organic papers

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Key indicators

Powder X-ray study
T = 298 K
Mean σ(C–C) = 0.008 Å
R factor = 0.037
wR factor = 0.047
Data-to-parameter ratio = 0.0

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

Amodiaquinium dichloride dihydrate from laboratory powder diffraction data

The title compound (systematic name: {5-[(7-chloro-quinolinium-4-yl)amino]-2-hydroxybenzyl}dimethyl-ammonium dichloride dihydrate), $C_{20}H_{24}ClN_3O^{2+}\cdot 2Cl^- \cdot 2H_2O$, has one amodiaquinium dication, two Cl^- anions and two water molecules in the asymmetric unit. The crystal structure was solved by simulated annealing from laboratory X-ray powder diffraction data, with data collected at room temperature. Rietveld refinement of this model led to a final R_{wp} of 0.047 to 1.79 Å resolution. A three-dimensional network of hydrogen bonding links the amodiaquinium cations *via* water molecules and Cl^- ions.

Comment

Amodiaquine, 4-[(7-chloro-4-quinolinyl)amino]-2-[(diethyl-amino)methyl]phenol, is an antimalarial drug (Olliaro & Mussano, 2003), often formulated as a dihydrochloride salt. This salt is known to exist in anhydrous, monohydrate and dihydrate forms. The crystal structure of the monohydrate form has been reported by Yennawar & Viswamitra (1991). Here, the crystal structure of the dihydrate form, (I), is reported and compared with that of the monohydrate.

(I)
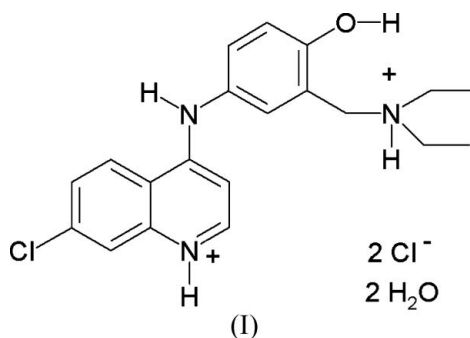
The asymmetric unit of the dihydrate structure is shown in Fig. 1. It was assumed that the same N atoms were protonated on hydrochloride salt formation as in the monohydrate form (see *Experimental*). Yennawar & Viswamitra (1991) found that the bonds that link the benzene and quinoline units through an N atom show strong double-bond character, as indicated by short C—N bond lengths and close-to-planar C—C—N—C torsion angles (Table 2). A search of the Cambridge Structural Database (CSD, Version 5.27; Allen, 2002) was performed in order to determine typical values for these parameters. The average C_{ar}—NH bond length was found to be *ca* 1.39 (3) Å and the distribution of the C—C—N—C torsion angles showed sharp maxima at 0° and 180°.
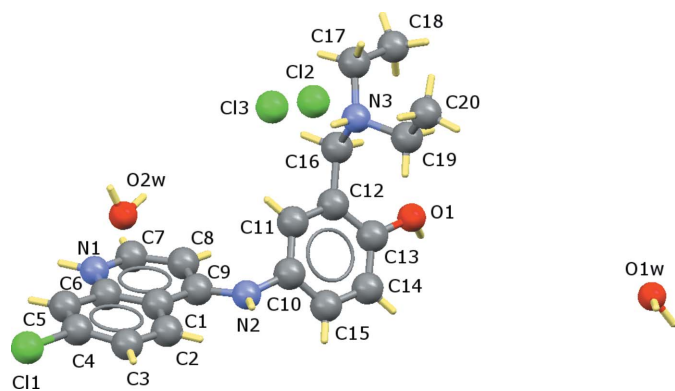
Figure 1
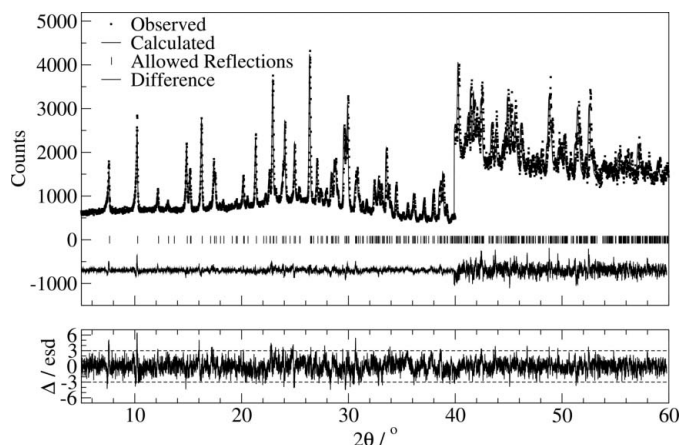A view of (I), with the atom-numbering scheme.
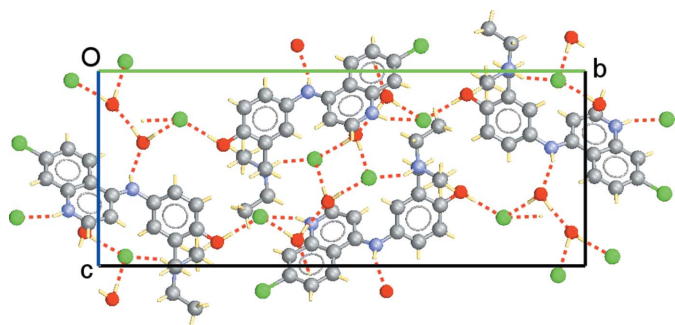
Figure 2
The crystal packing of (I), viewed along the *a* axis. Hydrogen bonds are indicated by dashed lines.

Figure 3
Final observed (points), calculated (line), difference $[(y_{obs} - y_{calc})]$ and weighted difference $[(y_{obs} - y_{calc})/\sigma]$ profiles for the Rietveld refinement of the title compound. Change of scale at 40° is a factor of 10 and the increment in 2θ is 0.01°.

In the dihydrate form, the C8—C9—N2—C10 torsion angle is closer to the ideal value of 0° than in the monohydrate form, which suggests an increased C—N double-bond character (Table 1). Even though the resolution of our data does not permit the determination of H-atom positions, the coordinates of both H2 and H2N can reasonably be estimated using idealized bond geometry and normalized bond lengths. The distance between the calculated H2 and H2N positions is 1.85 Å in the dihydrate, while 2.08 Å was reported for the monohydrate. Thus, the C8—C9—N2—C10 torsion angle in the dihydrate form approaches planarity despite considerable steric congestion. This behaviour is indicative of strong C9—N2 double-bond character.

The C9—N2—C10—C11 torsion angles are far from planar in both forms (Table 1). The coplanarity of the quinoline and benzene rings is sterically hindered by the close approach of the C8—H8 and the C11—H11 H atoms (Fig. 1).

The most apparent difference between the conformations of amodiaquine in the two structures is a rotation around the C12—C16 bond (Table 1), which moves the diethylamino group to opposite sides (above/below; see Fig. 1) of the benzene ring. In the dihydrate structure, one of the H atoms attached to atom C16 is involved in a close intramolecular contact of 2.41 Å with atom O1.

The amodiaquinium cations donate hydrogen bonds to two Cl⁻ ions and a water molecule in both forms (Table 2;

Yennawar & Viswamitra, 1991). The roles of the donor groups, however, differ in the two forms. In the dihydrate, N2—H2N···OH₂ and O1—H1O···Cl⁻ hydrogen bonds are formed, while in the monohydrate there are N—H···Cl⁻ and O—H···OH₂ bonds.

Stacking interactions between the phenol and quinoline rings of screw-related molecules were found in the mono-hydrate structure (Yennawar & Viswamitra, 1991). No such interactions are present in the crystal structure of the di-hydrate form (Fig. 2). The monohydrate structure appears to be deficient in hydrogen-bond donors, since one of the Cl⁻ ions accepts only one hydrogen bond instead of the usual two or three (Infantes & Motherwell, 2004). The additional donating ability of the extra water molecule in the dihydrate form permits a more optimal hydrogen-bonding scheme, and the stacking interactions between amodiaquinium cations are replaced by indirect hydrogen-bonded links through the solvent molecules and the counterions.

Experimental

Amodiaquinium dihydrochloride dihydrate was obtained from Sigma and used without further purification. No impurities were detected by X-ray powder diffraction. The sample was ground lightly and loaded into a 0.7 mm-diameter Lindemann glass capillary. Data were collected at room temperature and pressure in Debye–Scherrer geometry employing Co $K\alpha_1$ radiation.

Crystal data

$C_{20}H_{24}ClN_3O^{2+}\cdot2Cl^-\cdot2H_2O$	Co $K\alpha_1$ radiation
$M_r = 464.8$	$\mu = 0$ mm⁻¹
Monoclinic, $P2_1/c$	$T = 298$ K
$a = 7.83868$ (10) Å	Specimen shape: cylinder
$b = 26.9917$ (5) Å	$12 \times 0.7 \times 0.7$ mm
$c = 10.80804$ (18) Å	Specimen prepared at 100 kPa
$\beta = 92.9632$ (13)°	Specimen prepared at 298 K
$V = 2283.6$ (2) Å³	Particle morphology: fine powder,
$Z = 4$	yellow
$D_x = 1.352$ Mg m⁻³	

Data collection

Stoe linear PSD diffractometer
Specimen mounting: 0.7 mm Lindemann glass capillary
Specimen mounted in transmission mode

Scan method: step
Absorption correction: none
$2\theta_{min} = 2.0$, $2\theta_{max} = 60.0°$
Increment in $2\theta = 0.01°$

Refinement

Refinement on I_{net}
$R_p = 0.037$
$R_{wp} = 0.047$
$R_{exp} = 0.038$
$R_B = 0.0622$
$S = 1.29$
Wavelength of incident radiation: 1.78892 Å
Excluded region(s): none
Profile function: pseudo-Voigt (Thompson *et al.*, 1987) with asymmetry correction (Finger *et al.*, 1994)
392 reflections
181 parameters

H atoms treated by a mixture of independent and constrained refinement
Weighting scheme based on measured s.u.'s, $1/\sigma(y_{obs})^2$
$(\Delta/\sigma)_{max} = 0.14$
Preferred orientation correction: March–Dollase, as implemented and documented in *GSAS* (Larson & Von Dreele, 2000), along the (100 axis), ratio = 1.066 (2), range: min = 0.82398, max = 1.10164

Table 1
Selected geometric parameters (°) of amodiaquine in the crystal structures of amodiaquinium dihydrochloride monohydrate (CSD refcode VOTFIT; Yennawar & Viswamitra, 1991) and amodiaquinium dihydrochloride dihydrate, (I). Atom labels are given in Fig. 1.

Parameter	Monohydrate	Dihydrate
C8—C9—N2—C10	17.2 (7)	5.0 (12)
C9—N2—C10—C11	34.7 (7)	46.9 (12)
Quinoline–phenyl interplanar angle	48	54.6 (4)
C11—C12—C16—N3	−91.4	77.4 (8)

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

$D—H\cdots A$	$D—H$	$H\cdots A$	$D\cdots A$	$D—H\cdots A$
N1—H1N$\cdots$Cl2^i	0.93 (1)	2.26 (1)	3.160 (6)	162 (1)
N2—H2N$\cdots$O2W^{ii}	0.93 (2)	2.07 (2)	2.902 (12)	148 (1)
N3—H3N$\cdots$Cl3	0.93 (1)	2.15 (1)	3.016 (7)	155 (1)
O1—H1O$\cdots$Cl2^{iii}	0.98	2.06	3.037 (7)	177
O1W—H1WA$\cdots$Cl3	0.97	2.16	3.127 (11)	175
O1W—H1WB$\cdots$Cl3^{iv}	1.02	2.28	3.297 (11)	177
O2W—H2WA$\cdots$O1W	0.98	1.84	2.816 (14)	171
O2W—H2WB$\cdots$Cl2^{iv}	1.06	2.13	3.188 (12)	177

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

The program *DASH* (David *et al.*, 2004) was employed for structure solution. The powder pattern was truncated to 48.35° in 2θ (Co Kα), corresponding to a real-space resolution of 2.2 Å. The background was subtracted with a Bayesian high-pass filter (David & Sivia, 2001). Peak positions for indexing were obtained by fitting with an asymmetry-corrected Voigt function (Thompson *et al.*, 1987; Finger *et al.*, 1994). Indexing with the program *DICVOL91* (Boultif & Louër, 1991) failed, but the same 24 peak positions could be indexed with the program *DICVOL04* (Boultif & Louër, 2004) without allowing for impurity peaks. Pawley refinement was used to extract integrated intensities and their correlations, from which the space

group was determined using Bayesian statistical analysis (Markvardsen *et al.*, 2001). $P2_1/c$ was returned as the only possible space group, which resulted in a Pawley χ^2 of 0.70. Simulated annealing was used to solve the crystal structure of compound (I) from the powder pattern in direct space. The starting molecular geometry was taken from the crystal structure of amodiaquinium dihydrochloride monohydrate (Yennawar & Viswamitra, 1991) from the CSD (refcode VOTFIT). The molecule was assumed to be a salt in the solid state, based on the single-crystal structure of the monohydrate, where the two H atoms on the two positively charged N atoms had been located from the difference Fourier map. We note, however, that the three H atoms that were located only render two of the N atoms positive; charge balance therefore requires the hydroxide counterion that is stated to be present to be a water molecule. The structure of VOTFIT is therefore the monohydrate, and this has now been corrected in the CSD.

Because H atoms do not contribute significantly to the powder diffraction pattern, due to their low X-ray scattering power, they can be ignored during the structure solution process. Hence, a water molecule can be reduced to an O atom, which reduces its number of degrees of freedom from six to three. The amodiaquine molecule has six flexible torsion angles, which, combined with the two water molecules and the two Cl$^-$ ions, give a total of 24 degrees of freedom. Because of the large number of degrees of freedom, it cannot be expected that the default settings for simulated annealing in *DASH* (ten simulated annealing runs of 10 000 000 moves each) would be sufficient. Instead, 50 simulated annealing runs of 100 000 000 moves each were performed. In 50 simulated annealing runs, the correct crystal structure was found ten times, with a profile χ^2 of 1.60, 2.3 times the Pawley χ^2. The next best solution had a significantly higher profile χ^2 of 7.66.

The background subtraction, peak fitting, Pawley refinement, space-group determination and simulated-annealing algorithms were used as implemented in the program *DASH*.

Rietveld refinement was carried out on the solution with the lowest profile χ^2, with H atoms added in calculated positions. Bond lengths and angles involving heavy atoms were restrained to values taken from CSD entry VOTFIT (Yennawar & Viswamitra, 1991). Planar group restraints were applied for aromatic rings. The CH, CH$_2$ and CH$_3$ distances were restrained to be 0.93 (1), 0.97 (1) and 0.96 (1) Å respectively, with idealized bond angles. The refinement (Fig. 3), using the *GSAS* software suite (Larson & Von Dreele, 2000), converged readily to yield acceptable figures of merit ($\chi^2 = 1.655$, $R_p = 0.0366$, $R_{wp} = 0.0465$) and a chemically reasonable structural model. A single overall isotropic displacement parameter was employed. The orientations of the water molecules were kept fixed to enforce a chemically reasonable hydrogen-bonding geometry. Reported standard deviations are taken from the program employed and represent statistical uncertainties rather than estimates of the absolute error, which are likely to be considerably greater.

Data collection: *WinXPow* (Stoe, 1999); cell refinement: *GSAS* (Larson & Von Dreele, 2000); data reduction: *WinXPow*; program(s) used to solve structure: *DASH* (David *et al.*, 2004); program(s) used to refine structure: *GSAS*; molecular graphics: *MERCURY* (Macrae *et al.*, 2006); software used to prepare material for publication: *vi* (http://www.vim.org/).

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.

Boultif, A. & Louër, D. (1991). *J. Appl. Cryst.* **24**, 987–993.

Boultif, A. & Louër, D. (2004). *J. Appl. Cryst.* **37**, 724–731.

David, W. I. F., Shankland, K., van de Streek, J., Pidcock, E. & Motherwell, S. (2004). *DASH.* Version 3.0. Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, England.

David, W. I. F. & Sivia, D. S. (2001). *J. Appl. Cryst.* **34**, 318–324.

Finger, L. W., Cox, D. E. & Jephcoat, A. P. (1994). *J. Appl. Cryst.* **27**, 892–900.

Infantes, L. & Motherwell, W. D. S. (2004). *Chem. Commun.* pp. 1166–1167.

Larson, A. C. & Von Dreele, R. B. (2000). *GSAS.* Report LAUR 86-748. Los Alamos National Laboratory, New Mexico, USA.

Macrae, C. F., Edgington, P. R., McCabe, P, Pidcock, E., Shields, G. P., Taylor, R., Towler, M. & van de Streek, J. (2006). *J. Appl. Cryst.* **39**, 453–457.

Markvardsen, A. J., David, W. I. F., Johnson, J. C. & Shankland, K. (2001). *Acta Cryst.* A**57**, 47–54.

Olliaro, P. & Mussano, P. (2003). *Amodiaquine for Treating Malaria* in *The Cochrane Database of Systematic Reviews*. (http://www.cochrane.org/reviews/index.htm)

Stoe (1999). *WinXPow*. Stoe & Cie, Darmstadt, Germany.

Thompson, P., Cox, D. E. & Hastings, J. B. (1987). *J. Appl. Cryst.* **20**, 79–83.

Yennawar, H. P. & Viswamitra, M. A. (1991). *Curr. Sci.* **61**, 39–43.