Structure Analyses of Two Crystal Forms of Paroxetine Hydrochloride

Masaaki Yokota,† Hidehiro Uekusa, and Yuji Ohashi*

Department of Chemistry and Materials Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551

†Department of Applied Chemistry and Materials Science, Iwate University, Ueda, Morioka 020-8551

(Received January 25, 1999)

Two crystal forms of (−)-*trans*-4-(*p*-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine hydrochloride salt (paroxetine HCl) have been analyzed by X-rays. One form (Form I) is obtained as a hemihydrate and the other (Form II) is crystallized as the propan-2-ol solvate. The crystal of Form I belongs to the monoclinic system and the space group is $P2_1$. The unit-cell dimensions are; a = 14.5888(10), b = 10.1591(7), c = 13.0255(10) Å, β = 107.095(3)°, and V = 1845.2(2) Å^3. There are two crystallographically independent protonated paroxetine molecules with different conformations and chloride anions, and one water molecule in an asymmetric unit. The crystal of Form II also belongs to the monoclinic system and the space group is $P2_1$. The unit-cell dimensions are; a = 11.6504(7), b = 5.7374(3), c = 16.4107(10) Å, β = 90.959(2)°, and V = 1096.79(11) Å^3. There are one protonated paroxetine molecule, one chloride anion, and one solvent propan-2-ol molecule in an asymmetric unit. The protonated paroxetine molecule in Form II has a different conformation from those in Form I. The solvent propan-2-ol molecule is disordered in the channel formed by paroxetine molecules and chloride anions. The crystal was easily decomposed in open air at room temperature because the propan-2-ol molecules are easily released through the channel.

Paroxetine is a potent and selective 5-hydroxytryptamine (serotonin) reuptake inhibitor and is useful as a therapeutic agent for various diseases such as depression and Parkinson's diseases. The published works relating to paroxetine are mainly concerned with synthesis,[1] clinical study,[2] and solid-state characterization.[3,4] For an active ingredient of anti-depressant drugs, paroxetine has been used as its hydrochloride (Chart 1) crystals.[4] Depending on the conditions of syntheses, two different crystal forms (Forms I and II) were obtained.[3] Although the two forms have been studied using various methods such as IR spectra, powder X-ray diffraction patterns, differential scanning calorimeters, solubility, and thermogravimetric analysis,[3,4] the crystal structures have not been analyzed yet. This paper reports the X-ray crystallographic analyses of the two crystal forms using a new diffractometer that has just been designed by us and has been made by Rigaku for rapid data collection, called the R-AXIS RAPID.

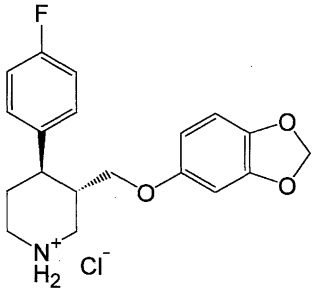

Chart 1. Paroxetine HCl.

Experimental

All the crystals used were prepared by recrystallization of paroxetine HCl (Form II) provided by Sumika Fine Chemicals, Co., Ltd.[1]

It is already reported that the crystals of Form I are easily obtained from an aqueous/propan-2-ol solution.[3] The solutions with various compositions of water/propan-2-ol solvent, the volume ratios of water, 1, 5, 10, and 50 vol% in the solvents were tried, to obtain the different crystal forms. In every case, only the crystals of Form I with a rod-like shape were crystallized. On the other hand, the crystals of Form II were obtained from a propan-2-ol solution as needle crystals.

Detailed information on X-ray crystallographic analyses of Forms I and II are summarized in Table 1. Intensity data of Form I were successfully collected at room temperature even when the crystal was kept in open air for a long time. However, the intensity data of Form II was obtained at 163 K, since the crystal was gradually decomposed at room temperature. To avoid frost attached to the crystal surface, the new diffractometer for rapid data collection (R-AXIS RAPID) was used for the data collections for both forms. Although it is possible to obtain the intensity data of Form I using the conventional four-circle diffractometer, the data were also collected using the new diffractometer to compare the two structures at the same precision. Both of the structures were solved by the direct method with the program SIR92[5] and were refined by the full-matrix least-squares with the program SHELXL-97.[6] The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were located at the calculated positions. The absolute configuration was identified by the Flack parameter.[7] The atomic scattering factors including the anomalous terms were taken from International Tables for Crystallography.[8] The atomic coordinates and the equivalent isotropic temperature factors are given in Ta-

Table 1. Crystal Data and Experimental Details for Form I and Form II Crystals of Paroxetine HCl

	Form I	Form II
Crystal data		
Chemical formula	$C_{19}H_{21}ClFNO_3 \cdot 0.5H_2O$	$C_{19}H_{21}ClFNO_3 \cdot C_3H_8O$
Chemical formula weight	374.84	425.93
Cell setting	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$
a/Å	14.5888(10)	11.6504(7)
b/Å	10.1591(7)	5.7374(3)
c/Å	13.0255(10)	16.4107(10)
β/°	107.095(3)	90.959(2)
V/Å^3	1845.2(2)	1096.79(11)
Z	4	2
D_x/Mg m^{-3}	1.349	1.290
Radiation type	Mo $K\alpha$	Mo $K\alpha$
Wavelength/Å	0.71069	0.71069
No. of reflections for cell parameters	6794	4296
θ range/°	2.48—27.48	2.13—27.48
μ/mm^{-1}	0.237	0.210
Temperature/K	295	163
Crystal form	Rod	Needle
Crystal size/mm	0.40 × 0.20 × 0.10	0.40 × 0.10 × 0.05
Crystal color	Colorless	Colorless
Data collection method		
Diffractometer	Rigaku R-AXIS Rapid (imaging plate diffractometer)	
Data collection method	Oscillation (IP) photograph	
Absorption correction ($T_{min,\ max}$)	0.644, 1.000	0.721, 1.000
No. of measured reflections	16769	9021
No. of independent reflections	7977	4181
No. of observed reflections	5112	2347
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
Rint	0.048	0.072
θ_{max}/°	27.48	27.48
Range of h, k, l	$-18 \rightarrow h \rightarrow 18$	$-14 \rightarrow h \rightarrow 15$
	$-13 \rightarrow k \rightarrow 13$	$-7 \rightarrow k \rightarrow 6$
	$-16 \rightarrow l \rightarrow 16$	$-21 \rightarrow l \rightarrow 21$
Completeness	0.970	0.936
Refinement		
Refinement on	F^2	F^2
$R(F)$ $[F^2 > 2\sigma(F^2)]$	0.0439	0.0655
$wR(F^2)$	0.1023	0.1608
S	0.897	0.956
No. of reflections used in refinement	7977	4181
No. of parameters used	469	260
H-atom treatment	Calculated	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (aP)^2]$ where $P = (F_o^2 + 2F_c^2)/3$	
	$a = 0.0559$	$a = 0.0917$
$(\Delta/\sigma)_{max}$	0.000	0.001
$\Delta\rho_{max}$/eÅ^{-3}	0.177	0.529
$\Delta\rho_{min}$/eÅ^{-3}	−0.192	−0.299
Extinction correction	None	None
Source of atomic scattering factors	International Tables for X-Ray Crystallography (Vol. C)[8]	
Flack parameter[7]	0.06(5)	0.24(12)
Computer programs		
Data collection	RAPID AUTO (Rigaku, 1998)[10]	
Cell refinement	RAPID AUTO (Rigaku, 1998)[10]	
Data reduction	RAPID AUTO (Rigaku, 1998)[10]	
Structure solution	SIR92 (Altomare et al., 1994)[5]	
Structure refinement	SHELXL-97 (Sheldrick, 1997)[6]	
Preparation of material for publication	ORTEP III for Windows (Farrugia, 1997)[9]	

ble 2. The CIF data including F_o–F_c Tables and for the two crystal forms are deposited as Document No. 72025 at the Office of the Editor of Bull. Chem, Soc. Jpn. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition numbers 125003-125004.

In order to observe the instability of the Form II crystals at room temperature, a crystal was left in the open air and the profiles of several reflections were measured several times at a constant interval at room temperature, using an AFC-5R four-cycle diffractometer.

Results and Discussion

Structure of Form I. The crystal structure viewed along the *b* axis is shown in Fig. 1. There are two protonated paroxetine molecules and two chloride ions together with one water molecule in an asymmetric unit. The ORTEP[9] drawing of the molecular structure with the numbering of atoms is shown in Fig. 2. The two crystallographically independent paroxetine molecules have different conformations. Selected bond distaces, bond angles, and torsion angles are given in Table 3. The two nitrogen atoms of the paroxetine molecules, the two Cl^- ions, and the water molecule are linked with hydrogen bonds to form an infinite chain along the *b* axis (Cl1A···N1A, N1A···Cl1B, Cl1B···N1B, N1B···O7, and O7···Cl1A are 3.216(3), 3.104(2), 3.074(2),

Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Paroxetine Hydrochloride

Atom	*x*	*y*	*z*	*U*(eq)	Atom	*x*	*y*	*z*	*U*(eq)
[Form I]					C13B	−2544(2)	29(3)	4657(2)	46(1)
Cl1A	−844(1)	374(1)	9460(1)	65(1)	C18B	−3391(2)	688(3)	4208(2)	56(1)
F1A	−5844(2)	163(2)	10547(2)	99(1)	C17B	−4129(2)	133(4)	3399(3)	65(1)
O1A	−4482(1)	−1747(2)	6232(2)	58(1)	C16B	−3957(2)	−1073(4)	3050(2)	61(1)
O2A	−7577(2)	−1135(2)	2684(2)	67(1)	C15B	−3116(2)	−1737(3)	3500(2)	57(1)
O3A	−6435(1)	−2705(2)	2646(2)	64(1)	C14B	−2387(2)	−1223(3)	4319(2)	54(1)
N1A	−1533(2)	−2143(2)	7929(2)	56(1)	C19B	−4001(3)	−2946(5)	2143(3)	94(1)
C1A	−5234(3)	−380(4)	10037(3)	70(1)	O7	607(2)	−1599(3)	10880(2)	75(1)
C2A	−4300(2)	−8(3)	10345(3)	69(1)					
C3A	−3690(2)	−577(3)	9834(3)	63(1)	[Form II]				
C4A	−4011(2)	−1512(3)	9033(2)	51(1)	Cl1	−227(1)	4514(2)	837(1)	41(1)
C5A	−4972(2)	−1851(3)	8741(3)	65(1)	F1	5750(2)	6437(6)	4005(2)	65(1)
C6A	−5594(2)	−1275(4)	9251(3)	73(1)	O1	1406(3)	−1105(5)	3749(2)	39(1)
C7A	−3350(2)	−2122(3)	8456(2)	46(1)	O2	2130(3)	−2386(7)	7028(2)	57(1)
C8A	−2414(2)	−2632(3)	9234(2)	55(1)	O3	1133(3)	939(7)	6634(2)	54(1)
C9A	−1727(2)	−3180(3)	8655(2)	60(1)	N1	628(3)	−541(9)	1213(2)	39(1)
C10A	−2422(2)	−1678(3)	7127(2)	55(1)	C1	4969(4)	5059(9)	3604(3)	46(1)
C11A	−3121(2)	−1115(3)	7671(2)	47(1)	C2	4532(4)	5798(10)	2853(4)	54(2)
C12A	−4022(2)	−624(3)	6832(2)	53(1)	C3	3746(4)	4401(10)	2457(3)	47(1)
C13A	−5263(2)	−1469(3)	5372(2)	48(1)	C4	3369(4)	2267(9)	2791(3)	39(1)
C14A	−5367(2)	−2250(3)	4461(2)	50(1)	C5	3850(4)	1625(10)	3544(3)	41(1)
C15A	−6165(2)	−2033(3)	3616(2)	50(1)	C6	4651(4)	3010(10)	3955(3)	44(1)
C16A	−6839(2)	−1109(3)	3644(2)	52(1)	C7	2510(4)	682(9)	2351(3)	35(1)
C17A	−6770(2)	−352(3)	4520(2)	62(1)	C8	2644(4)	709(10)	1419(3)	48(1)
C18A	−5961(2)	−547(3)	5400(2)	60(1)	C9	1848(4)	−988(9)	1004(3)	44(1)
C19A	−7238(3)	−2002(4)	2005(3)	79(1)	C10	447(4)	−515(10)	2111(2)	39(1)
Cl1B	−748(1)	−3453(1)	6206(1)	60(1)	C11	1253(4)	1214(9)	2551(2)	33(1)
F1B	2266(2)	−3732(2)	8029(2)	96(1)	C12	1019(4)	1138(9)	3454(3)	38(1)
O1B	−1895(1)	676(2)	5501(2)	58(1)	C13	1567(4)	−1397(8)	4575(3)	31(1)
O3B	−3149(2)	−2982(2)	3055(2)	85(1)	C14	1166(4)	213(8)	5148(3)	38(1)
O2B	−4567(2)	−1876(3)	2290(2)	89(1)	C15	1442(4)	−341(11)	5955(2)	39(1)
N1B	−275(2)	3762(2)	7133(2)	58(1)	C16	2032(4)	−2277(10)	6190(3)	42(1)
C1B	1872(2)	−2507(3)	7751(3)	66(1)	C17	2402(4)	−3902(10)	5627(3)	44(1)
C6B	1981(2)	−1920(4)	6857(3)	72(1)	C18	2165(4)	−3387(9)	4808(3)	37(1)
C5B	1594(2)	−680(3)	6588(3)	61(1)	C19	1847(5)	−41(11)	7260(3)	60(2)
C4B	1102(2)	−38(3)	7192(2)	49(1)	C20A	2482(14)	−5530(40)	9097(12)	101(5)
C3B	1012(2)	−682(3)	8102(3)	64(1)	O4A	3839(11)	−4270(30)	10150(8)	130(5)
C2B	1393(2)	−1933(3)	8386(3)	68(1)	C21A	3736(15)	−4940(30)	9322(10)	101(6)
C7B	711(2)	1338(3)	6892(2)	49(1)	C22A	4171(14)	−7580(30)	9113(9)	93(5)
C8B	1126(2)	2328(3)	7795(3)	62(1)	C20B	4143(15)	−4100(40)	8633(11)	126(7)
C9B	790(2)	3713(3)	7496(3)	65(1)	O4B	2815(10)	−1640(20)	8959(7)	119(4)
C10B	−701(2)	2826(3)	6244(2)	54(1)	C21B	2886(18)	−4190(40)	8767(13)	156(9)
C11B	−388(2)	1409(3)	6578(2)	47(1)	C22B	2684(12)	−5640(30)	9588(9)	91(4)
C12B	−886(2)	480(3)	5674(2)	50(1)					

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

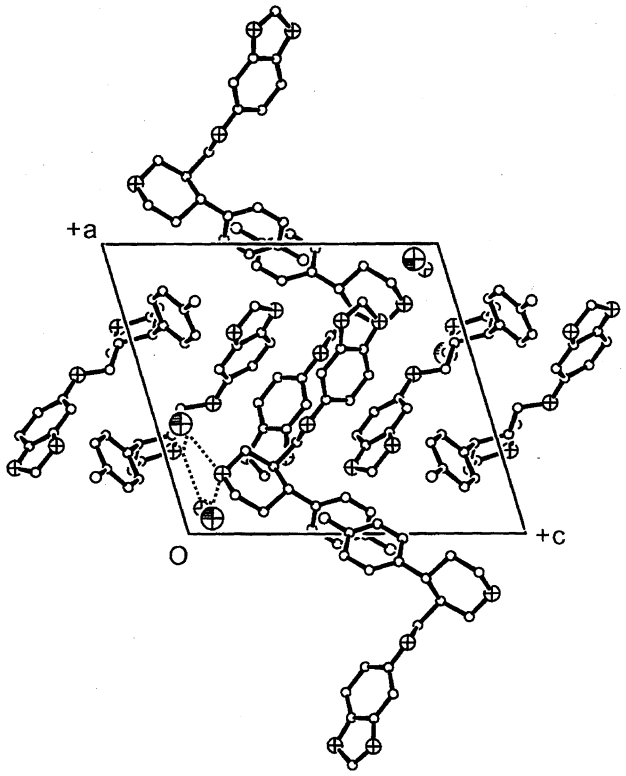

Fig. 1. Crystal structure of Form I viewed along the *b* axis. Non-hydrogen atoms are shown (C and F: sphere, N and O: principal axis and boundary, and Cl: shaded octant). Hydrogen bonds are shown by dotted lines.

2.794(4), and 3.141(3) Å, respectively).

Structure of Form II. The crystal structure viewed along the *b* axis is shown in Fig. 3. There are one protonated paroxetine molecule, one Cl^- ion, and one propan-2-ol molecule disordered in two sites. The molecular structure with the numbering of atoms is shown in Fig. 4. The conformation of the paroxetine molecule in Form II is different from either of the two paroxetine molecules found in Form I as indicated in Table 3, although the bond distances and angles are in good agreement with the corresponding ones in Form I. The paroxetine molecules in Form II are linked with hydrogen bonds between the N–H group and Cl^- ion to

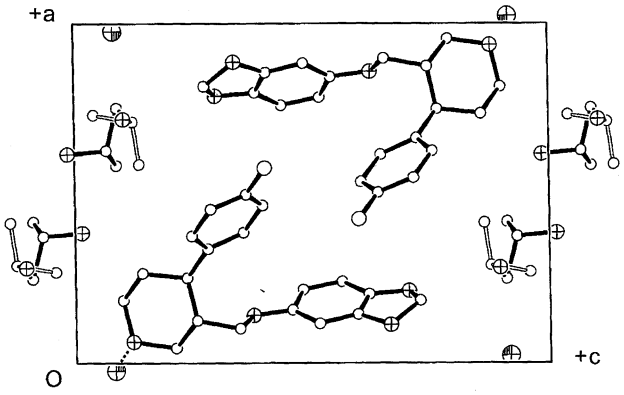

Fig. 3. Crystal structure of paroxetine HCl Form II viewed along the *b* axis. Non-hydrogen atoms are shown (C and F: sphere, N and O: principal axis and boundary; and Cl; shading octant). Hydrogen bonds are shown bt dotted lines.

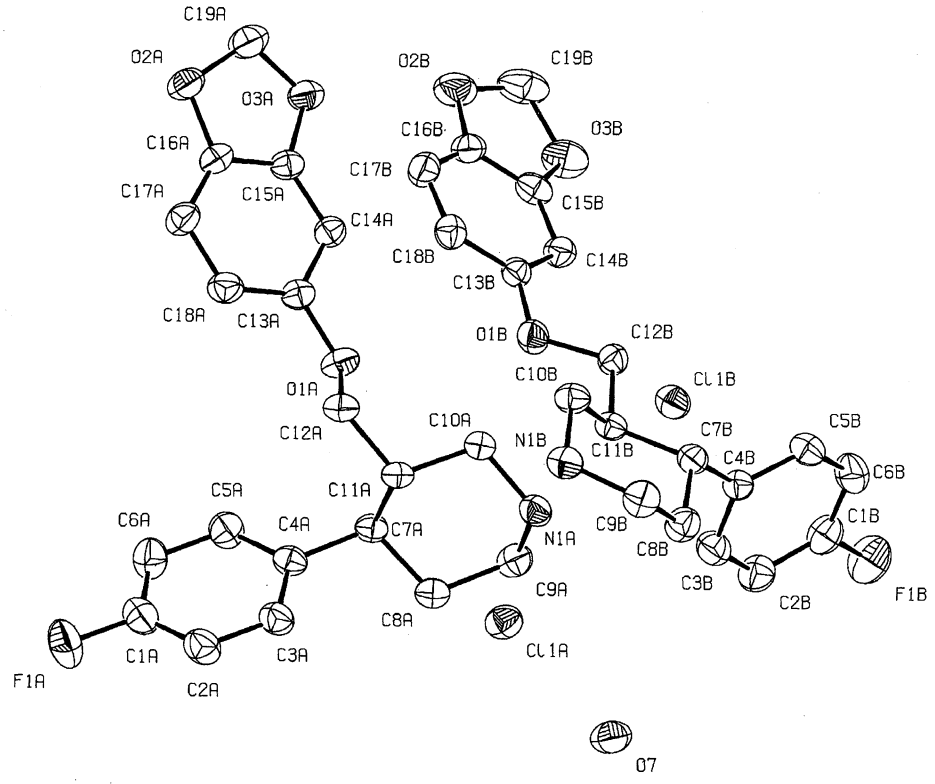

Fig. 2. ORTEP[9] drawing with the numbering of atoms for paroxetine HCl in Form I, showing two independent protonated paroxetine molecules in the asymmetric unit. Thermal ellipsoids are scaled to enclose 30% probability.

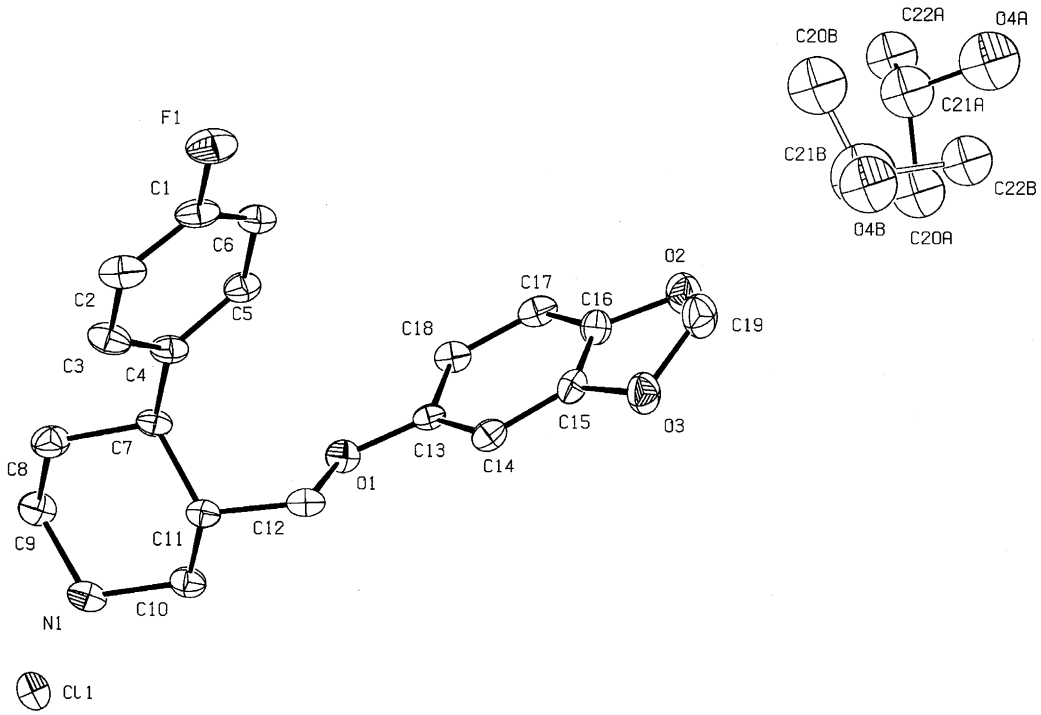

Fig. 4. ORTEP[9] drawing of paroxetine HCl and propan-2-ol molecules in the Form II crystal. The propan-2-ol molecules are disordered. Thermal ellipsoids scaled to enclose 30% probability. The minor part of propane-2-ol is indicated as open bonds.

Table 3. Selected Bond Lengths [Å], Angles [°], and Torsion Angles [°] for Paroxetine Hydrochloride in Forms I and II

	Form I		Form II
	Mol. A	Mol. B	
O1–C13	1.372(3)	1.387(3)	1.375(5)
O1–C12	1.433(3)	1.436(3)	1.445(6)
C11–C12	1.525(4)	1.517(4)	1.512(6)
C7–C11	1.551(4)	1.536(4)	1.537(6)
C4–C7	1.517(4)	1.516(4)	1.526(6)
C13–O1–C12	115.1(2)	119.2(2)	118.4(3)
O1–C12–C11	107.3(2)	105.7(2)	107.1(4)
C12–C11–C7	112.4(2)	113.7(2)	113.1(3)
C4–C7–C11	110.4(2)	113.3(2)	113.6(4)
C12–O1–C13–C14	142.4(2)	34.5(4)	12.7(6)
C12–O1–C13–C18	−42.2(4)	−149.2(3)	−166.7(4)
C13–O1–C12–C11	−174.3(2)	175.0(2)	163.4(4)
C7–C11–C12–O1	−60.4(3)	179.5(2)	−54.3(5)
C4–C7–C11–C12	−58.7(3)	−55.6(3)	−55.6(6)
C5–C4–C7–C11	104.7(3)	116.1(3)	92.0(5)
C3–C4–C7–C11	−73.1(3)	−66.3(3)	−89.9(5)

form infinite chains along the *b* axis. The N···Cl distances are 3.066(5) and 3.125(5) Å.

The propan-2-ol molecules are disordered in the channel formed by paroxetine molecules and Cl^- ions. The channel is extended along the *b* axis and has a considerably large cavity. There are no hydrogen bonds between paroxetine and propan-2-ol molecules.

To observe the decomposition of the crystal, several reflection profiles were measured at a constant interval using the four-cycle diffractometer. The sharp profiles were gradually changed to broad ones and no peaks were detected after seven hours. An amorphous solid material was left on the diffractometer. Since the thermal and spectroscopic analyses indicated a desolvation during the crystal decomposition,[3,4] the mechanism can be easily expected that propan-2-ol molecules are released through the cavity at room temperature.

One of the authors (M. Y.) was given a fund (Naichi Kenshuu) from the Ministry of Education, Science and Culture, to do this work at the Tokyo Institute of Technology.

References

1 K. Sugi, N. Itaya, T. Katsura, M. Igi, S. Yamazaki, T. Ishibashi, T. Yamaoka, Y. Kawada, and Y. Tagami, European Patent EP 0812827 (1997).

2 P. Plenge, E. T. Mellerup, T. Honore, and P.-Le-F. Honore, *J. Pharm. Pharmacol.*, **39**, 877 (1987).

3 P. C. Buxton, I. R. Lynch, and J. M. Roe, *Int. J. Pharm.*, **42**, 135 (1988).

4 R. D. Barnes, M. W. Wood-Kaczmar, A. D. Curzons, I. R. Lynch, J. E. Richardson, and P. C. Buxton, U.S. Patent 4721723 (1988).

5 A. Altomare, M. C. Burla, M. Camalli, M. Cascarano, C. Giacovazzo, A. Guagliardi, and G. Polidori, *SIR92*, *J. Appl. Crystallogr.*, **27**, 435 (1994).

6 G. M. Sheldrick, "SHELXL-97 Program for the Refinement of Crystal Structures," University of Goettingen, Germany (1997).

7 H. D. Flack, *Acta Crystallogr., Sect. A*, **A39**, 876 (1983).

8 "International Tables for X-Ray Crystallography," Kluwer

Academic Publishers, Dordrecht, Boston, and London (1992), Vol. C.

9 L. J. Farrugia, "ORTEP-III for Windows," *J. Appl. Crystallogr.*, **30**, 565 (1997).

10 "RAPID AUTO: IP image processing program," RIGAKU Corporation (1998).