around two non-equivalent centers of symmetry, two 2-(2,6-dichlorophenylamino)phenylacetate anions in general positions and two water molecules. The solid-state structure is strongly hydrogen bonded.

Comment

The structure of the title salt has been investigated by X-ray diffraction as a part of a systematic study (Castellari & Sabatino, 1994, 1996; Castellari & Ottani, 1995, 1996, 1997) of diclofenac [2-(2,6-dichlorophenylamino)phenylacetic acid] salts, an important group of non-steroidal anti-inflammatory drugs. Alterations in solubility and chemical stability have important pharmaceutical consequences since they can modify the bioavailability of a drug. Such alterations depend on the presence of polymorphic forms, crystalline stoichiometry and water molecules in the solid. Thus, the successful design of a dosage form of the drug depends strongly on knowledge of its solid-state chemistry. The asymmetric unit of the title compound, $(\text{H}_2\text{PZ})\text{D}_2 \cdot 2\text{H}_2\text{O}$ [where H_2PZ is the piperazinium dication and D is the 2-(2,6-dichlorophenylamino)phenylacetate anion] is shown in Fig. 1.



The asymmetric unit contains two bivalent piperazinium cations located around the symmetry centers $(0,0,\frac{1}{2})$ and $(\frac{1}{2},\frac{1}{2},\frac{1}{2})$, two 2-(2,6-dichlorophenylamino)phenylacetate anions and two water molecules. The structure is characterized by the presence of several hydrogen bonds (Table 2). The cations, anions and water molecules are connected by intermolecular hydrogen bonds to form a two-dimensional network in the *ab* plane. No short contact is detected along the *c* direction of the cell. The carboxylate groups, cations and water molecules are arranged along the [010] direction to form a hydrophilic tunnel. Water molecules interact with both H_2PZ and D ions, but not with each other.

The H_2PZ cations form salt bridges with the carboxylate groups. The $\text{N} \cdots \text{O}$ distances are short, as expected for hydrogen bonds in which both donor and acceptor atoms carry a formal charge. However, while both the ammonium H atoms (H11 and H12) at each end of the cation at $(0,0,\frac{1}{2})$ interact with carboxylate O atoms, only one H atom (H12A) from each end of the cation at $(\frac{1}{2},\frac{1}{2},\frac{1}{2})$ forms a salt bridge. As detailed in Table 2, the other ammonium H atom (H11A) is strongly bonded to the O3 water molecule. As a consequence, O3 is more closely packed than the O3A water molecule [mean contact distances 2.853(2) and 2.994(2) Å for O3 and O3A, respectively]. This feature is probably related to the simultaneous donor and acceptor character of O3 in the hydrogen-bonding

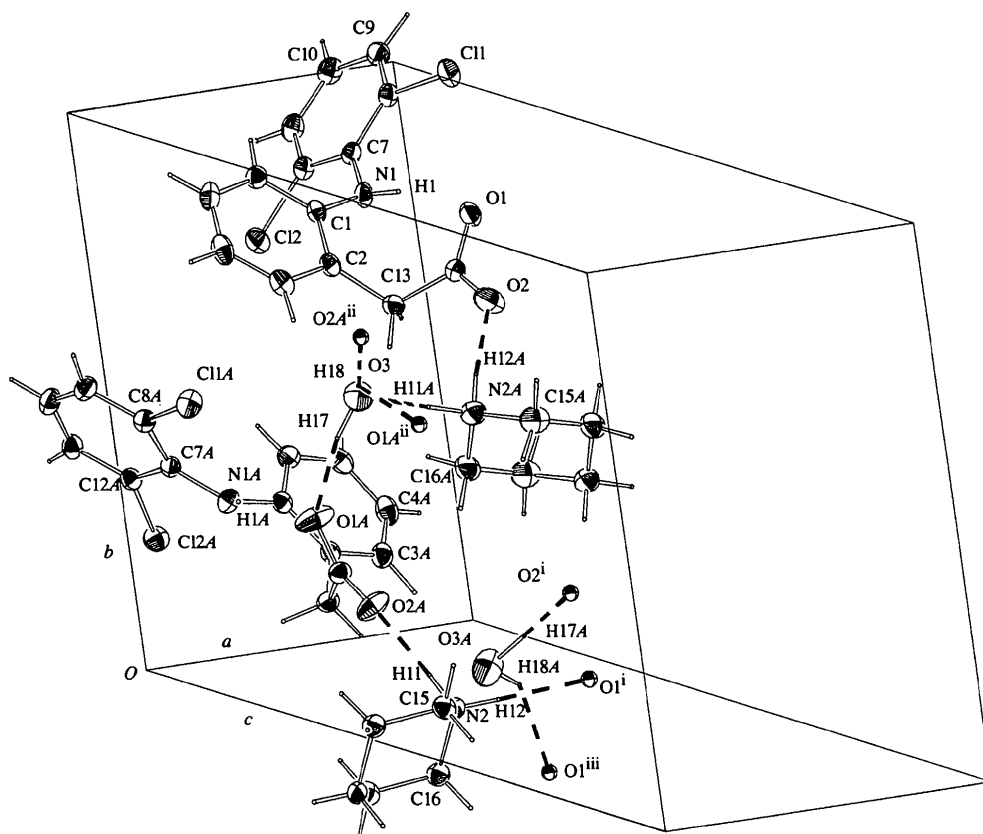


Fig. 1. ORTEP (Johnson, 1976) diagram of the asymmetric unit. Dashed lines show intermolecular hydrogen bonds. Non-H atoms are represented by displacement ellipsoids drawn at the 50% probability level. Symmetry-related acceptor and H atoms are drawn as circles of arbitrary size. Symmetry codes are as given in Table 2.

network. Such a difference in packing is also consistent with the value of the equivalent isotropic displacement parameter (IDP) of O3A [0.0875 (8) Å²], which is higher than the corresponding one of O3 [0.0652 (6) Å²]. These high IDP's are also responsible for the low precision in the bond angles of the water molecules, resulting in too acute values [H17—O3—H18 98 (4) and H17A—O3A—H18A 87 (4)°]. Differential scanning calorimetry (DSC) scans with sealed pans of solution-grown crystals show a melting peak at 425.3 (5) K. In contrast, DSC scans on samples quenched from the melt show a recrystallization exotherm at 347.7 (5) K and a melting peak at 423.1 (5) K (peak melting temperatures). The derivative curve of thermogravimetric (TGA) scans on solution-grown crystals displays a single dehydration peak at 347.9 (5) K, followed by decomposition above 425.3 (5) K. The % weight loss at 347.9 K corresponds to the evaporation of two water molecules.

The data confirm the space-filling role of the two water molecules. They also seem to indicate that the exceptionally low solubility of the title compound, (H₂PZ)*D*₂·2H₂O (Fini *et al.*, 1993), can in part be ascribed to the cooperative network of hydrogen bonds

which is further strengthened by water molecules in the crystal.

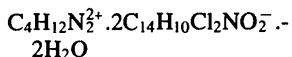
The geometry of the ions is normal. Both cations are in chair conformations. In the anions, the C—O distances (Table 1) are similar and suggest a complete charge delocalization. The dihedral angle between the two phenyl rings of *D* are 65.1 (1) and 65.5 (1)° for molecules (1) and (2), respectively. These distances and angles lie within the ranges found by us in other diclofenac salts [C—O: 1.237 (3)–1.263 (3) Å; dihedral angles: 59.3 (1)–73.6 (1)°]. The N1—H1 and N1A—H1A distances are rather short [0.77 (2) Å]. However, similar distances, between 0.88 and 0.75 Å, have been found for different salts of this same acid (Castellari & Sabatino, 1994, 1996; Castellari & Ottani, 1995, 1996, 1997). In all cases, the presence of the bifurcated intramolecular hydrogen bond involving the amine group stabilizes the conformation of the anion and appears to be independent of the nature of the cation.

Experimental

Diclofenac acid (IBSA, Lugano, Switzerland) was dissolved in acetone. Piperazine (Fluka, Buchs, Switzerland) was added

to the solution in the ratio 2:1. Crystals were grown by slow evaporation at room temperature. TGA and DSC thermal analyses were performed on polycrystalline powders using the TA-TGA 2950 and TA-DSC 2910 systems, respectively.

Crystal data



$M_r = 714.45$

Triclinic

$P\bar{1}$

$a = 8.897(2) \text{ \AA}$

$b = 11.242(4) \text{ \AA}$

$c = 17.13(2) \text{ \AA}$

$\alpha = 104.46(2)^\circ$

$\beta = 93.79(2)^\circ$

$\gamma = 90.30(2)^\circ$

$V = 1655(2) \text{ \AA}^3$

$Z = 2$

$D_x = 1.434 \text{ Mg m}^{-3}$

$D_m = 1.44 \text{ Mg m}^{-3}$

D_m measured by flotation in a mixture of 1-bromo-2-chloroethane and *p*-xylene

Mo $K\alpha$ radiation

$\lambda = 0.71069 \text{ \AA}$

Cell parameters from 24 reflections

$\theta = 6\text{--}13^\circ$

$\mu = 0.408 \text{ mm}^{-1}$

$T = 293(2) \text{ K}$

Prism

$0.33 \times 0.23 \times 0.20 \text{ mm}$

Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer

Profile data from ω scans

Absorption correction: none

8212 measured reflections

7950 independent reflections

4559 reflections with

$I > 2\sigma(I)$

$R_{\text{int}} = 0.016$

$\theta_{\text{max}} = 27.97^\circ$

$h = -11 \rightarrow 11$

$k = -14 \rightarrow 14$

$l = 0 \rightarrow 22$

3 standard reflections

frequency: 160 min

intensity decay: none

Refinement

Refinement on F^2

$R[F^2 > 2\sigma(F^2)] = 0.041$

$wR(F^2) = 0.115$

$S = 1.012$

7943 reflections

556 parameters

All H atoms refined

$w = 1/[\sigma^2(F_o^2) + (0.0445P)^2 + 0.7629P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\text{max}} = 0.655$, for H17A

$\Delta\rho_{\text{max}} = 0.477 \text{ e \AA}^{-3}$

$\Delta\rho_{\text{min}} = -0.316 \text{ e \AA}^{-3}$

Extinction correction: none

Scattering factors from

International Tables for Crystallography (Vol. C)

Table 1. Selected geometric parameters (\AA , $^\circ$)

C14—O2	1.237(3)	C14A—O1A	1.231(3)
C14—O1	1.245(3)	C14A—O2A	1.240(3)
N2—C16	1.482(3)	N2A—C16A	1.465(4)
N2—C15	1.485(3)	N2A—C15A	1.507(4)
C16—C15 ⁱ	1.504(4)	C15A—C16A ⁱⁱ	1.477(5)
O2—C14—O1	122.2(2)	O1A—C14A—O2A	122.2(2)
C16—N2—C15	111.2(2)	C16A—N2A—C15A	111.3(2)
N2—C15—C16 ⁱ	111.3(2)	C16A ⁱⁱ —C15A—N2A	109.8(3)
C16—N2—C15—C16 ⁱ	−56.2(3)		
C16A—N2A—C15A—C16A ⁱⁱ	55.9(4)		

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

Table 2. Hydrogen-bonding geometry (\AA , $^\circ$)

D—H...A	H...A	D...A	D—H...A
N1A—H1A...C11A	2.59(3)	2.973(2)	113(2)
N1—H1...C11	2.62(2)	2.986(2)	112(2)
N1A—H1A...O1A	2.10(3)	2.768(4)	146(3)
N1—H1...O1	2.15(2)	2.845(4)	152(2)
N2A—H12A...O2	1.73(3)	2.652(3)	173(3)
N2—H11...O2A	1.80(2)	2.683(3)	164(3)
N2—H12...O1 ⁱ	1.91(3)	2.791(3)	165(3)
N2A—H11A...O3	1.61(4)	2.679(4)	176(3)
O3—H18...O2A ⁱⁱ	1.82(2)	2.739(3)	161(4)
O3—H17...O1A	1.85(3)	2.725(3)	150(4)
O3A—H17A...O2 ⁱ	1.85(3)	2.787(4)	151(4)
O3A—H18A...O1 ⁱⁱⁱ	2.08(3)	2.937(3)	142(3)
O3—H18...O1A ⁱⁱ	2.51(4)	3.265(2)	136(3)

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

No absorption correction was applied. All of the H atoms were experimentally located and their coordinates and displacement coefficients were refined isotropically. A common isotropic displacement parameter was refined for the H atoms of the water molecules. The excessively high value of $(\Delta/\sigma)_{\text{max}}$ of 0.655 can be attributed to the H17A atom, which does not converge, even after several refinement cycles.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *MolEN* (Fair, 1990). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *XPMA-97* (Zsolnai, 1997). Software used to prepare material for publication: *SHELXL93*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1032). Services for accessing these data are described at the back of the journal.

References

- Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans. 2*, pp. S1–S19.
- Castellari, C. & Ottani, S. (1995). *Acta Cryst. C51*, 2612–2615.
- Castellari, C. & Ottani, S. (1996). *Acta Cryst. C52*, 2619–2622.
- Castellari, C. & Ottani, S. (1997). *Acta Cryst. C53*, 482–486.
- Castellari, C. & Sabatino, P. (1994). *Acta Cryst. C50*, 1723–1726.
- Castellari, C. & Sabatino, P. (1996). *Acta Cryst. C51*, 1708–1712.
- Enraf–Nonius (1989). *CAD-4 Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
- Fair, C. K. (1990). *MolEN. An Interactive Intelligent System for Crystal Structure Analysis*. Enraf–Nonius, Delft, The Netherlands.
- Fini, A., Fazio, G. & Rapaport, I. (1993). *Drugs Exptl Clin. Res.* **19**, 81–88.
- Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
- Sheldrick, G. M. (1990). *Acta Cryst. A46*, 467–473.
- Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
- Zsolnai, L. (1997). *XPMA-97. Graphics Program for the Manipulation of Small Structures*. University of Heidelberg, Germany.