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1-[2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl]dimethylammonium chloride (venlafaxine hydrochloride)

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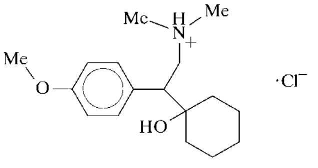
The crystal structure of racemic venlafaxine hydrochloride, $C_{17}H_{28}NO_2^+\cdot Cl^-$, consists of two types of parallel chains formed by translated venlafaxine$^+$ cations, hydrogen bonded by Cl^- anions, and characterized by the opposite chirality of their constituent molecules. These chains organize in two different types of broad layers of opposite handedness, related by a glide plane.

Comment

The title compound, (I), is a representative of a novel group of antidepressants and is characterized by its ability to inhibit selectively the presynaptic reuptake of both serotonin and noradrenaline, with no affinity for the histaminergic, adrenergic and cholinergic receptors responsible for the toxicity associated with traditional antidepressant treatment (Briley, 1998; Burnett & Dinan, 1998). These novel pharmacological properties of venlafaxine may enhance its efficacy as well as its safety/tolerability profile, especially in the treatment of severely depressed patients (Holliday & Benfield, 1995; Dinan & Burnett, 1997; Leonard, 1999).



(I)

The clinical administration and the antidepressant activity determinations were mainly performed on the racemic venlafaxine hydrochloride derivative. However, the only known structural study was performed on an *S* enantiomorph of a hydrobromide derivative (hereafter VHBr), which crystallizes in space group $P2_1$ [this structure is in the Cambridge Structural Database (Allen *et al.*, 1983) with refcode KIDGUZ; it was deposited as supplementary material for a paper by Yardley *et al.* (1990), but in the final publication this structure is not actually described].

Two different crystalline forms of the racemic venlafaxine hydrochloride derivative could be identified by X-ray powder methods, while single crystals of only one of them could be obtained (hereafter VHCl). Its X-ray structure determination was carried out in order to study its molecular conformation and to compare it with VHBr.

The asymmetric unit of the title compound (Fig. 1) consists of a $C_{17}H_{28}NO_2^+$ cation and a Cl^- anion. The dimethylammonium N atom, N1, shows quaternary character due to proton transfer from HCl and consequently bears the positive charge in the molecular cation. The N1 bond angles range from 107 to 114° (see Table 1) confirming the tetrahedral bond configuration. The hexanolic ring adopts a chair conformation, with C8, C10, C11 and C13 defining a plane (mean deviation 0.004 Å), and C9 and C12 being 0.645 (5) and −0.661 (5) Å out of the plane, respectively.

The comparison of both the VHCl and VHBr structures shows no significant differences between the relevant geometric parameters except for a torsion angle at the methoxy substituent and differences expected due to the unequal size of the halogen anion. A least-squares fit, using the facilities provided by *XP* in the *SHELXTL*/*PC* package (Sheldrick, 1991), gave an r.m.s. deviation of 0.05 Å. The maximum deviations occur at the halogen (0.11 Å) and C17 (0.14 Å) locations. C17 is the C atom of the methoxy substituent of the benzene and the location difference is evidence of the dissimilarity between the C3—C4—O1—C17 torsion angle in VHCl [−10.9 (7)°] and the corresponding one in VHBr (−0.5°).

A pair of [010] translated molecular cations of venlafaxine are linked by two hydrogen bonds to the chloride anion (Table 2). A search of hydrogen bonds to Cl atoms in the Cambridge Structural Database (Allen *et al.*, 1983; version of October 1999, *ca* 200 000 entries), restricted to bond distances H···Cl < 2.8 Å and to angles O—H···Cl and N—H···Cl > 130°, shows that the second (N1—H1*A*···Cl1) is a very strong one; only 8% of those hydrogen bonds found (661 over 7988)

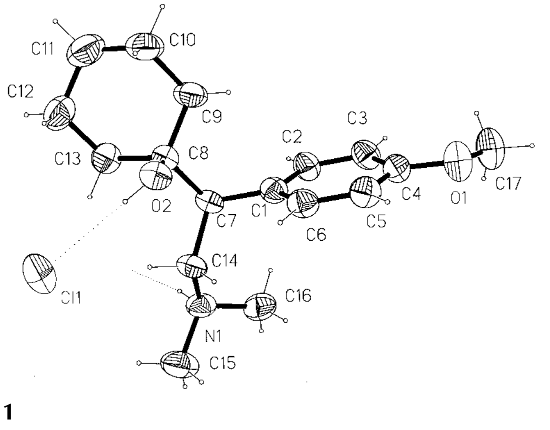


Figure 1
View of the molecular cation and the chloride anion showing the numbering scheme used, with displacement ellipsoids drawn at the 50% probability level. The Cl hydrogen bonds are depicted by dotted lines.

were shorter than the one present in this structure [mean value H···Cl 2.403 (2) Å over 7988 hits, this work 2.141 (9) Å]; meanwhile, the first one falls within a normal hydrogen-bond range [mean value H···Cl 2.310 (3) Å, over 3288 hits, this work 2.331 (9) Å]. Thus, the main structural cohesion is provided by the two hydrogen bonds determining a chain running along the crystallographic *b* axis [*b* = 5.8810 (12) Å]. A similar chain is responsible for the structural cohesion in VHBr, where two [100] translated molecular cations are linked through a bromide anion by a pair of hydrogen bonds (N1···Br1 3.164 and O2···Br1 3.333 Å), the chain running along the crystallographic *a* axis [*a* = 5.905 (2) Å].

The twofold screw axis, along [001] in VHCl [*c* = 11.448 (2) Å] and along [010] in VHBr [*b* = 11.625 (3) Å], packs chains of molecular cations of the same chirality determining a broad layer parallel to (100) and (001), respectively. In VHCl, another layer, which contains chains of molecular cations of opposite handedness, is generated by the presence of the *c* glide plane as a consequence of the racemic condition of VHCl, determining a stacking of sheets of opposite chirality. In VHBr, instead, due to its non-racemic constitution, layers containing molecular cations of the same handedness are stacked. The interlayer spacing is almost the same in both structures, equal to $0.5d_{100}$ for VHCl [13.1153 (5) Å] and to d_{001} for VHBr [13.430 (4) Å].

Experimental

The title compound was obtained from Laboratorios Gador. Crystals suitable for X-ray diffraction were obtained by slow evaporation from a water solution.

Crystal data

$C_{17}H_{28}NO_2^+\cdot Cl^-$
$M_r = 313.85$
Orthorhombic, $Pca2_1$
$a = 26.230$ (5) Å
$b = 5.8810$ (12) Å
$c = 11.448$ (2) Å
$V = 1766.0$ (6) Å^3
$Z = 4$
$D_x = 1.180$ Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 10$–20°
$\mu = 0.221$ mm^{-1}
$T = 293$ (2) K
Prism, colorless
0.44 × 0.32 × 0.28 mm

Data collection

CAD-4 diffractometer
ω–2θ scans
Absorption correction: numerical integration (Sheldrick, 1976)
$T_{\min} = 0.92$, $T_{\max} = 0.93$
2879 measured reflections
2094 independent reflections (plus 380 Friedel-related reflections)
1629 reflections with $I > 2\sigma(I)$

$R_{\rm int} = 0.087$
$\theta_{\max} = 29.99°$
$h = 0 \rightarrow 30$
$k = -1 \rightarrow 8$
$l = 0 \rightarrow 16$
2 standard reflections every 98 reflections intensity decay: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.043$
$wR(F^2) = 0.149$
$S = 1.046$
2474 reflections
190 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0652P)^2 + 0.7255P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.005$
$\Delta\rho_{\max} = 0.23$ e Å^{-3}
$\Delta\rho_{\min} = -0.27$ e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter: 0.14 (13)

Table 1
Selected geometric parameters (Å, °).

C4—O1	1.367 (5)	C15—N1	1.501 (6)
C8—O2	1.432 (4)	C16—N1	1.482 (6)
C14—N1	1.504 (5)	C17—O1	1.401 (6)
C16—N1—C15	110.7 (4)	C15—N1—C14	108.9 (3)
C16—N1—C14	114.2 (3)	C4—O1—C17	118.8 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2B···Cl1	0.85	2.33	3.181 (9)	180
N1—H1A···Cl1$^{\rm i}$	0.91	2.14	3.046 (9)	173

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

H atoms attached to carbon were placed at idealized positions and allowed to ride with isotropic displacement parameters 1.2 times larger than those of their hosts. Those bonded to oxygen were located in a ΔF synthesis and were subsequently refined with restrained O—H distances and individual isotropic displacement parameters. Data collection was performed at the Laboratorio Nacional de Difraccion (LANADI).

Data collection: *CAD*-4/*PC* (Enraf–Nonius, 1993); cell refinement: *CAD*-4/*PC*; data reduction: *MolEN* (Fair, 1990); program(s) used to solve structure: *XS* in *SHELXTL*/*PC* (Sheldrick, 1991); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL*/*PC*; software used to prepare material for publication: *PARST* (Nardelli, 1983) and *CSD* (Allen *et al.*, 1983).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1473). Services for accessing these data are described at the back of the journal.

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