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Norfloxacin dihydrate

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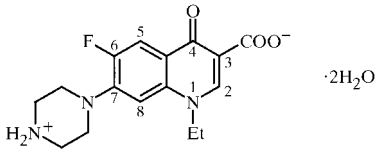
The antibiotic norfloxacin recrystallizes from acetonitrile as a dihydrate with the norfloxacin molecule in a zwitterionic form, *i.e.* 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazin-4-io)-3-quinolinecarboxylate dihydrate, $C_{16}H_{18}FN_3O_3\cdot 2H_2O$.

Comment

Norfloxacin is a broad-spectrum 4-fluoroquinolone antibiotic used in the treatment of urinary tract infections. Norfloxacin has been reported to exist in a number of solid forms: two anhydrous polymorphs (Šuštar *et al.*, 1993), an amorphous form (Šuštar *et al.*, 1993), a hemihydrate (The Merck Index, 1983), a sesquihydrate (Katdare *et al.*, 1986), a dihydrate (Katdare *et al.*, 1986), a hemipentahydrate (Mazuel, 1991) and a pentahydrate (Mazuel, 1991). Although no crystal structures are available in the literature for any of these anhydrous or hydrated forms of norfloxacin, crystal structures are available for the following chemical entities: norfloxacin·2DCl·D_2O (Wallis *et al.*, 1994), norfloxacin·2HCl·H_2O (Turel *et al.*, 1996), and two isostructural salts formed by crystallizing norfloxacin from concentrated hydrochloric acid containing either $CuCl_2$ or $ZnCl_2$ (Turel *et al.*, 1996). The current study was carried out for the purpose of unambiguous phase identification of a suspected hydrate, (I).



(I)

Atom N3 of the piperazine ring (Fig. 1) is observed to be protonated, and there is no evidence of a proton on either O1 or O2. The bond lengths observed for C3—O1 and C3—O2 [1.253 (4) and 1.268 (4) Å, respectively] are in good agreement with the mean value observed for C—O bonds in carboxylate ions [1.255 (10) Å; Allen *et al.*, 1987]. We conclude, therefore, that the norfloxacin molecule exists as a zwitterion in the dihydrate crystal structure. The least-squares plane through atoms C2, C3, O1 and O2 is rotated by 16.65 (17)° with respect to the least-squares plane through the quinoline moiety. This may be a consequence of electrostatic repulsion between atoms O2 and O3.

The length of the C7—F1 bond [1.370 (4) Å] compares well with the mean value [1.363 (8) Å; Allen *et al.* 1987] from 38 structures containing C_{ar}—F bonds. Atom F1 forms a short intramolecular C—H···F contact with atom H11*A* [H11*A*···F1 = 2.2 Å, C11···F1 = 2.873 (4) Å and C11—H11*A*···F1 = 126°] forming a six-membered pseudo-ring comprising atoms H11*A*—C11—N2—C8—C7—F1.

The quinoline moiety is planar, with the maximum displacement from the least-squares plane being observed for atom C2 [0.019 (4) Å]. The ethyl substituent on N1 is approximately perpendicular to the quinoline moiety, with a C1—N1—C15—C16 torsion angle of −100.1 (4)°. The piperazine ring adopts a slightly distorted chair conformation, with puckering parameters Q = 0.579 (4) Å, θ = 3.1 (4)° and φ = 68 (6)° (Cremer & Pople, 1975). The dihedral angle between the piperazine and quinoline least-squares planes equals 30.38 (15)°.

A total of seven unique N—H···O and O—H···O intermolecular hydrogen-bond interactions are observed in the crystal structure (Table 1), specifically: (*a*) N3—H17···O5 bonds norfloxacin to a water of crystallization; (*b*) N3—H18···O2^{i} and N3—H18···O3^{i} link adjacent norfloxacin molecules to produce an infinite chain extending along the *b* axis [symmetry code: (i) $-x, \frac{1}{2}+y, \frac{3}{2}-z$]; (*c*) the two water molecules donate a total of three hydrogen bonds to norfloxacin *i.e.* O4—H19···O2^{ii} [symmetry code: (ii) $1-x, \frac{1}{2}+y, \frac{5}{2}-z$], O4—H20···O2^{iii} and O5—H21···O1^{iii} [symmetry code: (iii) $1-x, -y, 2-z$] and (*d*) the molecules of water are connected to each other by a single hydrogen bond, O5—H22···O4^{iv} [symmetry code: (iv) $x, \frac{1}{2}-y, -\frac{1}{2}+z$]. Thus, parallel chains of norfloxacin molecules are interconnected *via* an extensive network of hydrogen bonds with water. As is commonly observed in the crystal structures of small molecule

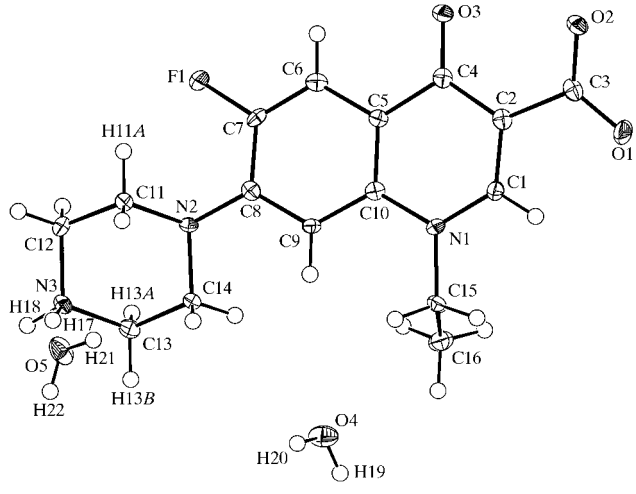


Figure 1
ORTEP (Johnson, 1965) plot of norfloxacin dihydrate. Displacement ellipsoids are shown at the 50% probability level. H atoms referred to in the text are labelled.

hydrates (Jeffrey & Saenger, 1991), the water molecules are three-coordinated, with each molecule acting as a donor to two hydrogen bonds and an acceptor to a single hydrogen bond.

Table 1 also highlights three short C—H···O intermolecular contacts involving the H atoms bonded to C13. Atom H13*A* makes a close contact with O2 (H···O = 2.47 Å) in the norfloxacin molecule at $-x, -y, 2 - z$. Atom H13*B* makes a close approach to atom O3 in the norfloxacin molecule at $-x, \frac{1}{2} + y, \frac{3}{2} - z$ (H···O = 2.50 Å) and atom O5 in the molecule of water at $x, \frac{1}{2} - y, \frac{1}{2} + z$ (H···O = 2.48 Å).

Experimental

Single crystals of norfloxacin dihydrate were obtained by slow evaporation from a saturated solution in acetonitrile.

Crystal data

$C_{16}H_{18}FN_3O_3\cdot 2H_2O$
$M_r = 355.37$
Monoclinic, $P2_1/c$
$a = 8.265$ (3) Å
$b = 21.698$ (4) Å
$c = 9.5250$ (17) Å
$\beta = 110.794$ (19)°
$V = 1596.9$ (6) Å^3
$Z = 4$
$D_x = 1.478$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 18 reflections
$\theta = 9.18$–11.95°
$\mu = 0.118$ mm^{-1}
$T = 123$ (2) K
Tabular, colourless
0.40 × 0.30 × 0.15 mm

Data collection

Rigaku AFC-7*S* diffractometer
$\omega/2\theta$ scans
3918 measured reflections
3676 independent reflections
1701 reflections with $I > 2\sigma(I)$
$R_{int} = 0.058$
$\theta_{max} = 27.53°$
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 28$
$l = -12 \rightarrow 11$
3 standard reflections
every 150 reflections
intensity decay: 1.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.053$
$wR(F^2) = 0.168$
$S = 0.962$
3676 reflections
251 parameters
H atoms: see text
$w = 1/[\sigma^2(F_o^2) + (0.0782P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.37$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}

All H atoms were located from difference Fourier synthesis. Those bonded to O or N atoms were then refined independently and isotropically, whilst those attached to C atoms were placed in geometrically calculated positions and allowed to ride on their parent atoms with $U_{iso}(H) = 1.2U_{eq}(C)$ and C—H distance restraints of 0.93, 0.96 and 0.97 Å for aromatic, methylene and methyl groups, respectively.

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H17···O5	0.94 (5)	1.79 (5)	2.706 (4)	163 (4)
N3—H18···O2^{i}	0.89 (4)	2.21 (5)	2.939 (4)	139 (4)
N3—H18···O3^{i}	0.89 (4)	2.06 (4)	2.759 (4)	135 (4)
O4—H19···O2^{ii}	0.84 (4)	2.02 (4)	2.862 (4)	179 (4)
O4—H20···O2^{iii}	0.90 (5)	2.11 (5)	2.977 (4)	161 (4)
O5—H21···O1^{iii}	0.79 (4)	1.84 (4)	2.626 (4)	171 (4)
O5—H22···O4^{iv}	0.83 (5)	2.04 (5)	2.776 (4)	149 (4)
C13—H13*A*···O2^{v}	0.97	2.47	3.397 (5)	161
C13—H13*B*···O5^{vi}	0.97	2.48	3.136 (5)	125
C13—H13*B*···O3^{i}	0.97	2.50	2.946 (4)	108

Symmetry codes: (i) $-x, \frac{1}{2} + y, \frac{3}{2} - z$; (ii) $1 - x, \frac{1}{2} + y, \frac{5}{2} - z$; (iii) $1 - x, -y, 2 - z$; (iv) $x, \frac{1}{2} - y, z - \frac{1}{2}$; (v) $-x, -y, 2 - z$; (vi) $x, \frac{1}{2} - y, \frac{1}{2} + z$.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1985); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1993); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP* (Johnson, 1965); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1423). Services for accessing these data are described at the back of the journal.

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