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The three-dimensional hydrogen-bonded framework structure in the 1:1 proton-transfer compound of the drug quinacrine with 5-sulfosalicylic acid

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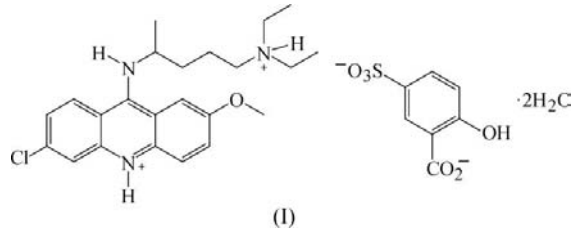
For the hydrated proton-transfer compound 6-chloro-9-[(4-diethylammonio-2-methylbutyl)amino]-2-methoxyacridinium 3-carboxylato-4-hydroxybenzenesulfonate dihydrate, $C_{23}H_{32}ClN_3O^{2+}\cdot C_7H_4O_6S^{2-}\cdot 2H_2O$, (I), the conformational features, specifically those of the extended side chain at the 9-position of the acridine parent, have been compared with those of quinacrinium dichloride dihydrate (the drug atabrine or mepacrine). Racemic compound (I) has a three-dimensional hydrogen-bonded framework structure similar to atabrine but also involves the water molecules and both the carboxylate and sulfonate groups of the anion in structure extension. The comparable conformational features found in this uncommon derivative of quinacrine indicate that (I) has potential as a possible pharmaceutical substitute for atabrine.

Comment

Quinacrine [*N*′-(6-chloro-2-methoxyacridin-9-yl)-*N*,*N*-diethylpentane-1,4-diamine] was first synthesized in 1931 at Bayer–I. G. Farben (Mietzsch & Mauss, 1934) and, as the dihydrochloride dihydrate (atabrine or mepacrine), introduced as a drug which was the first alternative to quinine for the treatment of malaria (Mauss & Mietzsch, 1934) and other parasite-borne diseases (*e.g.* Chaga's disease, giardiasis). Its use in the treatment of malaria has largely been superceded by chloroquine, which has fewer of the undesirable adverse physiological side effects of quinacrine, *e.g.* aplastic anaemia and hyperpigmentation (Wilson *et al.*, 1991). However, its more recent experimental and sometimes controversial uses include the possible treatment of Creutzfeldt–Jacob disease, where it has been found to inhibit the accumulation of pathogenic prion protein in cultured neuroblastoma cells (Doh-Ura *et al.*, 2000), and for nonsurgical female sterilization (Zipper *et al.*, 1980). The crystal structure of the *Trypanosoma cruzi* trypanothione reducatase (TR) complex with quinacrine (Jacobi *et al.*, 1996) showed that specific sites on the acridine ring system (the hetero N, C2 methoxy O and C6 chloro substituent groups), as well as the two amino groups of the C9 substituent side chain, are fixed at active sites of the TR enzyme.

The crystal structure of racemic atabrine (quinacrine dihydrochloride dihydrate; Courseille *et al.*, 1973) showed the molecule to be protonated at the N atom of the acridine ring and at the tertiary terminal N atom of the C9 side chain. In addition, the acridine ring systems showed interactive π–π stacking effects. Considering the difficulty in obtaining good crystals of atabrine, we have prepared the salts of this base with the strong aromatic organic acids 3,5-dinitrosalicylic acid (DNSA) and 3-carboxy-4-hydroxybenzenesulfonic acid (5-sulfosalicylic acid, 5-SSA) for the purpose of crystallographic examination. This approach has been used previously by us and other research groups with reasonable success since these acids, particularly when used in their anionic forms, are recognized as useful synthons for molecular assembly achieved through hydrogen-bonding interactions involving potentially all interactive substituent functional groups. The method allows the structures of difficult-to-crystallize Lewis base compounds, such as many pharmaceuticals, to be determined.

The crystal structures have been reported of the 1:1 salts of 5-SSA with theophylline (a monohydrate; Madarasz *et al.*, 2002), trimethoprim (a dihydrate; Raj *et al.*, 2003), and pyrimethamine (Hemamalini *et al.*, 2005) and brucine (Smith, Wermuth, Healy & White, 2006) (both anhydrates). With DNSA, the structures of 1:1 anhydrous salts with both brucine (Smith, Wermuth, Healy & White, 2006) and strychnine (Smith *et al.*, 2005) are also known. With the 5-SSA anions formed in the reaction of the acid with Lewis bases, all of the substituent groups provide hydrogen-bonding donor or acceptor atoms with potential for both primary and secondary structure extension. In some examples, particularly those salts with polycyclic heteroaromatic amines (Smith, Wermuth & White, 2004), the structures feature anion–anion or anion–cation π–π interactions. We obtained good crystals of the atabrine salt with 5-SSA from an aqueous ethanol solution but not with the DNSA salt prepared under similar conditions.



(I)

The crystal structure of the 5-SSA salt reported here is that of racemic quinacrinium 5-sulfosalicylate dihydrate, (I). The quinacrine molecule is protonated at both the acridine N (N10) and the terminal tertiary diethylamino N atom (N141), while generating a 5-SSA dianion by deprotonation of both the sulfonic acid and carboxylic acid groups. Dianionic 5-SSA anions are not common among the known structures in the crystallographic literature but some are known, *e.g.* the salts

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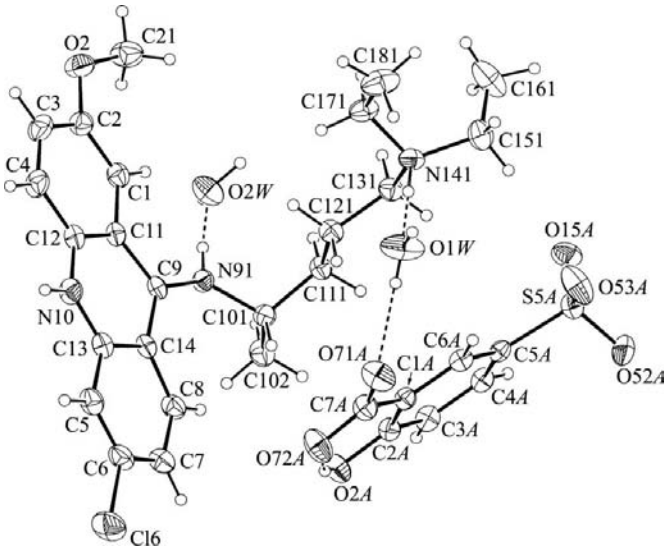

Figure 1
The molecular conformation and atom-numbering scheme for the quinacrine dication, the 5-sulfosalicylate dianion and the two solvent water molecules in (I). Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary size. Inter-species hydrogen-bonding associations are shown as dashed lines.

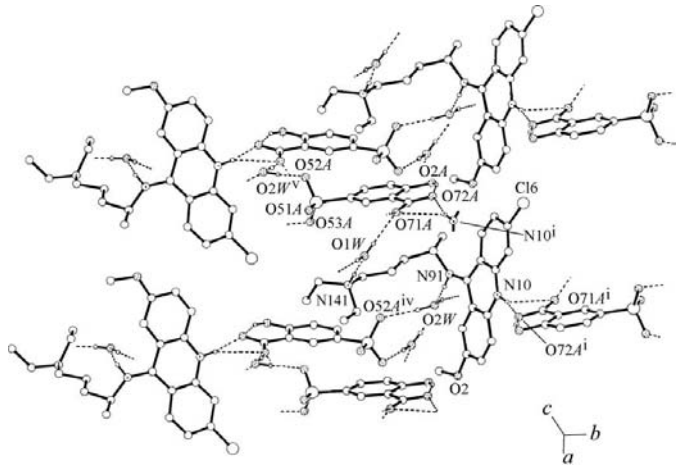

Figure 2
Hydrogen-bonding extensions in the structure of (I), shown in a partial view down the approximate *c* axial direction. [Symmetry code: (v) $x-\frac{1}{2}$, $-y+\frac{3}{2}$, $z+\frac{1}{2}$; for other symmetry codes, see Table 1.]

with guanidine (Smith, Wermuth & Healy, 2004), benzylamine (Smith, Wermuth & Healy, 2006), 2-aminopyridine (Yang & Qu, 2006) and piperazine (Su & Li, 2007).

In the asymmetric unit of (I) (Fig. 1), the dication has primary hydrogen-bonding interactions involving the protonated tertiary amine N atom (N141) and one of the water molecules (O1*W*), as well as the secondary amine N atom (N91) and the second water molecule (O2*W*), while the H atom of the acridinium N atom is involved in secondary interactions with a carboxyl group of the 5-SSA dianion [cyclic three-centre asymmetric, graph set $R_1^2(4)$ (Etter *et al.*, 1990)] (Table 1). Other secondary inter-species hydrogen bonds generate a three-dimensional framework structure (Fig. 2), which is also found in the structure of quinacrinium chloride dihydrate (Courseille *et al.*, 1973). However, in that structure, the acridinium H atom has a primary interaction with one of the chloride anions, which is in turn associated with the solvent water molecules in structure extension. Conformationally the two structures are similar, with the C91 side chain adopting a comparable perpendicular attitude with respect to the acridine ring (Table 2), which is also the case in the structures of other C9 extended-chain-substituted 6-chloro-2-methoxyacridines, *e.g.* in the antitumour acridine analogues (Berman & Glusker, 1972; Carrell, 1972; Glusker *et al.*, 1972). The only major difference between (I) and the dichloride is found, not unexpectedly, within the terminal diethylamino group. Also, in (I), there are no cation–cation or cation–anion aromatic ring π–π interactions, which are present in the structure of the hydrochloride [minimum centroid separation of the inversion-related six-membered rings N10/C9/C12–C13 and (C5–C8/C13/C14)^{ii} = 4.1834 (13) Å; symmetry code: (ii) $x+\frac{1}{2}$, $-y+\frac{3}{2}$, $z+\frac{1}{2}$].

With the 5-SSA anion species for (I), similar structural and conformational features to those previously observed (Smith, Wermuth & White, 2004) are found. The usual intramolecular phenol–carboxyl O—H···O hydrogen bond is found [series range 2.598 (3)–2.625 (2) Å], giving essentially coplanarity of the carboxyl group and the benzene ring [torsion angle C2—C1—C7—O71 = −175.0 (2)°]. In addition, the common aromatic–sulfonate C6*A*—H6*A*···O52*A* interaction [2.879 (2) Å] is present. It may be concluded that the chemically stable and structurally similar 5-sulfosalicylate salt of quinacrine, (I), could be considered a possible alternative to atabrine as a drug.

Experimental

The title compound was synthesized by heating together 1 mmol quantities of quinacrium dichloride dihydrate (atabrine or mepacrine) (O'Neil, 2001) and 3-carboxy-4-hydroxybenzenesulfonic acid (5-sulfosalicylic acid = 5-SSA) in 50% ethanol–water (50 ml) under reflux for 10 min. After concentration to *ca* 30 ml, partial room-temperature evaporation of the hot-filtered solution gave yellow block-shaped crystals of (I) (m.p. 523 K).

Crystal data

$C_{23}H_{32}ClN_3O^{2+}\cdot C_7H_4O_6S^{2-}\cdot 2H_2O$
M_r = 654.17
Monoclinic, $P2_1/n$
a = 10.1753 (3) Å
b = 30.8461 (7) Å
c = 10.3671 (2) Å
β = 99.966 (3)°
V = 3204.81 (14) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.24 mm^{-1}
T = 297 (2) K
0.20 × 0.20 × 0.15 mm

Data collection

Oxford Diffraction Gemini-S Ultra CCD detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.906, T_{max} = 0.960
29865 measured reflections
5455 independent reflections
3568 reflections with $I > 2\sigma(I)$
R_{int} = 0.049

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

D—H···A	D—H	H···A	D···A	D—H···A
O2A—H2A···O72A	0.92 (3)	1.69 (3)	2.554 (2)	156 (3)
N10—H10···O71A^{i}	0.90 (3)	2.49 (2)	3.178 (2)	134 (2)
N10—H10···O72A^{i}	0.90 (3)	1.94 (3)	2.825 (3)	168 (2)
N91—H91···O2W	0.90 (2)	2.00 (2)	2.869 (2)	163.6 (19)
N141—H141···O1W	0.91 (2)	1.80 (2)	2.700 (3)	173.3 (19)
O1W—H11W···O71A	0.77 (3)	1.97 (3)	2.740 (3)	179 (3)
O1W—H12W···O51A^{ii}	0.83 (3)	1.95 (3)	2.770 (3)	172 (3)
O2W—H21W···O71A^{iii}	0.89 (3)	1.88 (3)	2.759 (2)	170 (3)
O2W—H22W···O52A^{iv}	0.88 (3)	1.87 (3)	2.744 (2)	175 (3)

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

Table 2
Comparison of torsion angles (°) within the C9 side chain for (I) and quinacrinium dichloride dihydrate, (II) (Courseille *et al.*, 1973).

Torsion angle (°)	(I)	(II)
C11—C9—N91—C101	157.06 (19)	174.4 (5)
C9—N91—C101—C111	−125.0 (2)	−142.9 (6)
N91—C101—C111—C121	62.6 (2)	64.4 (5)
C101—C111—C121—C131	175.79 (16)	172.8 (4)
C111—C121—C131—N141	−170.13 (16)	−165.3 (4)
C121—C131—N141—C151	163.03 (18)	64.7 (5)
C121—C131—N141—C171	−67.9 (2)	−66.1 (6)
C131—N141—C151—C161	67.4 (2)	55.7 (8)
C131—N141—C171—C181	175.61 (19)	−147.1 (8)

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.100$
$S = 0.99$
5455 reflections
433 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.26$ e Å^{-3}
$\Delta\rho_{min} = -0.26$ e Å^{-3}

H atoms potentially involved in hydrogen-bonding interactions (aminium, carboxyl, phenol and water) 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 as riding atoms, with aromatic C—H = 0.93 Å and aliphatic C—H = 0.96 or 0.97 Å, and with U_{iso}(H) = 1.2U_{eq}(C).

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3093). Services for accessing these data are described at the back of the journal.

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
Berman, H. M. & Glusker, J. P. (1972). *Acta Cryst.* B**28**, 590–596.
Carrell, H. L. (1972). *Acta Cryst.* B**28**, 1754–1759.
Courseille, C., Busetta, B. & Hospital, M. (1973). *Acta Cryst.* B**29**, 2349–2355.
Doh-Ura, K., Iwaki, T. & Caughey, B. (2000). *J. Virol.* **74**, 4894–4897.
Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* B**46**, 256–262.
Glusker, J. P., Minkin, J. A. & Orehowsky, W. (1972). *Acta Cryst.* B**28**, 1–8.
Hemamalini, M., Muthiah, P. T., Sridhar, B. & Rajaram, R. K. (2005). *Acta Cryst.* E**61**, o1480–o1482.
Jacobi, E. M., Schlichting, I., Lantwin, C. B., Kabsch, W. & Krauth-Siegel, R. L. (1996). *Proteins Struct. Funct. Genet.* **24**, 73–80.
Madarasz, J., Bombicz, P., Jarmi, K., Ban, M., Pokol, G. & Gal, S. (2002). *J. Therm. Anal. Calorim.* **69**, 281–290.
Mauss, H. & Mietzsch, F. (1933). *Klin. Wochenschr.* **12**, 1276–1278.
Mietzsch, F. & Mauss, H. (1934). *Angew. Chem.* **47**, 633–636.
O'Neil, M. J. (2001). Editor. *The Merck Index*, 13th ed., p. 1440. Whitehouse Station, New Jersey: Merck & Co.
Oxford Diffraction (2008). *CrysAlis CCD* and *CrysAlis RED*. Versions 1.171.32.15. Oxford Diffraction, Abingdon, England.
Raj, S. B., Sethuraman, V., Francis, S., Hemamalini, M., Muthiah, P. T., Bocelli, G., Cantoni, A., Rychlewska, U. & Warzajtis, B. (2003). *CrystEngComm*, **5**, 70–76.
Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Smith, G., Wermuth, U. D. & Healy, P. C. (2004). *Acta Cryst.* E**60**, o687–o689.
Smith, G., Wermuth, U. D. & Healy, P. C. (2006). *Acta Cryst.* E**62**, o1863–o1865.
Smith, G., Wermuth, U. D., Healy, P. C. & White, J. M. (2006). *Aust. J. Chem.* **59**, 320–328.
Smith, G., Wermuth, U. D. & White, J. M. (2004). *Acta Cryst.* C**60**, o575–o581.
Smith, G., Wermuth, U. D. & White, J. M. (2005). *Acta Cryst.* C**61**, o464–o468.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Su, K.-M. & Li, Z.-H. (2007). *Acta Cryst.* E**63**, o4816.
Wilson, J. D., Braunwald, E., Isselbacher, K. J., Petersdorf, R. G., Martin, J. B., Fauci, A. S. & Root, R. K. (1991). *Harrison's Principles of Internal Medicine*, 12th ed., p. 803. New York: McGraw–Hill.
Yang, D.-J. & Qu, S.-H. (2006). *Acta Cryst.* E**62**, o5127–o5129.
Zipper, J., Cole, L. P., Goldsmith, A., Wheeler, R. & Rivera, M. (1980). *Asia Oceania J. Obstet. Gynaecol.* **18**, 275–290.