Acta Crystallographica Section E
Structure Reports
Online
ISSN 1600-5368

Tris(2-ammonioethyl)amine tris({2-[(2,6-dichlorophenyl)amino]phenyl}acetate) hexahydrate

Daniel E. Lynch,[a]* Ajmer S. Bening[a] and Simon Parsons[b]

[a]School of Science and the Environment, Coventry University, Coventry CV1 5FB, England, and [b]Department of Chemistry, The University of Edinburgh, Edinburgh EH9 3JJ, Scotland

Correspondence e-mail:
apx106@coventry.ac.uk

Received 8 July 2003
Accepted 11 August 2003
Online 15 August 2003

The structure of the title compound, $C_6H_{21}N_4^{3+}\cdot 3C_{14}H_{10}Cl_2NO_2^{-}\cdot 6H_2O$, comprises the 1:3 organic salt of tris(2-ethylamine)amine and diclofenac acid, with an approximated six water molecules in an extensive hydrogen-bonding network. Two water molecules exist as full-occupancy molecules but the remainder are all disordered with partial occupancies. Disorder is also present in the base molecule, with the ammonium group of one 2-ammonioethyl arm unequally disordered over two sites.

Key indicators

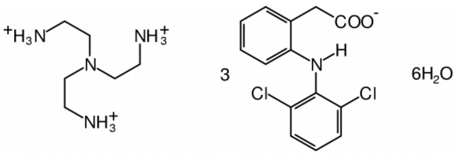
Single-crystal X-ray study
T = 150 K
Mean σ(C–C) = 0.007 Å
H-atom completeness 85%
Disorder in solvent or counterion
R factor = 0.070
wR factor = 0.222
Data-to-parameter ratio = 13.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Comment

{2-[(2,6-Dichlorophenyl)amino]phenyl}acetic acid, or diclofenac acid, was first synthesized in 1966 in the Netherlands (Calabro & Ehrlich, 1986). Diclofenac acid is most commonly used as a non-steroidal anti-inflammatory drug but also shows analgesic and antipyretic properties. The sodium salt of diclofenac acid is sold commercially as Voltaren, whereas the potassium salt is marketed as Cataflam. The molecular structure of diclofenac acid consists of a phenylacetic acid group, linked by a secondary amino group to a 2,6-dichlorophenyl group; there is the potential for maximum twist between the two rings. The dihedral angle between these rings is of great importance to the pharmacological activity of diclofenac acid. To obtain optimal activity, the two rings should be twisted as much as possible, so that the carboxylate group of the drug can bind to arachidonic acid, thus preventing the binding of the enzyme COX-2 which propagates inflammation (Castellari & Sabatino, 1994; Castellari & Ottani, 1997*b*).

A search of the April 2003 release of the Cambridge Structural Database (Allen, 2002) reveals that the crystal structure of diclofenac acid has been reported five times [Moser *et al.*, 1990; Kovala-Demertzi *et al.*, 1993; Castellari & Ottani, 1997*b* (2 polymorphic forms); Jaiboon *et al.*, 2001]. Moreover, in attempts to improve the structural characteristics of diclofenac acid, organic salts have been prepared, using small aliphatic bases, and their structures studied. Thus far, these bases include *N*-(2-hydroxyethyl)pyrrolidine (Castellari & Sabatino, 1994), *N*-(2-hydroxyethyl)piperazine, *N*-(2-hydroxyethyl)piperidine, *N*-(2-hydroxyethyl)morpholine (Castellari & Sabatino, 1996), bis(2-hydroxyethyl)amine (Castellari & Ottani, 1995), tris(2-hydroxyethyl)amine (Castellari & Sabatino, 1996), tris(2-hydroxymethyl)methylamine (Castellari & Ottani, 1997*a*), piperazine (Castellari & Ottani, 1998), diethylamine (Pomes-Hernandez *et al.*, 1997; Castellari *et al.*, 2000, 2001*a*) and pyrrolidine (Castellari *et al.*, 2001*b*). Here we report the 1:3 organic salt hexahydrate of tris(2-ethylamine)amine with diclofenac acid in an attempt to extend the use of small aliphatic bases to improve the structural characteristics of diclofenac acid.



(I)

The asymmetric unit of (I) comprises the 1:3 organic salt of tris(2-ethylamine)amine and diclofenac acid, with an approximated six water molecules (Fig. 1). Two water molecules, O1 and O2, exist as full-occupancy molecules but the remainder are all disordered with partial occupancies. Atoms O3 and O4 are associated as a disordered pair (O⋯O distances are listed in Table 1), with occupancies of 0.20 (2) and 0.50 (2), respectively. Atoms O5 and O6 are also associated as a disordered pair, each with an occupancy of 0.30 (2). Fragments O7–O13 are associated with each other and the respective occupancies are 0.70 (2), 0.20 (2), 0.30 (2), 0.50 (2), 0.50 (2), 0.30 (2) and 0.20 (2). Extensive refinement was required to determine each of these values and the total number of water molecules was determined to the nearest half-water molecule; thus, to satisfy the electron-density map there are 6.0 (5) water molecules. The three highest unassigned peaks in the difference map are greater than 0.60 e Å^{-3}; they are 0.70 e Å^{-3} at 1.17 Å from C6*A*, 0.65 e Å^{-3} at 1.55 Å from N10*A*, and 0.64 e Å^{-3} at 1.05 Å from C9*A*. Although no H atoms were located on C6*A* (or positioned geometrically), the residual peak close to C6*A* is not in a suitable position to be considered as one. Furthermore, removing the disordered fragments and calculating the void space that is left can afford a rough approximation to the number of water molecules. Thus, removal of O3–O13 leaves a void space of 482 Å^3 per unit cell; assuming 40 Å^3 per hydrogen-bonded water molecule, this corresponds to 12 full water molecules or three full molecules per asymmetric unit, giving a total of five water molecules per asymmetric unit. However, the displacement parameters for the water fragments could not sustain realistic occupancies that totalled only three full water molecules. Interestingly, two recent structures (Lynch, 2003*a*, 2003*b*), also containing tris(2-ethylamine)amine and benzoic acid derivatives, crystallized with 5.5 and four water molecules, respectively, in their asymmetric units.

The existence of ten water fragments in the hydrogen-bonding network and the difficultly involved with the assignment of H atoms to each has caused certain problems. The formal assignment of hydrogen-bonding associations is listed in Table 2, but does not include the *D*⋯*A* distances for the disordered water fragments. Atom O3 is 2.23 (3) Å from O5, 2.78 (3) Å from O6, 3.02 (3) Å from O2*D* and 3.15 (3) Å from N72*A*. Atom O4 is 2.57 (2) Å from N72*A*, 2.73 (2) Å from O5, 3.06 (2) Å from O2*C*, 3.18 (2) Å from O2*D*, and 3.24 (2) Å from O6. O5 is 2.27 (3) Å from O2*D* and 2.85 (3) Å from O1*B*. Atom O6 is 1.83 (3) Å from N71*A*, 2.65 (3) Å from O1*B* and 2.79 (3) Å from O2*D*. Atom O7 is 2.70 (2) Å from O2*B*, 2.75 (2) Å from N10*A* and 3.20 (2) Å from N71*A*. Atom O8 is 2.81 (3) Å from O11, 2.65 (3) Å from O2*B*, 2.79 (3) Å from N72*A*, 2.83 (3) Å from N71*A* and 3.23 (3) Å from N10*A*. Atom O10 is 2.99 (2) Å from O11 and 3.12 (2) Å from O2*B*. Atom O11 is 3.23 (3) Å from O13, 2.76 (2) Å from O1*C*, 3.06 (2) Å from N72*A* and 3.34 (2) Å from N4*A*. Atom O12 is 2.75 (3) Å from N72*A* and 3.18 (3) Å from O1*C*. Atom O13 is 3.03 (3) Å from O2*B*. The majority of these distances are appropriate for normal *D*—H⋯*A* associations, although

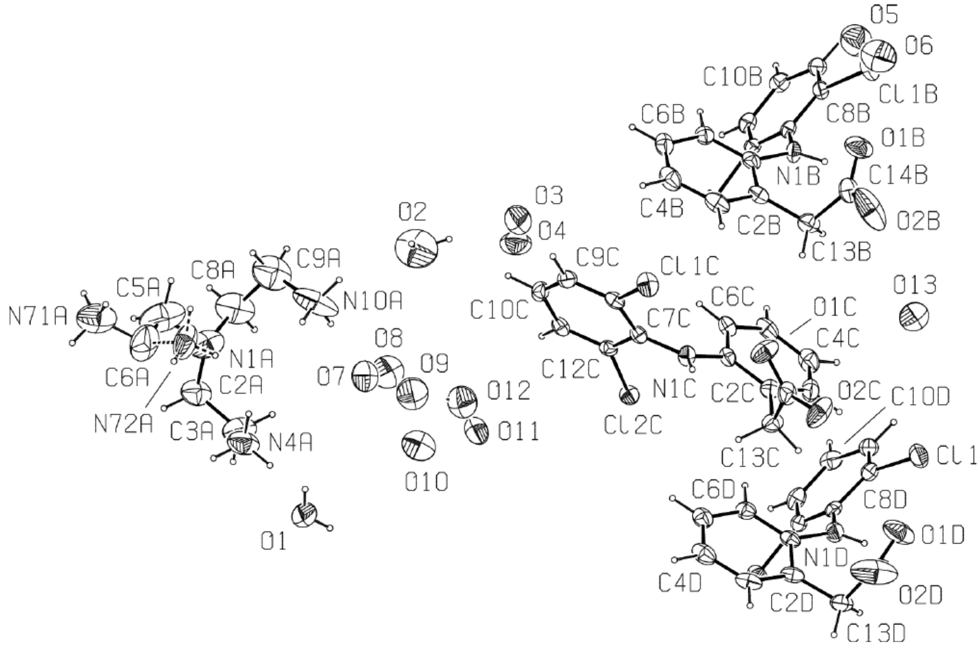


Figure 1

The asymmetric unit and atom-numbering scheme for the title compound. Displacement ellipsoids are drawn at the 50% probability level.

some are slightly short. However, the ‘problem’ distance is that between O5 and O2*D*, 2.27 (3) Å. Atom O5 has an occupancy of 0.30 (2), and is too heavy to be a partial-occupancy H atom but there does not seem to be any obvious explanation.

Disorder is also present in the base molecule, with the ammonium group of one 2-ammonioethyl arm disordered over two sites, N71*A* and N72*A*, with occupancies of 0.70 (2) and 0.30 (2), respectively. In all known structures where tris(2-ammonioethyl)amine is used as an organic base and not as a ligand, the base molecule adopts a tripod conformation, as it does when containing a metal centre. In the title structure, the tris(2-ammonioethyl)amine adopts two conformations, with the major one, occupancy = 0.70 (2), having one arm twisted away from the rest of the molecule; this contrasts with the minor conformation that adopts the standard tripod shape of previously reported structures. The dihedral angles between the two aromatic rings in the three diclofenac acid molecules are 59.57 (15)° for molecule *B*, 59.25 (14)° for molecule *C* and 58.92 (15)° for molecule *D*; these values are low compared to those in the previously reported structures of diclofenac acid (range 59–74°), including the salt structures.

Experimental

Tris(2-aminoethyl)amine and diclofenac acid (1:3 molar ratio) were refluxed in ethanol for 20 min. Total evaporation of the solvent gave colourless prisms (m.p. 422 K).

Crystal data

$C_6H_{21}N_4^{3+}\cdot 3C_{14}H_{10}Cl_2NO_2^{-}\cdot 6H_2O$
$M_r = 1142.75$
Monoclinic, $P2_1/n$
$a = 22.677$ (4) Å
$b = 9.3735$ (17) Å
$c = 26.415$ (5) Å
$\beta = 105.176$ (17)°
$V = 5419.0$ (18) Å^3
$Z = 4$

$D_x = 1.401$ Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 48 reflections
$\theta = 15$–16°
$\mu = 0.38$ mm^{-1}
$T = 150$ (2) K
Prism, colourless
0.77 × 0.58 × 0.31 mm

Data collection

Stoe Stadi-4 diffractometer
ω/*θ* scans
Absorption correction: *ψ* scan (Stoe & Cie, 1995)
$T_{\rm min} = 0.757$, $T_{\rm max} = 0.891$
9857 measured reflections
9532 independent reflections
5678 reflections with $I > 2\sigma(I)$

$R_{\rm int} = 0.025$
$\theta_{\rm max} = 25.0°$
$h = -26 \rightarrow 26$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 31$
3 standard reflections
frequency: 60 min
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.070$
$wR(F^2) = 0.222$
$S = 1.02$
9532 reflections
734 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.1165P)^2 + 6.6139P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.70$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.50$ e Å^{-3}

Table 1
Selected geometric parameters (Å).

O3—O4	0.65 (3)	O9—O10	1.691 (19)
O5—O6	0.84 (2)	O9—O13	1.69 (3)
O7—O8	0.72 (3)	O9—O12	1.58 (2)
O7—O9	1.480 (17)	O10—O13	0.77 (2)
O8—O9	1.40 (3)	O11—O12	1.069 (17)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4*A*—H41*A*···O2*C*$^{\rm i}$	0.91	1.99	2.841 (6)	156
N4*A*—H42*A*···O1	0.91	2.05	2.845 (6)	145
N4*A*—H43*A*···O1$^{\rm ii}$	0.91	1.97	2.876 (7)	174
N71*A*—H71*A*···O2*D*$^{\rm iii}$	0.91	1.80	2.692 (9)	166
N71*A*—H72*A*···O2$^{\rm iv}$	0.91	1.90	2.785 (10)	163
N71*A*—H73*A*···O1*B*$^{\rm v}$	0.91	2.13	2.999 (11)	161
N72*A*—H74*A*···O2*C*$^{\rm i}$	0.91	1.90	2.758 (17)	156
N72*A*—H75*A*···O8$^{\rm iv}$	0.91	2.00	2.79 (4)	145
N72*A*—H75*A*···O12$^{\rm iv}$	0.91	1.95	2.75 (3)	146
N72*A*—H75*A*···O11$^{\rm iv}$	0.91	2.44	3.06 (2)	125
N72*A*—H75*A*···O9$^{\rm iv}$	0.91	2.60	3.50 (3)	177
N72*A*—H76*A*···O4$^{\rm iv}$	0.91	1.79	2.57 (2)	141
N72*A*—H76*A*···O2$^{\rm iv}$	0.91	2.19	2.816 (18)	125
N72*A*—H76*A*···O3$^{\rm iv}$	0.91	2.32	3.15 (3)	152
N10*A*—H11*A*···O2*C*$^{\rm i}$	0.91	1.92	2.816 (6)	169
N10*A*—H12*A*···O1*D*$^{\rm i}$	0.91	2.03	2.932 (7)	172
N10*A*—H12*A*···O2*D*$^{\rm i}$	0.91	2.30	2.935 (7)	126
N10*A*—H13*A*···O7	0.91	1.86	2.751 (10)	167
N10*A*—H13*A*···O8	0.91	2.34	3.23 (3)	167
N1*B*—H1*B*···O1*B*	0.88	2.37	2.961 (5)	124
N1*C*—H1*C*···O1*C*	0.88	2.30	2.872 (5)	123
N1*D*—H1*D*···O1*D*	0.88	2.32	2.941 (5)	128
O1—H11···O1*C*$^{\rm i}$	0.817	1.909	2.726 (6)	179
O1—H12···O2*B*$^{\rm i}$	0.820	1.878	2.698 (6)	179
O2—H21···O3	0.894	2.13	2.92 (3)	146
O2—H21···O4	0.894	2.212	2.863 (13)	129
O2—H22···O1*D*$^{\rm i}$	0.826	1.906	2.732 (7)	179

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

All amine H atoms were initially located in difference syntheses, but were then included in the refinement (along with all non-water H atoms), at calculated positions, in the riding-model approximation, with N—H set to 0.88 Å (NH) and 0.91 Å (NH_3^+), and C—H set to 0.99 Å (CH_2) and 0.95 Å (Ar–H). The isotropic displacement parameters were set equal to $1.25U_{\rm eq}$ of the carrier atom. The H atoms for O1 and O2 were included in the refinement at calculated positions, while the isotropic displacement parameters were set equal to $1.25U_{\rm eq}$(O). No H atoms on C6*A* or any of the water fragments (O3–O13) were either located or positioned geometrically. Poor crystal quality restricted the measured data to only 94% of the possible total.

Data collection: *DIF*4 (Stoe & Cie, 1990); cell refinement: *DIF*4; data reduction: *REDU*4 (Stoe & Cie, 1990); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON*97 (Spek, 1997); software used to prepare material for publication: *SHELXL*97.

The authors thank the EPSRC Chemical Database Service at Daresbury (Fletcher *et al.*, 1996).

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Calabro, J. J. & Ehrlich, G. E. (1986). *Am. J. Med. Suppl.* **4**B, 80.

o1316 Daniel E. Lynch *et al.* • $C_6H_{21}N_4^{3+}\cdot 3C_{14}h_{10}cl_2no_2^{-}\cdot 6h_2o$ *Acta Cryst.* (2003). E**59**, o1314–o1317

Castellari, C., Comelli, F. & Ottani, S. (2000). Private communication to the Cambridge Structural Database. Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, England.

Castellari, C., Comelli, F. & Ottani, S. (2001*a*). *Acta Cryst.* C**57**, 437–438.

Castellari, C., Comelli, F. & Ottani, S. (2001*b*). *Acta Cryst.* C**57**, 1182–1183.

Castellari, C. & Ottani, S. (1995). *Acta Cryst.* C**51**, 2612–2615.

Castellari, C. & Ottani, S. (1997*a*). *Acta Cryst.* C**53**, 482–486.

Castellari, C. & Ottani, S. (1997*b*). *Acta Cryst.* C**53**, 794–797.

Castellari, C. & Ottani, S. (1998). *Acta Cryst.* C**54**, 415–417.

Castellari, C. & Sabatino, P. (1994). *Acta Cryst.* C**50**, 1723–1726.

Castellari, C. & Sabatino, P. (1996). *Acta Cryst.* C**52**, 1708–1712.

Fletcher, D. A., McMeeking, R. F. & Parkin, D. (1996). *J. Chem. Inf. Comput. Sci.* **36**, 746–749.

Jaiboon, N., Yos-In, K., Ruangchaithaweesuk, S., Chaichit, N., Thutivoranath, R., Siritaedmukul, K. & Hannongbua, S. (2001). *Anal. Sci.* **17**, 1465–1466.

Kovala-Demertzi, D., Mentzafos, D. & Terzis, A. (1993). *Polyhedron*, **12**, 1361–1370.

Lynch, D. E. (2003*a*). *Acta Cryst.* E**59**, o1076–o1078.

Lynch, D. E. (2003*b*). *Acta Cryst.* E**59**, o1157–o1158.

Moser, P., Sallmann, A. & Wiesenberg, I. (1990). *J. Med. Chem.* **33**, 2358–2368.

Pomes-Hernandez, R., Duque-Rodriguez, J., Novoa-de-Armas, H. & Toscano, R. A. (1997). *Z. Kristallogr.* **212**, 61–62.

Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.

Spek, A. L. (1997). *PLATON*97. University of Utrecht, The Netherlands.

Stoe & Cie (1990). *DIF*4 and *REDU*4. Stoe & Cie, Darmstadt, Germany.

Stoe & Cie (1995). *X-SHAPE*. Stoe & Cie, Darmstadt, Germany.