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Desvenlafaxine succinate monohydrate[1]

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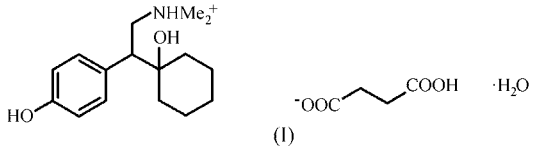
The title compound {systematic name: [2-(1-hydroxycyclohexyl)-2-(4-hydroxyphenyl)ethyl]dimethylammonium 3-carboxypropanoate monohydrate}, $C_{16}H_{26}NO_2^+\cdot C_4H_5O_4^-\cdot H_2O$, is a succinate salt of *O*-desmethylvenlafaxine (desvenlafaxine). The present structure is one of four reported polymorphs of this salt, which is a new antidepressant drug. The carboxyl group of the succinate anion adopts a rare *anti* conformation and is engaged in a very short O—H···O$^-$ hydrogen-bond contact. Both cations and anions are involved separately in the formation of distinct O—H···O hydrogen-bonded networks. Desvenlafaxine cations and water molecules self-assemble to generate a honeycomb layer, while the succinate anions form a linear tape structure. These hydrogen-bonded networks are interlinked *via* N—H···O and O—H···O hydrogen bonds. The hydrogen-bonding network is so strong that desolvation and melting occur together at approximately 402 K. Thus, the crystal structure may be used to understand the thermal stability and solubility of the compound at the molecular level.

Comment

The title compound, (I), is a monohydrate of the 1:1 salt of 1-[2-dimethylamino-1-(4-hydroxyphenyl)ethyl]cyclohexanol with succinic acid. Desvenlafaxine succinate is an antidepressant drug belonging to the class of serotonin–norepinephrine reuptake inhibitors and is expected to be marketed as Pristiq (Deecher *et al.*, 2006). It is a racemic mixture and is reported to exist in four crystalline polymorphs (Hadfield *et al.*, 2004). The crystalline form reported here is form I.



(I)

The asymmetric unit consists of one desvenalfaxine cation, a succinate anion and a water molecule (Fig. 1). The dimethylaminomethyl group of the desvenlafaxine molecule is protonated by succinic acid. The hydroxy group lies in an axial position with respect to the cyclohexane ring, while the bulkier dimethylaminohydroxyphenylethyl group lies in an equatorial position, adopting a rigid T-shaped geometry with the dimethylaminomethyl and cyclohexanol groups representing the arms. The cyclohexyl ring assumes a chair conformation, with the endocyclic bond angles close to the tetrahedral value [109.5 (2)–112.7 (2)°] and with average endocyclic torsion angles of about ±55°. Interestingly, the carboxyl group adopts the uncommon *anti* conformation (*i.e.* the acid H atom points away from the carbonyl O atom). The occurrence and energetics of this conformation have been discussed by DeVita Dufort *et al.* (2007).

Desvenlafaxine cations and water molecules self-assemble to form a honeycomb-like hydrogen-bonded network parallel to the *ab* crystallographic plane, in such a way that all the dimethylammonium groups point in one direction perpendicular to the hydrogen-bonded layer, while all the cyclohexane groups point in the opposite direction, generating a series of hydrophilic and hydrophobic grooves on opposite sides of the hydrogen-bonded layer (Fig. 2). The cations and water molecules in this layer are connected by infinite $(OH)_{phenyl}\cdots(OH)_{cyclohexyl}\cdots(OH)_{water}\cdots(OH)_{phenyl}$ hydrogen-bonded chains running parallel to [100] (entries 1–3, respectively, in Table 1). The hydrophilic grooves are lined with the OH and NH$^+$ groups of water molecules and desvenlafaxine cations, respectively. Infinite hydrogen-bonded tapes of succinate anions connected by a short O—H···O$^-$ hydrogen bond (entry 4 in Table 1) fill these hydrophilic grooves. The succinate anion also forms hydrogen-bonding contacts with both NH$^+$ and OH groups, coating the grooves (entries 5–7 in Table 1). In addition, there is a C—H···O hydrogen bond with an *N*-methyl group (entry 8 in Table 1; Desiraju & Steiner, 1999). Thus, in order to maximize the attractive interactions,

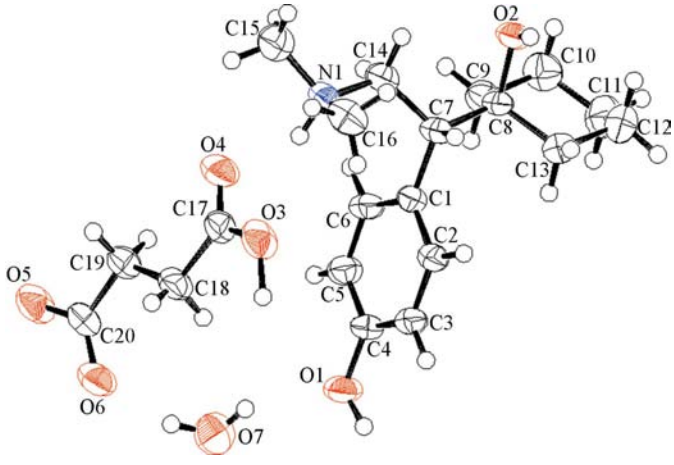


Figure 1
A view of the molecule of (I), showing the atomic numbering scheme. Displacement ellipsoids of non-H atoms are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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the carboxyl group must adopt the *anti* conformation. Inversion-related layers stack to form alternating hydrophobic and hydrophilic layers along [001], with layer thicknesses of about 7 and 11 Å, respectively. The hydrophobic grooves interdigitate with one another, while the hydrophilic grooves filled with the succinate anion tapes do not. As a result, the hydrophobic layer is thinner than the hydrophilic layer.

The water molecules are so tightly held in the crystal structure that desolvation and melting occur almost simultaneously. A differential scanning calorimetry trace shows a single endotherm with a mid-point temperature of 401.8 K (heating rate 10 K min^{-1}). The water molecule is involved in the formation of as many as three strong hydrogen bonds, bridging the desvenlafaxine ions and linking the desvenlafaxine cations and succinate anions (Fig. 2 and Table 1). In addition, it also accepts a C—H···O hydrogen bond from atom C14 (entry 9 in Table 1). The donor and acceptor groups around the water molecules are in nearly ideal tetrahedral positions.

Another interesting feature is the occurrence of a short O—H···O^- hydrogen bond between the indistinguishable carboxyl and carboxylate groups. Thus, one C—O bond [C17—O3 = 1.286 (3) Å and C20—O5 = 1.291 (3) Å] is longer than the other [C17—O4 = 1.224 (4) Å and C20—O6 = 1.234 (4) Å] on each acid group. If the acidic H atom were owned completely by one acid group, one would expect two sets of C—O bond distances, one corresponding to the carboxyl group (one C—O bond distance much longer than the other) and the other corresponding to a delocalized carboxylate group (nearly equivalent C—O distances). The acidic H atom is actually shared between atoms O3 and O5 in the short hydrogen bond. Such interactions are known as low-barrier hydrogen bonds and are considered to be very strong (Vishweshwar *et al.*, 2004; Hibbert & Emsley, 1990).

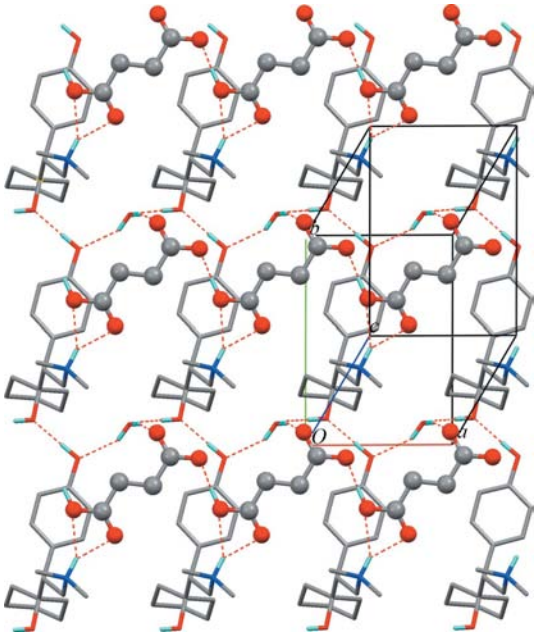

Figure 2
The packing of (I), showing a honeycomb layer parallel to the *ab* crystallographic plane consisting of desvenlafaxine cations and water molecules connected by O—H···O hydrogen bonds (dashed lines). Infinite O—H···O hydrogen-bonded tapes of succinate anions fill the hydrophilic grooves. Also note the bifurcated N—H···O hydrogen bonds between the cations and anions.

Experimental

The title compound was synthesized and purified in our laboratory according to a (proprietary) process of Dr Reddy's Laboratories. Diffraction quality single crystals of (I) were obtained by slow evaporation from an isopropyl alcohol solution under ambient conditions.

Crystal data

$C_{16}H_{26}NO_2^+·C_4H_5O_4^-·H_2O$
M_r = 399.48
Triclinic, $P\overline{1}$
a = 6.542 (5) Å
b = 9.324 (8) Å
c = 17.631 (14) Å
α = 77.594 (17)°
β = 84.00 (2)°
γ = 89.39 (2)°
V = 1044.5 (15) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 298 K
0.50 × 0.30 × 0.12 mm

Data collection

Rigaku Mercury diffractometer
Absorption correction: multi-scan (Jacobson, 1998)
T_{min} = 0.964, T_{max} = 0.989
11016 measured reflections
3875 independent reflections
2265 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.045

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.065
$wR(F^2)$ = 0.101
S = 1.25
3875 reflections
299 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···O2^{i}	0.94 (3)	1.72 (3)	2.655 (4)	179 (3)
O2—H21···O7^{ii}	0.88 (3)	1.83 (3)	2.698 (4)	171 (2)
O7—H72···O1	0.79 (4)	2.13 (3)	2.836 (4)	149 (3)
O3—H31···O5^{iii}	1.18 (4)	1.28 (4)	2.450 (3)	176 (3)
N1—H11···O3	0.96 (3)	2.25 (3)	3.085 (4)	145 (2)
N1—H11···O4	0.96 (3)	2.01 (3)	2.870 (4)	149 (2)
O7—H71···O6	0.94 (4)	1.84 (4)	2.753 (4)	162 (3)
C16—H163···O6^{ii}	0.95	2.56	3.386 (5)	145
C14—H141···O7^{iv}	0.95	2.66	3.485 (4)	145

Symmetry codes: (i) $x, y+1, z$; (ii) $x-1, y-1, z$; (iii) $x-1, y, z$; (iv) $x, y-1, z$.

H atoms bound to C atoms were positioned geometrically [C—H = 0.95 Å and U_{iso}(H) = 1.2U_{eq}(C)] and refined using a riding model. The positions of H atoms bound to N and O atoms were refined [U_{iso}(H) = 1.2U_{eq}(N, water and hydroxyl O) and 1.5U_{eq}(carbonyl O)].

Data collection: *CrystalClear* (Rigaku, 1999); cell refinement: *CrystalClear*; data reduction: *CrystalStructure* (Rigaku/MSC, 2004); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *X-SEED* (Barbour, 2001) and *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *CrystalStructure*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ3139). Services for accessing these data are described at the back of the journal.

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