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Unusual hydrate stabilization in the two-dimensional layered structure of quinacrinium bis(2-carboxy-4,5-dichlorobenzoate) tetrahydrate, a proton-transfer compound of the drug quinacrine

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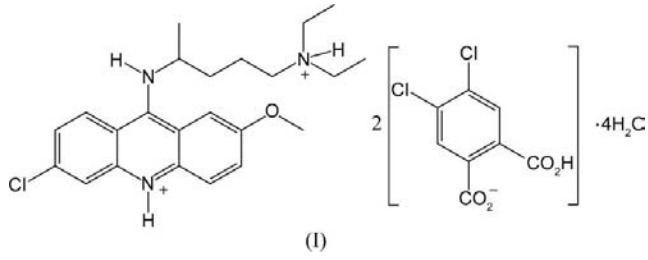
The crystal structure of the hydrated proton-transfer compound of the drug quinacrine [*rac*-*N*′-(6-chloro-2-methoxyacridin-9-yl)-*N*,*N*-diethylpentane-1,4-diamine] with 4,5-dichlorophthalic acid, $C_{23}H_{32}ClN_3O^{2+}\cdot 2C_8H_3Cl_2O_4^{-}\cdot 4H_2O$, has been determined at 200 K. The four labile water molecules of solvation in the structure form discrete $\cdots$O—H$\cdots$O—H$\cdots$ hydrogen-bonded chains parallel to the quinacrine side chain, the two N—H groups of which act as hydrogen-bond donors for two of the water acceptor molecules. The other water molecules, as well as the acridinium H atom, also form hydrogen bonds with the two anion species and extend the structure into two-dimensional sheets. Between these sheets there are also weak cation–anion and anion–anion π–π aromatic ring interactions. This structure represents the third example of a simple quinacrine derivative for which structural data are available but differs from the other two in that it is unstable in the X-ray beam due to efflorescence, probably associated with the destruction of the unusual four-membered water chain structures.

Comment

Quinacrine [*rac*-*N*′-(6-chloro-2-methoxyacridin-9-yl)-*N*,*N*-diethylpentane-1,4-diamine] is a substituted acridine which, as the dihydrochloride dihydrate, briefly found use as the antimalarial drug atabrine (or mepacrine). More recently, it has been used as an experimental drug for a number of other medical conditions which have been described previously (Smith & Wermuth, 2008). The crystal structures of racemic atabrine (Courseille *et al.*, 1973) and, more recently, racemic quinacrinium 5-sulfosalicylate dihydrate (Smith & Wermuth, 2008), represent the only two simple quinacrine salt structures which have been reported to date. In both of these compounds, the quinacrinium dication is protonated at the hetero N atom (N10) of the acridine ring and at the terminal tertiary N atom of the C9 side chain (N141). Hydrogen-bonding interactions involving these centres, the anion species and the solvent water molecules provide three-dimensional structures which form stable crystalline solids with relatively high melting points (*ca* 523 K). Interactive aromatic cation–cation π–π stacking effects are found in the dichloride but not in the 5-sulfosalicylate (5-SSA salt). Weak π–π interactions are also found in the crystal structure of the *Trypanosoma cruzi* trypanothione reductase (TR) complex with quinacrine (Jacobi *et al.*, 1996). The TR complex shows that specific sites on the acridine ring system (the hetero N, the C2 methoxy O and the C6 chloro substituent groups) and the two amino groups of the substituent side chain at C9 are fixed at the active sites of the TR enzyme.

The halogenated phthalic acid 4,5-dichlorophthalic acid (DCPA) has proved very effective in the stabilization of crystalline aromatic amine salts, particularly as the acid phthalates, and we have determined a number of these structures (Smith *et al.*, 2008*a*,*b*, 2009). Using this acid and the same experimental conditions and solvent system (aqueous ethanol) as employed in the preparation of the 5-SSA salt, we obtained apparently good crystals of the title DCPA salt, racemic quinacrinium bis(2-carboxy-4,5-dichlorobenzoate) tetrahydrate, (I), which were stable in a closed container but quickly underwent decomposition with efflorescence in the X-ray beam at room temperature. Diffraction data were therefore collected at 200 K from a specimen immersed in an oil drop. These crystal characteristics contrast with the hydrated dichloride and 5-SSA salts, which are chemically stable with relatively high melting points of *ca* 523 K, *cf.* 343 K for (I), the structure of which we report here.



(I)

As expected, the quinacrine molecule of (I) is protonated at both the acridine hetero N atom (N10) and the terminal tertiary diethylamino N atom (N141) (Fig. 1). The four solvent water molecules form discrete $\cdots$O—H$\cdots$O—H$\cdots$ associated hydrogen-bonded chains, with two of these (O1*W* and O2*W*) also acting as acceptors for the two N—H groups of the quinacrine side chain (Table 1). These water chains are parallel to the side chains and also form hydrogen-bonding associations with the carboxyl O-atom acceptors of the two DCPA anions (Fig. 1). These interactions and an acridinium N—H$\cdots$$O_{carboxyl}$ hydrogen bond result in a two-dimensional layered structure (Fig. 2), which is also found in the structures of quinacrinium dichloride dihydrate (Courseille *et al.*, 1973)

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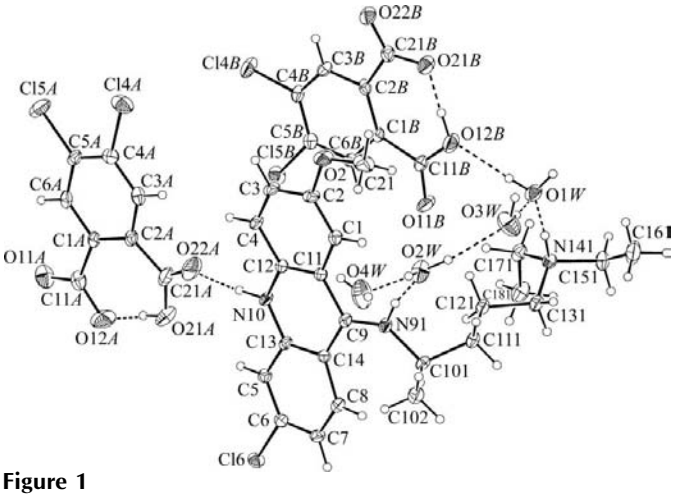

Figure 1
The molecular conformation and atom-numbering scheme for the quinacrine dication, the two DCPA anions (*A* and *B*) and the four solvent water molecules of (I). Displacement ellipsoids are drawn at the 40% probability level and H atoms are shown as small spheres of arbitrary radii. Hydrogen-bonding associations are shown as dashed lines.

and the 5-SSA dihydrate salt (Smith & Wermuth, 2008). In the 5-SSA salt, the two side-chain N—H groups also act as donors for the two discrete water molecules, whereas in the dichloride only one of the water molecules is associated directly with a quinacrine N atom, the other being involved in interactions with the chloride anions. Conformationally all three structures are similar, with the C91 side chains, not unexpectedly, adopting perpendicular attitudes with respect to the acridine ring.

In the structure of (I), there are also weak cation–anion and anion–anion aromatic ring π–π interactions, with minimum centroid separations for the six-membered N10/C12/C11/C9/C14/C13 and C1–C4/C12/C11 acridine rings from the C1*A*–C6*A* anion ring of 3.599 (3) and 3.686 (3) Å, respectively, and for the C1*A*–C6*A* anion ring from the C1*B*–C6*B* anion ring of 3.693 (3) Å. These π–π associations are present in the structure of the dichloride but are absent in the 5-SSA salt. In addition, there is a short acridine Cl$\cdots$O$_{carboxyl}$ association [Cl6$\cdots$O11*B*^{v} = 3.205 (4) Å; symmetry code: (v) $-x+1, -y+1, -z+2$], similar to the values of 3.2279 (14) and 3.1582 (15) Å observed in the structures of DCPA salts with 3-aminobenzoic acid (Smith *et al.*, 2008*b*) and nicotinamide (Smith *et al.*, 2009), respectively. However, no intermolecular DCPA Cl$\cdots$Cl interactions, such as are present in a number of DCPA structures (Smith *et al.*, 2009), are found in (I).

The DCPA anion species in (I) (*A* and *B*) are conformationally similar and are essentially planar [torsion angle C2—C1—C11—O11 = 177.1 (5)° for species *A* and 178.5 (4)° for species *B*, and C1—C2—C21—O22 = −172.5 (5)° for *A* and −174.3 (4)° for *B*]. The planarity is maintained by the presence of short intramolecular carboxyl–carboxylate O—H$\cdots$O hydrogen bonds (Table 1, entries 4 and 5). This planar species, rather than the nonplanar one, is typically found in the acid salts of DCPA (Smith *et al.*, 2008*a*,*b*, 2009).

From the structure of (I) it may be concluded that the inherent physical instability in the X-ray beam compared with the stable dihydrochloride dihydrate and 5-SSA salts may be attributed to the somewhat more fragile tetrahydrate chain structure. This is also reflected in the significantly lower melting point of (I) compared with the other two compounds. However, such properties would not preclude the possibility that compound (I) might be used as an alternative to atabrine as a drug.

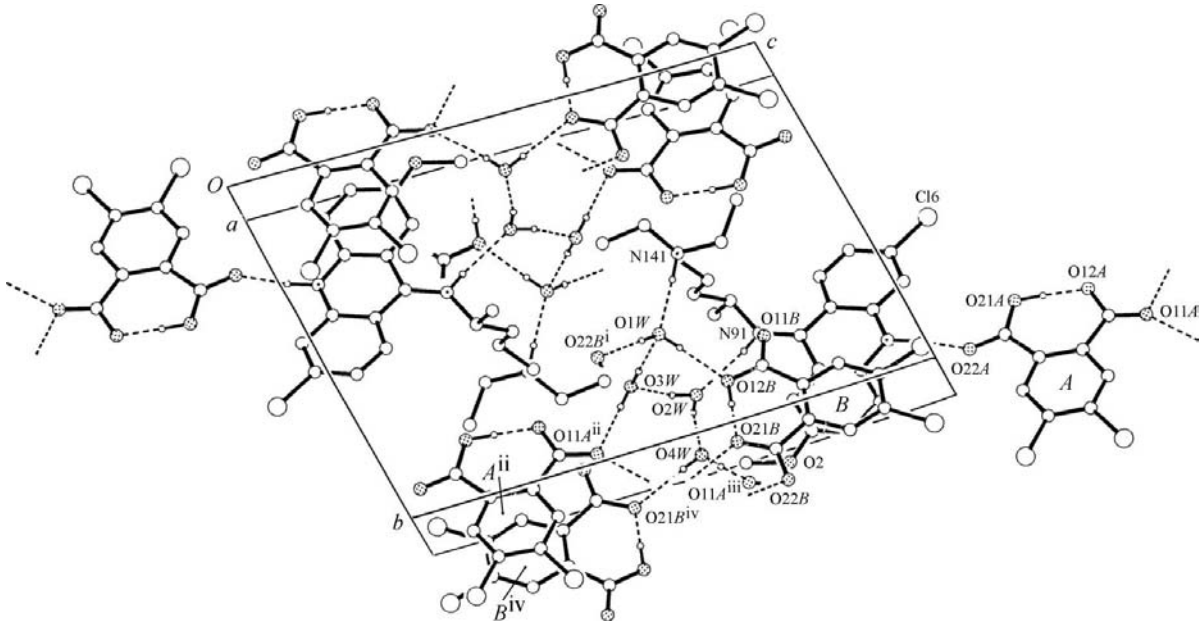

Figure 2
Hydrogen-bonding extensions in the two-dimensional structure of (I), shown in a perspective view down the approximate *a*-axis direction of the unit cell. *A* and *B* represent the two DCPA anion species. H atoms not involved in the interactions shown have been omitted. See Table 1 for symmetry codes.

Experimental

The title compound was synthesized by heating together under reflux for 10 min quinacrinium dichloride dihydrate (atabrine or mepacrine; O'Neil, 2001) (1 mmol) and 4,5-dichlorophthalic acid (DCPA) (1 mmol) in 50% ethanol–water (50 ml). After concentration to *ca* 30 ml, partial room-temperature evaporation of the hot-filtered solution gave pale-yellow prisms of (I) (m.p. 343 K) which, although chemically stable in a closed container, rapidly effloresced in the X-ray beam. This necessitated the use of low-temperature (200 K) collection of X-ray data from a crystal immersed in a silicone oil drop.

Crystal data

$C_{23}H_{32}ClN_3O^{2+}\cdot 2C_8H_3Cl_2O_4^-\cdot 4H_2O$
M_r = 942.04
Triclinic, $P\overline{1}$
a = 10.6392 (6) Å
b = 11.6737 (5) Å
c = 18.2030 (12) Å
α = 77.961 (5)°
β = 89.549 (5)°
γ = 76.432 (5)°
V = 2147.4 (2) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.41 mm^{-1}
T = 200 K
0.20 × 0.20 × 0.15 mm

Data collection

Oxford Diffraction Gemini-S CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.909, T_{max} = 0.948
14440 measured reflections
7444 independent reflections
4778 reflections with $I > 2\sigma(I)$
R_{int} = 0.057

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.078
$wR(F^2)$ = 0.195
S = 1.01
7444 reflections
593 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.70 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}

H atoms potentially involved in hydrogen-bonding interactions were located by difference methods and their positional and isotropic displacement parameters were refined. Other H atoms were included in the refinement at calculated positions and treated as riding atoms, with C—H = 0.93 Å (aromatic) and 0.96 or 0.97 Å (aliphatic), and with U_{iso}(H) = 1.2U_{eq}(C). All collected data were used in the refinement. The data set is missing 313 unique reflections which were inaccessible because of instrumental limitations.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *PLATON*.

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

D—H···A	D—H	H···A	D···A	D—H···A
N10—H10···O22*A*	1.00 (5)	1.73 (5)	2.716 (6)	172 (5)
N91—H91···O2*W*	0.85 (5)	2.10 (5)	2.905 (5)	158 (5)
N141—H141···O1*W*	0.91 (5)	1.83 (5)	2.733 (5)	169 (4)
O21*A*—H21*A*···O12*A*	0.92 (5)	1.45 (5)	2.366 (7)	172 (6)
O12*B*—H12*B*···O21*B*	0.91 (6)	1.47 (6)	2.378 (5)	180 (8)
O1*W*—H11*W*···O12*B*	0.81 (6)	1.91 (6)	2.722 (5)	179 (9)
O1*W*—H12*W*···O22*B*^{i}	0.79 (6)	1.91 (6)	2.702 (5)	179 (9)
O2*W*—H21*W*···O3*W*	0.88 (5)	1.97 (5)	2.809 (5)	160 (4)
O2*W*—H22*W*···O4*W*	0.76 (6)	2.06 (6)	2.804 (6)	164 (5)
O3*W*—H31*W*···O11*A*^{ii}	0.83 (7)	2.22 (7)	3.031 (6)	168 (6)
O3*W*—H32*W*···O1*W*	0.84 (6)	2.07 (6)	2.913 (5)	179 (8)
O4*W*—H41*W*···O11*A*^{iii}	0.76 (7)	2.08 (7)	2.842 (6)	175 (8)
O4*W*—H42*W*···O21*B*^{iv}	0.81 (7)	2.20 (7)	3.009 (5)	179 (8)

Symmetry codes: (i) $-x, -y+2, -z+1$; (ii) $x, y, z-1$; (iii) $-x+1, -y+2, -z+2$; (iv) $-x+1, -y+2, -z+1$.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3117). Services for accessing these data are described at the back of the journal.

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