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Sertraline hydrochloride form II

K. Ravikumar,[a]* B. Sridhar[a] and M. N. Bhanu[b]

[a]Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India, and [b]Lupin Ltd (Research Park), Generic Division, Pune 411 042, India

Correspondence e-mail: ravikumar_iict@yahoo.co.in

Key indicators

Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.004 Å
R factor = 0.045
wR factor = 0.119
Data-to-parameter ratio = 16.3

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

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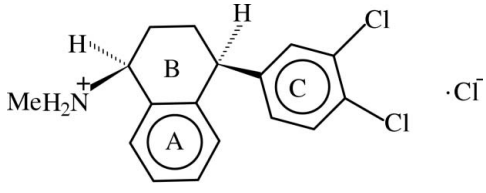
A second polymorph of sertraline hydrochloride {systematic name: [(1*S*-*cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthy]methylammonium chloride}, a potent antidepressant drug, $C_{17}H_{18}Cl_2N^+\cdot Cl^-$, crystallizes in the same orthorhombic space group as form I. The molecules in both forms exhibit nearly identical bond distances and angles, but some aspects of the molecular conformation are significantly different. Hydrogen bonds involving N atoms and Cl^- anions form chains in both forms.

Comment

The serotonin transporter (SERT) located on presynaptic nerve endings is responsible for the regulation of 5-HT levels in the synaptic cleft. It functions as the primary target site for selective serotonic reuptake inhibitors (SSRIs), which are primarily used as antidepressants (Schloss & Williams, 1998). Sertraline hydrochloride, (I), the generic version of Pfizer's Zoloft, is a selective serotonin reuptake inhibitor indicator for use in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder and premenstrual dysphoric disorder. The first SSRI to be marketed was fluoxetine (Prozac). Although sertraline's mechanism appears similar to that of fluoxetine, it is more selective and more potent in inhibiting serotonin uptake. Owing to the enormous commercial value of the drug, the patent literature on crystal forms of sertraline hydrochloride is substantial. Data for 28 reported phases of sertraline hydrochloride (polymorphs, solvates, hydrates and an amorphous phase) have been extracted from patents and listed (Almarsson *et al.*, 2003). As part of our continuing effort to study the relationship between the conformational and biological activity in this class of compounds (Ravikumar, Sridhar *et al.*, 2005; Ravikumar, Swamy *et al.*, 2005), an X-ray structure determination of form II of sertraline hydrochloride was performed.



(I)

All bond distances and angles (Table 1) fall within expected ranges and agree well with form I of sertraline hydrochloride reported previously (Caruso *et al.*, 1999). From the molecular

perspective, the forms differ primarily in the relative orientation of the dichlorophenyl (*C*) and tetrahydronaphthyl fragments (*A* and *B*). In the present structure, form II (Fig. 1), the orientation of these fragments about the C4—C11 bond, characterized by the torsion angle C10—C4—C11—C16, is −42.5 (4)°, while it is nearly perpendicular [115.9 (1)°] in form I. Furthermore, the dichlorophenyl ring (*C*) and the fused benzene ring (*A*) are inclined at 64.9 (1)° in form II, whereas the dihedral angle is close to a right angle, 83.5 (1)°, in form I.

The quaternary atom N1 is in an axial position in both forms [N1—C1—C9—C10 = −108.7 (3)° in form II and −97.9 (1)° in form I]. However, a striking difference is seen in the orientation of the methylammonium side chain in the two forms. As indicated by the torsion angle C17—N1—C1—C2 of 63.4 (3)°, it is *gauche* in the form II structure, while it is anti [162.6 (1)°] in form I. An r.m.s. overlay using the central unsaturated ring atoms C1/C4/C9/C10 (r.m.s deviation = 0.023 Å) of forms II and I shows the significant difference in the orientation of the dichlorophenyl ring and the methylammonium side chain (Fig. 2). The pharmacophoric feature for 5-HT receptor binding is identified in the lengths of the vectors connecting the centroids of the aromatic rings with a protonated N atom (Dalpiaz *et al.*, 1996). Viewing the present structure in this way, the distances between the N atom and the centroids of the two benzene rings (*A* and *C*) are found to be 3.75 Å (3.69 Å, form I) and 6.26 Å (6.11 Å, form I), respectively.

The conformation of the unsaturated ring (*B*) in both form II and form I is a half-chair with N1 [1.349 (2) and 1.426 Å, respectively] and C3 [0.427 (3) and 0.405 Å, respectively] deviating from the mean plane described by the four remaining ring atoms.

As also observed in form I, the chloride anion Cl3 in form II is involved in hydrogen bonding with amino atom N1 (Table 2). The packing of form II shows the chloride anions situated along the *c* axis, near *z* = 0 and *z* = 1/2 (Fig. 3), while they are near *z* = 1/4 and 3/4 in form I (Fig. 4). Incidentally, the chloride anion Cl3 and Cl1 have a separation of 8.228 (3) Å in form II, whereas it is only 4.472 Å in form I. It is noteworthy that the chloride anion Cl3 is involved in possible C—H···Cl interactions (You *et al.*, 2004) in both crystal forms (Table 2).

Experimental

Suitable crystals of sertraline hydrochloride [Lupin (Research Park), Generic Division, Pune] for X-ray studies were obtained from DMF solution.

Crystal data

$C_{17}H_{18}Cl_2N^+\cdot Cl^-$
M_r = 342.67
Orthorhombic, $P2_12_12_1$
a = 7.289 (6) Å
b = 7.396 (7) Å
c = 32.66 (3) Å
V = 1761 (3) Å^3
Z = 4
D_x = 1.293 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3254 reflections
θ = 2.5–21.2°
μ = 0.51 mm^{-1}
T = 273 (2) K
Block, colorless
0.14 × 0.10 × 0.07 mm

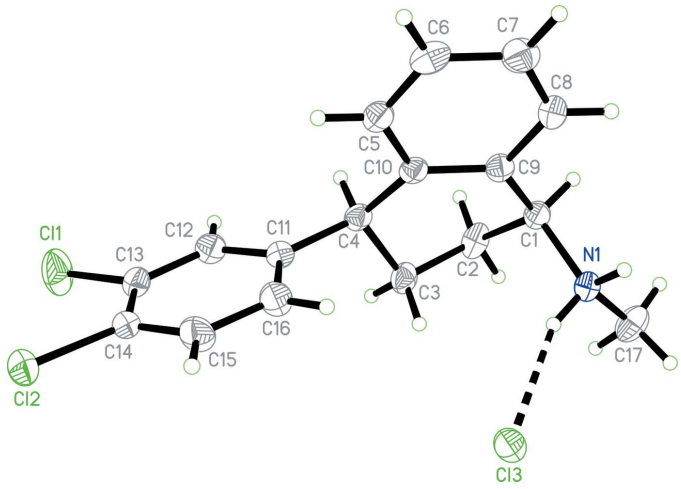


Figure 1
A view of form II, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms are shown as small spheres of arbitrary radii and the hydrogen bond as a dashed line.

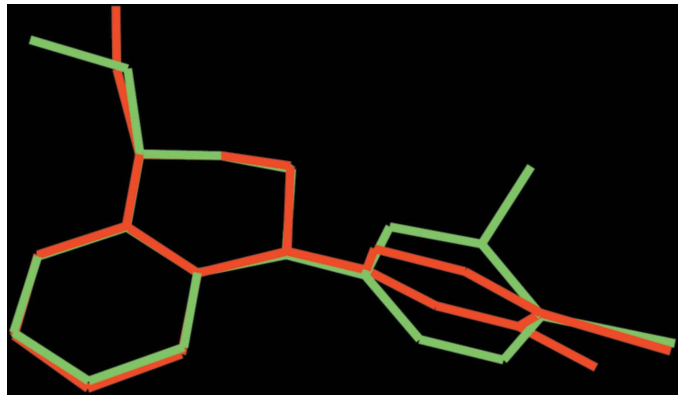


Figure 2
A least-squares overlay of form II (red) and form I (green).

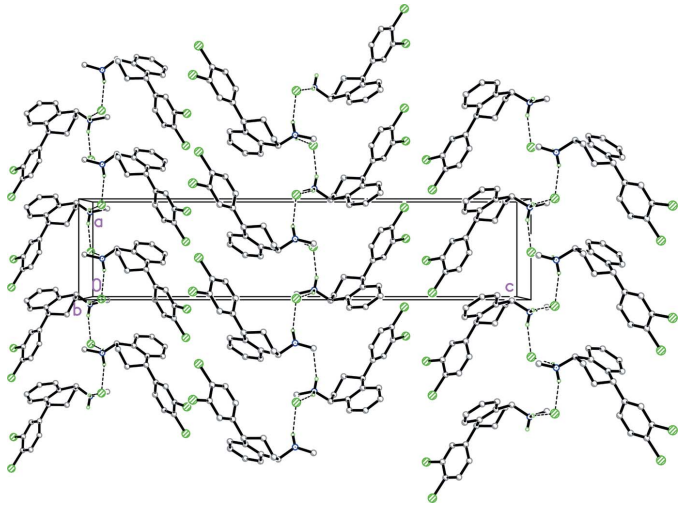


Figure 3
View, along the *b* axis, of the packing of form II. Dashed lines indicate N—H···Cl hydrogen bonds, showing the chain formation. H atoms attached to C atoms have been omitted for clarity.

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
Absorption correction: none
12731 measured reflections
3114 independent reflections
2815 reflections with $I > 2\sigma(I)$
$R_{int} = 0.038$
$\theta_{max} = 25.0°$
$h = -8 \rightarrow 8$
$k = -8 \rightarrow 8$
$l = -38 \rightarrow 38$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.045$
$wR(F^2) = 0.119$
$S = 1.14$
3114 reflections
191 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0675P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.33$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}
Absolute structure: Flack (1983), 1276 Friedel pairs
Flack parameter: 0.01 (8)

Table 1
Selected geometric parameters (Å, °).

Cl1—C13	1.751 (3)	C1—C9	1.526 (4)
Cl2—C14	1.740 (3)	C3—C4	1.525 (4)
N1—C17	1.479 (4)	C4—C11	1.524 (4)
N1—C1	1.515 (4)	C4—C10	1.533 (5)
C17—N1—C1	113.8 (2)	C11—C4—C3	111.2 (3)
N1—C1—C9	109.8 (2)	C11—C4—C10	114.8 (3)
N1—C1—C2	111.6 (3)	C3—C4—C10	112.3 (2)
N1—C1—C2—C3	77.9 (3)	C2—C3—C4—C10	−49.5 (3)
C9—C1—C2—C3	−46.0 (4)	C11—C4—C10—C5	−39.4 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···Cl3^{i}	0.90	2.31	3.144 (3)	154
N1—H1B···Cl3	0.90	2.26	3.120 (4)	160
C1—H1···Cl3^{ii}	0.98	2.73	3.683 (4)	166
C2—H2B···Cl3^{iii}	0.97	2.81	3.741 (4)	161

Symmetry codes: (i) $x+\frac{1}{2}, -y-\frac{1}{2}, -z$; (ii) $x+1, y, z$; (iii) $x+\frac{1}{2}, -y+\frac{1}{2}, -z$.

All H atoms were included in calculated positions (C—H = 0.93–0.98 Å and N—H = 0.90 Å) and refined using a riding model, with U_{iso}(H) values set at 1.2(N,C) or 1.5(CH_3) times U_{eq} of the parent atoms. The methyl groups were allowed to rotate but not to tip.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990) and *QMOL* (Gans & Shalloway, 2001); software used to prepare material for publication: *SHELXL97*.

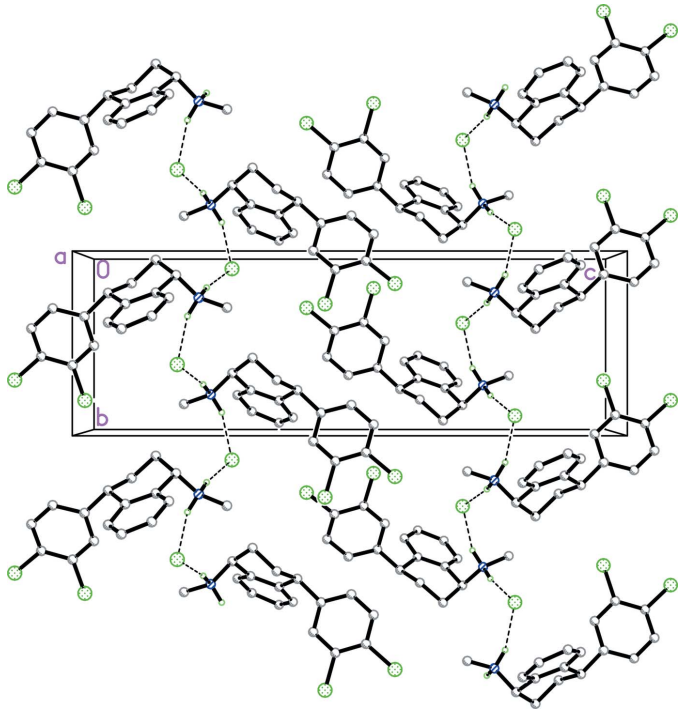


Figure 4
View, along the *a* axis, of the packing of form I. Dashed lines indicate N—H···Cl hydrogen bonds, showing the chain formation. H atoms attached to C atoms have been omitted for clarity.

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