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A monoclinic polymorph of venlafaxine hydrochloride

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Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.007 Å
R factor = 0.068
wR factor = 0.068
Data-to-parameter ratio = 9.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Venlafaxine hydrochloride, [(±)-*N*,*N*-dimethyl-2-(1-hydroxycyclohex-1-yl)-2-(4-methoxyphenyl) ethylamine hydrochloride, $C_{17}H_{28}ClNO_2$] is found to crystallize in both orthorhombic and monoclinic crystal systems. The molecular structures in the two polymorphs differ in the conformations of the substituents at the ethylamine group. In the monoclinic crystal structure, the molecules translated along the *a* axis are linked by Cl^- ions through O—H···Cl and N—H···Cl hydrogen bonds to form infinite one-dimensional chains.

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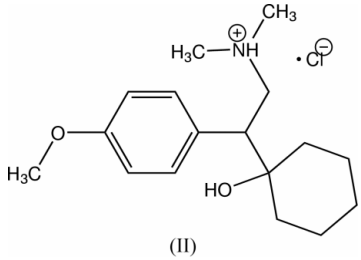
Comment

Venlafaxine hydrochloride, [(±)–N,*N*-dimethyl-2-(1-hydroxycyclohex-1-yl)-2-(4-methoxyphenyl) ethylamine hydrochloride, $C_{17}H_{28}ClNO_2$] is used as an antidepressant and an anxiolytic. Recrystallization of the compound for purification yielded crystals of two different morphologies, *viz*. blocks (form I) and needles (form II), as observed under the microscope. They were separated manually and characterized by different solid-state techniques such as differential scanning calorimetry, infrared spectroscopy, powder X-ray diffraction and single-crystal X-ray diffraction. These polymorphic forms were patented along with their characteristic physicochemical data (Rao *et al.*, 1999,, 2002). Recently, the crystal structure of form I has been reported in the orthorhombic space group $Pca2_1$ byVega *et al.* (2000). In this paper we report the structure of form II and compare it with that of form I.



(II)

Form II of venlafaxine hydrochloride is found to crystallize in the monoclinic space group $P2_1/n$. The structure of the molecule in the monoclinic form is shown in Fig. 1. All the bond lengths (Table 1) show normal values (Allen *et al.*, 1987) and agree well with the corresponding values observed for the orthorhombic polymorph (Vega *et al.*, 2000). In both polymorphs, the cyclohexane ring adopts a chair conformation. An intermolecular hydrogen bond links the N atom of the dimethylammonium group of the venlafaxine cation to the chloride anion. The chloride ion is also involved in another

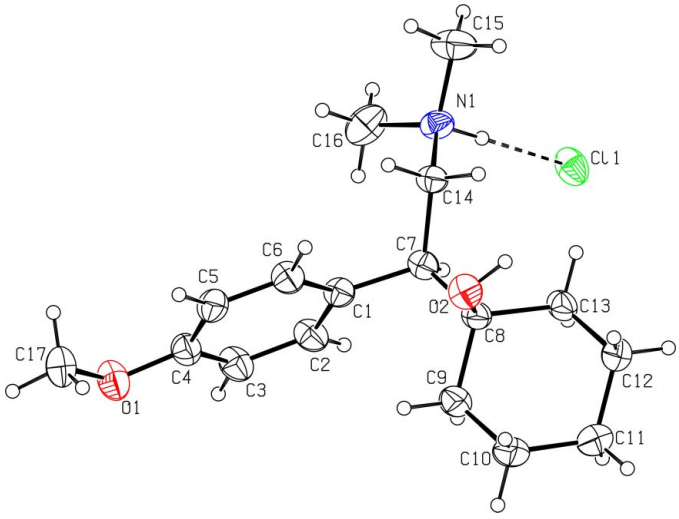


Figure 1
A perspective view of venlafaxine hydrochloride. Displacement ellipsoids are drawn at the 30% probability level.

hydrogen bond, with the O atom of the hydroxyl group of the cation translated one unit along the *a* axis. These hydrogen bonds (Table 2), which stabilize the crystal structure (Fig. 2), lead to chains of molecules along the short *a* (= 5.797 Å) axis. An identical hydrogen-bonding scheme constitutes the molecular chain in the orthorhombic polymorph, along the short *b* (= 5.881 Å) axis (Vega *et al.*, 2000). Hence the two polymorphic modifications have the same lattice stabilization mechanism. However, careful comparison of the torsion angles (Table 3) reveals that the molecules differ by 3 to 6° in the rotations about the bonds N1—C14, C1—C7 and C7—C14. Hence these two forms of venlafaxine hydrochloride are conformational polymorphs (Bilton *et al.*, 1999).

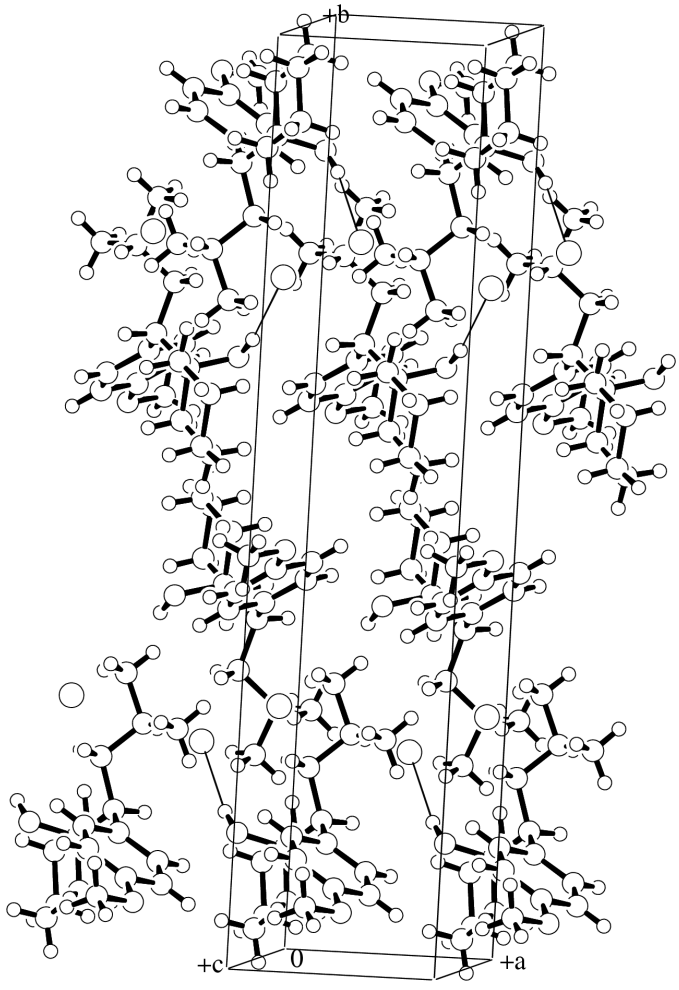


Figure 2
Packing of the molecules.

Experimental

Crystals of form II of venlafaxine hydrochloride suitable for X-ray diffraction were grown from a mixture of methanol and ethyl acetate (1:8).

Crystal data

$C_{17}H_{28}NO_2^+\cdot Cl^-$
M_r = 313.87
Monoclinic, $P2_1/n$
a = 5.797 (6) Å
b = 26.074 (7) Å
c = 11.722 (3) Å
β = 100.72 (5)°
V = 1741 (2) Å^3
Z = 4
D_x = 1.197 Mg m^{-3}
Cu Kα radiation
Cell parameters from 24 reflections
θ = 6.4–23.7°
μ = 1.97 mm^{-1}
T = 298.2 K
Needle, colourless
0.40 × 0.10 × 0.10 mm

Data collection

Rigaku AFC-7*S* diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.843, T_{max} = 0.996
3564 measured reflections
3304 independent reflections
3304 reflections with $I > 1.3\sigma(I)$
R_{int} = 0.078
θ_{max} = 70.1°
$h = 0 \rightarrow 6$
$k = 0 \rightarrow 31$
$l = -14 \rightarrow 14$
4 standard reflections
every 150 reflections
intensity decay: 0.3%

Refinement

Refinement on F
R = 0.068
wR = 0.068
S = 1.48
1816 reflections
199 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o) + 0.00016|F_o|^2]$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.40 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}
Extinction correction: Zachariasen (1967)
Extinction coefficient: 0.0000022 (7)

Table 1
Selected geometric parameters (Å, °).

O1—C4	1.363 (6)	N1—C15	1.486 (6)
O1—C17	1.426 (7)	N1—C16	1.487 (7)
O2—C8	1.442 (5)	N1—C14	1.495 (6)
C4—O1—C17	117.0 (4)	O1—C4—C5	125.4 (4)
C14—N1—C16	113.3 (4)	O2—C8—C9	106.3 (3)
C15—N1—C16	110.6 (4)	O2—C8—C13	110.2 (3)
C14—N1—C15	109.7 (4)	O2—C8—C7	108.7 (3)
O1—C4—C3	115.8 (4)	N1—C14—C7	114.4 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—H27···Cl1^{i}	0.91 (5)	2.33 (5)	3.213 (5)	164 (4)
N1—H28···Cl1	0.92 (6)	2.13 (6)	3.040 (5)	169 (5)

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

Table 3
Comparison of some torsion angles (°) in form I and form II.

Angle	form I	form II
C16—N1—C14—C7	58.8 (5)	62.0 (5)
C15—N1—C14—C7	−177.0 (4)	−173.9 (4)
C2—C1—C7—C8	−107.3 (4)	−101.8 (5)
C2—C1—C7—C14	129.1 (4)	133.0 (4)
C6—C1—C7—C8	71.7 (5)	77.0 (5)
C6—C1—C7—C14	−51.9 (5)	−48.3 (5)
C1—C7—C14—N1	−88.9 (4)	−95.1 (4)
C8—C7—C14—N1	144.7 (3)	137.6 (4)

H atoms bound to carbons were fixed geometrically, with C—H = 0.95 Å, and refined using a riding model. H atoms bound to O and N were refined isotropically.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1994); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *teXsan* (Molecular Structure Corporation, 1995); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *teXsan*; molecular graphics: *ORTEP*3 for Windows (Farrugia, 1999); software used to prepare material for publication: *teXsan*.

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References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L. & Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* **2**, pp. S1–19.
Altomare, A., Cascarano, G., Giacovazzo, C. & Guagliardi, A. (1993). *J. Appl. Cryst.* **26**, 343–350.
Bilton, C., Howard, J. A. K., Laxmi Madhavi, N. N., Nangia, A., Desiraju, G. R., Allen, F. H. & Wilson, C. C. (1999). *Chem. Commun.* pp. 1675–1676.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Molecular Structure Corporation. (1994). *MSC/AFC Diffractometer Control Software*. MSC, 9009 New Trails Drive, The Woodlands, TX 77381, USA.
Molecular Structure Corporation. (1995). *teXsan*. Version 1.7-2. MSC, 9009 New Trails Drive, The Woodlands, TX 77381, USA.
North, A. C. T., Philips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Rao, S. M., Vyas, K., Sivalakshmi Devi, A. & Reddy, G. O. (1999). Pat. Appl No. 748/MAS/99, dated 19-7-1999.
Rao, S. M., Vyas, K., Sivalakshmi Devi, A. & Reddy, G. O. (2002). Intl Pat. Appl. No. WO02/46140 A1, dated 13-6-2002.
Vega, D., Fernandez, D. & Echeverria, G. (2000). *Acta Cryst.* C**56**, 1009–1010.
Zachariasen, W. H. (1967). Acta Cryst. **23**, 558-564.