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Escitalopram oxalate: co-existence of oxalate dianions and oxalic acid molecules in the same crystal

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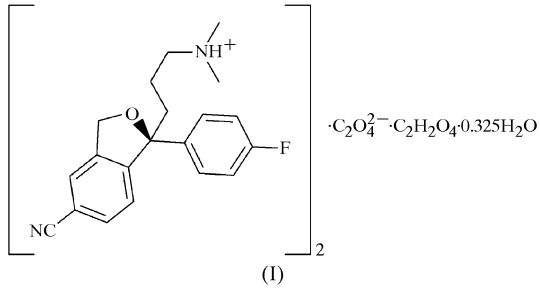
The title compound {systematic name: (+)-(*S*)-3-[5-cyano-2-(4-fluorophenyl)-1,3-dihydroisobenzofuran-2yl]propanaminium oxalate oxalic acid 0.325-hydrate}, $2C_{20}H_{22}FN_2O^+\cdot C_2O_4^{2-}\cdot C_2H_2O_4\cdot 0.325H_2O$, is a molecular salt of the N-protonated escitalopram cation. As well as charge-balancing oxalate dianions, neutral molecules of oxalic acid are present. The component species interact by way of N—H···O and short O—H···O hydrogen bonds, resulting in supramolecular chains.

Comment

(+)-(*S*)-1-[3-(Dimethylammonio)propyl]-1-(4-fluorophenyl)-5-phthalan-5-carbonitrile oxalate ($C_{20}H_{21}FN_2O$), common names escitalopram or *S*-(+)-citalopram, is a widely prescribed drug used to treat depression and related conditions (Burke, 2002). It is conveniently introduced as an oxalate salt, with a nominal formula usually given as $C_{20}H_{21}FN_2O\cdot C_2H_2O_4$, *i.e.* the presumed proton-transfer reaction is not specified (Sorbera *et al.*, 2001). As part of our ongoing crystallographic studies of pharmaceutical molecules (Harrison *et al.*, 2005), we now report the structure of the title compound, (I), in which two N-protonated escitalopram cations ($C_{20}H_{22}FN_2O^+$) and a $C_2O_4^{2-}$ oxalate dianon are accompanied by a neutral molecule of oxalic acid and a partially occupied water molecule (Fig. 1).



(I)

The bond lengths and angles in (I) fall within their expected ranges (Cambridge Structural Database, Version 5.27; Allen,

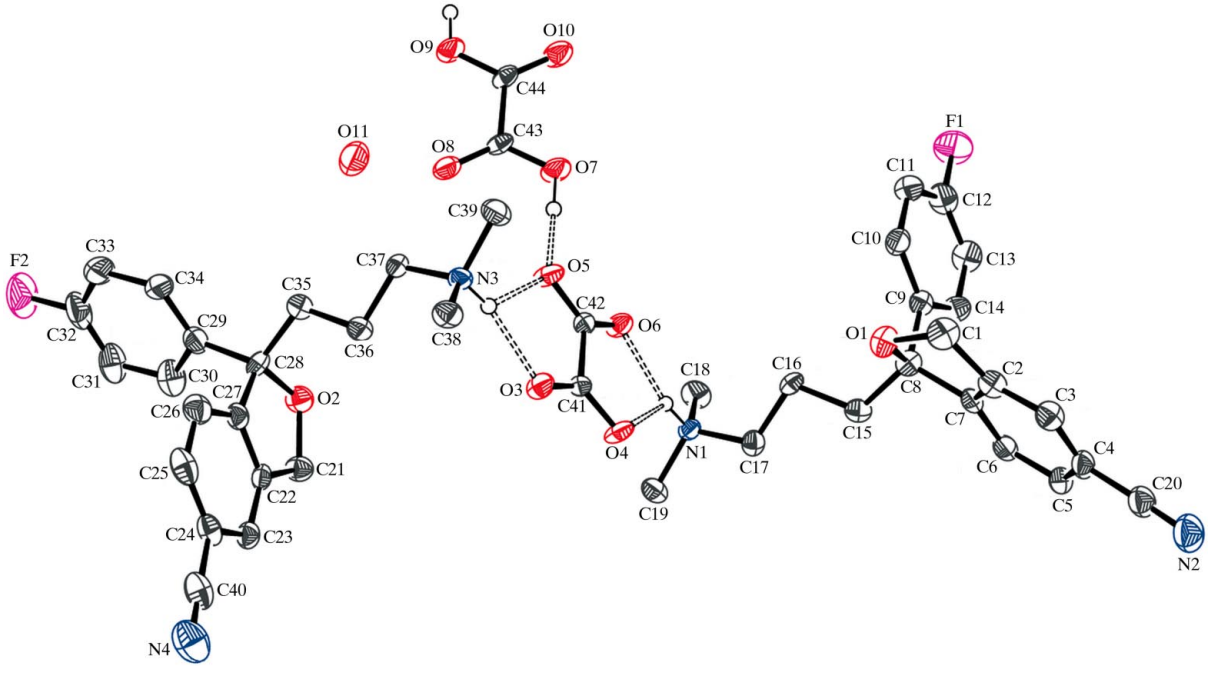


Figure 1
The molecular structure of (I), showing 50% probability displacement ellipsoids (arbitrary spheres for H atoms). All H atoms, except those involved in hydrogen bonds (dashed lines), have been omitted for clarity.

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2002). There are two $C_{20}H_{22}FN_2O^+$ cations in the asymmetric unit; atoms C8 and C28 are assumed to possess *S* configurations, consistent with the known absolute structure of the biologically active enantiomer of citalopram (Sanchez *et al.*, 2004). For the C1-containing molecule, the dihedral angle between the mean planes of the C2–C7 and C9–C14 benzene rings is 62.83 (13)°, and the C1/C2/C7/C8/O1 five-membered ring displays an envelope conformation with atom O1 in the flap position [the displacement from the C-atom mean plane is 0.435 (5) Å]. In the C21-containing molecule, the dihedral angle between the C22–C27 and C29–C34 mean planes is 81.99 (13)°, and the envelope conformation for C21/C22/C27/C28/O2 is less pronounced, with atom O2 displaced from the C-atom mean plane by 0.113 (6) Å. The oxalate species are both approximately planar; the dihedral angle between the C41/O3/O4 and C42/O5/O6 groupings is 4.4 (3)°, and the equivalent value for C43/O7/O8 and C44/O9/O10 is 2.8 (6)°.

The component species in (I) interact by way of N—H···O and O—H···O hydrogen bonds (Table 1), such that both $C_{20}H_{22}FN_2O^+$ cations make bifurcated N—H···(O,O) hydrogen bonds to the same oxalate dianion. Then, the $2C_{20}H_{22}FN_2O^+\cdot C_2O_4^{2-}$ units are linked into [001] chains by way of the oxalic acid molecules, *i.e.* the oxalate dianions and oxalic acid molecules alternate in the chains (Fig. 2). The short H···O separations of the oxalic acid-to-oxalate hydrogen bonds suggests that they are strong interactions.

Although it is not expected from a consideration of the pK_a values of oxalic acid (pK_{a1} = 1.23 and pK_{a2} = 4.19; Newkome *et al.*, 1985) the co-existence of oxalate dianions and oxalic acid molecules in the same crystal has been observed in a number of compounds, three examples being bis(pyridinium) oxalate oxalic acid (Newkome *et al.*, 1985), barium oxalate oxalic acid dihydrate (Chaix-Pluchery *et al.*, 1989) and 1-(α-pyrrolidiniobenzyl)-2-naphthol oxalate oxalic acid (Periasamy *et al.*, 2004). These three compounds show the same alternating oxalate–oxalic acid hydrogen-bonded chains seen in (I).

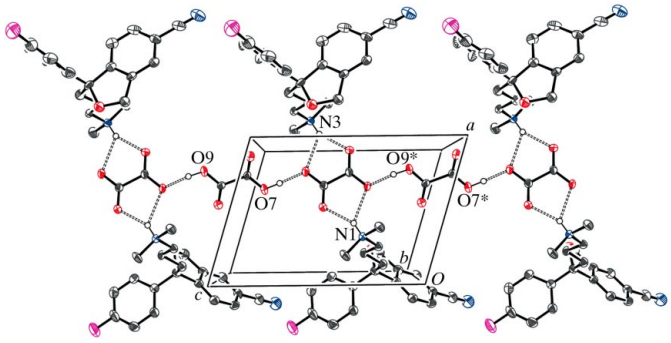

Figure 2
A view along [010] of part of an [001] chain in (I), with hydrogen bonds shown as dashed lines. Atoms labelled with an asterisk (*) are generated by the symmetry operation (x, y, $z-1$).

Experimental

The title compound was obtained as a gift sample from Jubilant Organosys, Nanjangud, India. The sample of (I) was recrystallized from ethanol (m.p. 420 K).

Crystal data

$2C_{20}H_{22}FN_2O^+\cdot C_2O_4^{2-}\cdot C_2H_2O_4\cdot 0.325H_2O$
M_r = 834.05
Monoclinic, $P2_1$
a = 7.9355 (3) Å
b = 24.7376 (9) Å
c = 11.1332 (5) Å
β = 106.589 (2)°
V = 2094.54 (14) Å^3
Z = 2
D_x = 1.324 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 120 (2) K
Block, colourless
0.32 × 0.24 × 0.18 mm

Data collection

Nonius KappaCCD diffractometer
ω and φ scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2003)
T_{min} = 0.969, T_{max} = 0.982
7581 measured reflections
3609 independent reflections
2652 reflections with $I > 2\sigma(I)$
R_{int} = 0.037
θ_{max} = 25.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.095
S = 1.02
3609 reflections
562 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0473P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.008
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0118 (16)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O6	0.93	1.91	2.768 (4)	152
N1—H1···O4	0.93	2.22	2.886 (4)	128
N3—H2···O3	0.93	1.91	2.764 (4)	152
N3—H2···O5	0.93	2.22	2.884 (4)	127
O7—H3···O5	0.91 (3)	1.56 (3)	2.466 (4)	177 (4)
O9—H4···O4^{i}	0.91 (3)	1.57 (3)	2.465 (4)	173 (4)

Symmetry code: (i) x, y, $z+1$.

Anomalous dispersion effects were negligible and Friedel pairs were merged before refinement. The absolute structure of (I) was assigned on the basis of the known chirality of escitalopram (Sanchez *et al.*, 2004). The C- and N-bound H atoms were placed in idealized locations (C—H = 0.95–0.99 Å and N—H = 0.93 Å) and refined as riding with U_{iso}(H) values of 1.2U_{eq}(carrier) or 1.5U_{eq}(methyl C). The oxalic acid H atoms were located in a difference map and refined with the restraint O—H = 0.90 (1) Å and the constraint U_{iso}(H) = 1.2U_{eq}(O). The H atoms of the partially occupied water molecule could not be located.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* and *DENZO* (Otwinowski & Minor, 1997), and *SORTAV* (Blessing, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3075). Services for accessing these data are described at the back of the journal.

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