

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

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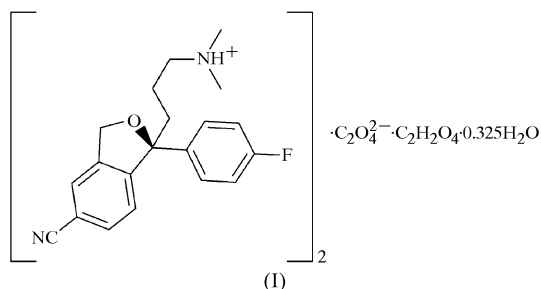
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The title compound {systematic name: (+)-(*S*)-3-[5-cyano-2-(4-fluorophenyl)-1,3-dihydroisobenzofuran-2yl]propanaminium oxalate oxalic acid 0.325-hydrate}, $2C_{20}H_{22}FN_2O^+ \cdot C_2O_4^{2-} \cdot C_2H_2O_4 \cdot 0.325H_2O$, is a molecular salt 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 dianion are accompanied by a neutral molecule of oxalic acid and a partially occupied water molecule (Fig. 1).



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

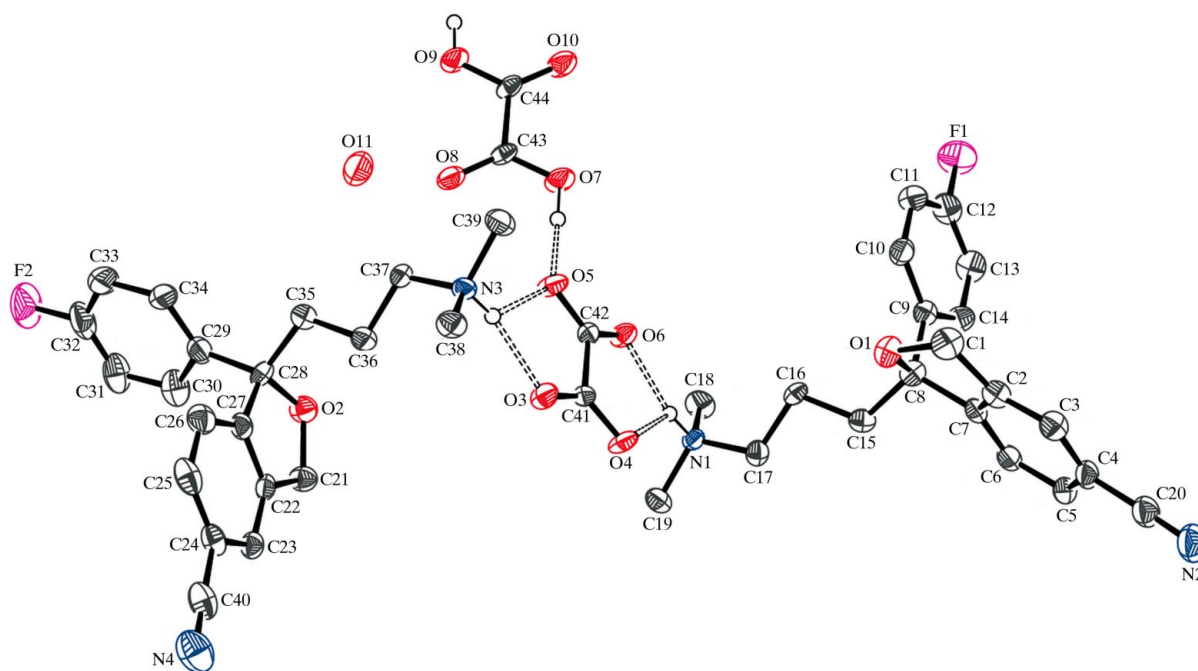


Figure 1

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.

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 $62.83(13)^\circ$, 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 $0.435(5) \text{ \AA}$]. In the C21-containing molecule, the dihedral angle between the C22–C27 and C29–C34 mean planes is $81.99(13)^\circ$, and the envelope conformation for C21/C22/C27/C28/O2 is less pronounced, with atom O2 displaced from the C-atom mean plane by $0.113(6) \text{ \AA}$. The oxalate species are both approximately planar; the dihedral angle between the C41/O3/O4 and C42/O5/O6 groupings is $4.4(3)^\circ$, and the equivalent value for C43/O7/O8 and C44/O9/O10 is $2.8(6)^\circ$.

The component species in (I) interact by way of $N-H \cdots O$ and $O-H \cdots O$ hydrogen bonds (Table 1), such that both $C_{20}H_{22}FN_2O^+$ cations make bifurcated $N-H \cdots (O,O)$ 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 $H \cdots O$ 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).

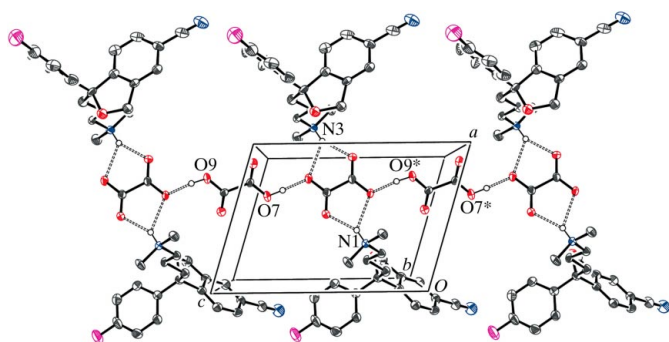


Figure 2

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

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

Data collection

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

Refinement

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

Table 1

Hydrogen-bond geometry ($\text{\AA}, ^\circ$).

| $D-H \cdots A$ | $D-H$ | $H \cdots A$ | $D \cdots A$ | $D-H \cdots A$ |
|--------------------------------|----------|--------------|--------------|----------------|
| N1–H1 \cdots O6 | 0.93 | 1.91 | 2.768 (4) | 152 |
| N1–H1 \cdots O4 | 0.93 | 2.22 | 2.886 (4) | 128 |
| N3–H2 \cdots O3 | 0.93 | 1.91 | 2.764 (4) | 152 |
| N3–H2 \cdots O5 | 0.93 | 2.22 | 2.884 (4) | 127 |
| O7–H3 \cdots O5 | 0.91 (3) | 1.56 (3) | 2.466 (4) | 177 (4) |
| O9–H4 \cdots 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 ($C-H = 0.95\text{--}0.99 \text{ \AA}$ and $N-H = 0.93 \text{ \AA}$) and refined as riding with $U_{\text{iso}}(\text{H})$ values of $1.2U_{\text{eq}}(\text{carrier})$ or $1.5U_{\text{eq}}(\text{methyl C})$. The oxalic acid H atoms were located in a difference map and refined with the restraint $O-H = 0.90(1) \text{ \AA}$ and the constraint $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{O})$. 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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