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Structure of a New Crystallographic Form of Chlorpromazine Hydrochloride Hemihydrate

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Abstract. 3-Chloro-10-(3-dimethylaminopropyl)-phenothiazine hydrochloride hemihydrate, $C_{17}H_{20}ClN_2S^+.Cl^-.\frac{1}{2}H_2O$, $M_r = 364{\cdot}3$, monoclinic, $P2_1/c$, $a = 11{\cdot}861\ (4)$, $b = 31{\cdot}671\ (8)$, $c = 9{\cdot}599\ (2)$ Å, $\beta = 99{\cdot}06\ (2)°$, $V = 3560{\cdot}9$ Å^3, $Z = 8$, $D_x = 1{\cdot}36$ g cm^{-3}, $\lambda(\text{Mo } K\alpha_1) = 0{\cdot}70930$ Å, $\mu = 4{\cdot}8$ cm^{-1}, $F(000) = 1528$, $T = 100$ K. Final $R = 0{\cdot}061$ for 2679 observed reflections. The title compound crystallizes with two unique molecules and one water molecule in the asymmetric unit. The two molecules differ in the orientation of their dimethylaminopropyl side chains. The fold angles between the two benzo rings are 139·6 and 135·6°. There is an H-bond network involving the protonated N atoms, the water molecule and the chloride ions.

Introduction. Chlorpromazine is a common drug that has been used in psychiatry to control schizophrenia, manic depression and neurosis. It is believed to act as a competitive antagonist of dopamine in the brain and peripheral nervous system (Anden, Butcher, Corrodi, Fuye & Ungerstedtm, 1970; Yeh, McNay & Goldberg, 1969; Brotzu, 1970). In order to form a better understanding of the mechanism of its action, we have been studying the structural characteristics of a series of phenothiazine derivatives (Klein, Conrad & Morris, 1985).

Experimental. Colorless crystal, approximate dimensions 0·25 × 0·30 × 0·60 mm obtained from Aldrich Chemical Company and recrystallized from aqueous ethanol. Enraf–Nonius CAD-4 diffractometer, graphite-crystal-monochromatized Mo $K\alpha$ radiation. Unit-cell dimensions and systematic absences, $h0l$, $l = 2n + 1$ and $0k0$, $k = 2n + 1$, uniquely determined the space group as $P2_1/c$ with $Z = 8$. Lattice constants determined by least-squares fit of 25 reflections, $33 \le 2\theta \le 41°$, measured on the diffractometer. Three-dimensional intensity data collected in ω:2θ scan mode; total of 4915 independent reflections, 2679 observed with $I > 3\sigma(I)$; $0 \le 2\theta \le 50°$; $-14 \le h \le 14$, $0 \le k \le 37$, $0 \le l \le 11$. Data corrected for Lorentz and polarization effects. Four standard reflections measured every 2 h ($\bar{8}$,17,3, 080, 400 and 002) showed no significant change in intensity. Absorption as a function of ψ observed to be minimal and therefore not corrected. Structure solved by direct methods using *MULTAN*11/82 (Main *et al.*, 1982). Initial E map contained 34 non-H atoms from two chlorpromazine molecules. Remaining non-H atoms and N(2) and N(2)′ H atoms located on successive difference Fourier maps. All other H atoms calculated on the basis of sp^2 or sp^3 geometry and a C—H bond length of 0·95 Å. Full-matrix least-squares refinement on F of 45 anisotropic non-H atoms with 42 H-atom positions and isotropic thermal parameters fixed. Final $R = 0{\cdot}061$, $wR = 0{\cdot}081$, where $w = 1/\sigma(F)^2$ and $\sigma(F^2) = [\sigma(I)^2_{cs} + (0{\cdot}05)^2(F^2)^2]^{1/2}$, $S = 1{\cdot}60$ for observed reflections. In final least-squares cycle $(\Delta/\sigma)_{max} = 0{\cdot}03$. Max. and min. peaks in difference Fourier map 0·77 and −0·47 e Å^{-3}. Scattering factors taken from *International Tables for X-ray Crystallography* (1974) are corrected for anomalous-scattering contributions, CAD-4 *SDP* (Frenz, 1978) programs used.

Discussion. Final fractional coordinates for the non-H atoms are given in Table 1.* The numbering system for the molecule may be found in Fig. 1. Bond lengths and bond angles have been deposited.

McDowell (1969) reported crystals with unit-cell dimensions approximately the same as those reported here to disintegrate readily. Crystals of chlorpromazine hydrochloride were obtained from a benzene/ethanol solution and were very unstable. The structure of a different crystallographic form of chlorpromazine hydrochloride was reported previously (Dorignac-Calas & Marsau, 1972) to have a unit-cell volume one-half the size of the unit cell of the title compound.

The chlorpromazine hydrochloride reported here crystallizes with two unique molecules in the asymmetric unit and eight molecules in the unit cell. The two molecules differ crystallographically in the orientation

* Lists of bond lengths and bond angles, structure factors, anisotropic thermal parameters, and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42898 (33 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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of the dimethylaminopropyl side chains. One way to describe the orientation of the alkyl chains is to report the asymmetry of the chain by calculating the intramolecular distance between the amine N atom and the centers of the benzo rings. These values can be found in Table 2. Calculation of the torsion angles in the dimethylaminopropyl side chain yields angles of 134·9° and −63·5° for C(12)–N(1)–C(13)–C(14) and C(12)′–N(1)′–C(13)′–C(14)′, respectively. These torsion angles as well as the other torsion angles in the alkyl chain (Table 3) indicate that the orientation of the dimethylaminopropyl chains differs in the two molecules found in the asymmetric unit.

Table 2 contains some structural parameters for a series of nine phenothiazine molecules that all have *N*-substituted dimethylaminopropyl substituents. The intramolecular distances between the amine N atoms and the centers of the rings vary considerably. The different forms of chlorpromazine (chlorpromazine HCl, 1-chlorpromazine HBr, chlorpromazine sulfoxide and chlorpromazine free base) show varied orientations of the side chain. The reasons for these differences seem only to be due to the inherent flexibility in the chains, and depend very much on the crystal packing and on the intermolecular interactions. The fold angles for all of the molecules except methoxypromazine (Marsau & Gauthier, 1973) and chlorpromazine sulfoxide (Dahl, Hjorth & Hough, 1982) fall between 130·8° and 145·7° although wider fold angles are not uncommon. It is most likely that the fold angles of these molecules in solution are not rigid and show the same angle variations as those that are seen in the crystal structures.

Table 1. *Positional parameters and equivalent isotropic thermal parameters with their e.s.d.'s*

Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as:

$$B_{eq} = \tfrac{4}{3}[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)].$$

	x	*y*	*z*	B_{eq}(Å²)
Cl	0·5064 (1)	0·21795 (7)	0·1184 (2)	2·63 (5)
Cl(4)	−0·1391 (2)	0·38574 (7)	0·1974 (3)	3·75 (6)
S(1)	0·3181 (2)	0·42090 (6)	0·5997 (3)	2·40 (5)
O(1)	0·0699 (4)	0·7219 (2)	0·7489 (7)	4·0 (2)
N(1)	0·2930 (4)	0·3652 (2)	0·3469 (7)	1·5 (1)
N(2)	0·2363 (4)	0·2098 (2)	0·3022 (7)	1·3 (1)
C(1)	0·1890 (6)	0·4109 (2)	0·4862 (9)	1·7 (2)
C(2)	0·0891 (6)	0·4291 (2)	0·514 (1)	2·4 (2)
C(3)	−0·0133 (6)	0·4200 (2)	0·426 (1)	2·5 (2)
C(4)	−0·0136 (6)	0·3932 (2)	0·3141 (9)	2·1 (2)
C(5)	0·0858 (6)	0·3748 (2)	0·2853 (9)	2·0 (2)
C(6)	0·1891 (6)	0·3838 (2)	0·3733 (8)	1·4 (2)
C(7)	0·4112 (5)	0·4202 (2)	0·4740 (9)	1·8 (2)
C(8)	0·5059 (6)	0·4462(2)	0·492 (1)	2·6 (2)
C(9)	0·5823 (6)	0·4443 (3)	0·3956 (9)	2·2 (2)
C(10)	0·5624 (6)	0·4179 (3)	0·2818 (9)	2·0 (2)
C(11)	0·4637 (6)	0·3921 (2)	0·2627 (9)	1·6 (2)
C(12)	0·3895 (5)	0·3926 (2)	0·3609 (9)	1·8 (2)
C(13)	0·2902 (5)	0·3277 (2)	0·2621 (9)	1·8 (2)
C(14)	0·2492 (5)	0·2891 (2)	0·3321 (9)	1·6 (2)
C(15)	0·2490 (5)	0·2517 (2)	0·2324 (8)	1·2 (2)
C(16)	0·3449 (6)	0·1975 (3)	0·3948 (9)	2·3 (2)
C(17)	0·2004 (6)	0·1769 (3)	0·194 (1)	2·8 (2)
Cl′	1·0365 (1)	0·29458 (6)	0·9628 (2)	2·12 (4)
Cl(4)′	0·2550 (1)	0·08620 (6)	0·4943 (2)	2·26 (5)
S(1)′	−0·1980 (1)	−0·00068 (6)	0·2172 (2)	1·98 (4)
N(1)′	−0·1651 (4)	0·0910 (2)	0·2536 (7)	1·3 (1)
N(2)′	−0·2976 (4)	0·2157 (2)	−0·0429 (6)	1·2 (1)
C(1)′	−0·0690 (5)	0·0233 (2)	0·2917 (8)	1·1 (2)
C(2)′	0·0284 (6)	−0·0006 (2)	0·3364 (8)	1·4 (2)
C(3)′	0·1298 (5)	0·0187 (2)	0·3939 (9)	1·8 (2)
C(4)′	0·1291 (5)	0·0620 (2)	0·4105 (8)	1·4 (2)
C(5)′	0·0352 (5)	0·0866 (2)	0·3708 (9)	1·5 (2)
C(6)′	−0·0656 (5)	0·0673 (2)	0·3064 (8)	1·2 (2)
C(7)′	−0·2894 (5)	0·0338 (2)	0·2901 (9)	1·6 (2)
C(8)′	−0·3876 (6)	0·0170 (2)	0·3375 (9)	2·1 (2)
C(9)′	−0·4650 (6)	0·0448 (3)	0·3819 (9)	2·0 (2)
C(10)′	−0·4453 (6)	0·0870 (3)	0·383 (1)	2·5 (2)
C(11)′	−0·3462 (6)	0·1043 (2)	0·3442 (9)	2·2 (2)
C(12)′	−0·2684 (5)	0·0765 (2)	0·2973 (8)	1·3 (2)
C(13)′	−0·1531 (5)	0·1351 (2)	0·2187 (8)	1·4 (2)
C(14)′	−0·2365 (5)	0·1498 (2)	0·0935 (8)	1·1 (2)
C(15)′	−0·2042 (5)	0·1937 (2)	0·0546 (9)	1·8 (2)
C(16)′	−0·3299 (6)	0·1940 (2)	−0·1790 (9)	2·3 (2)
C(17)′	−0·2703 (6)	0·2604 (2)	−0·0597 (9)	2·0 (2)

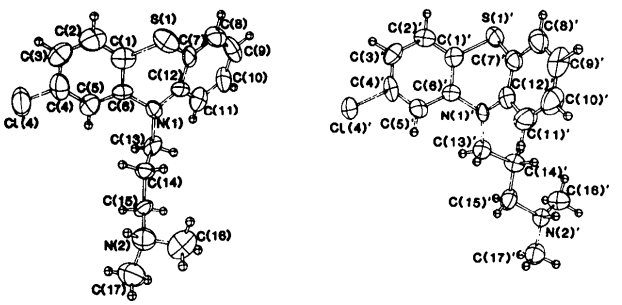

Fig. 1. Molecular structure and numbering system for both molecules of chlorpromazine hydrochloride. The thermal ellipsoids were drawn at 90% probability levels.

Table 2. *Comparison of structural parameters for several molecules with dimethylaminopropyl side chains*

Fold angles and distances between ring center and amine atoms were calculated from fractional coordinates except in promazine HCl. The '*A*' ring is defined as the one with the substituent on the 2-position.

	Fold angle (°)	N–*A* (Å)	N–*B* (Å)	Reference
Chlorpromazine HCl	139·6	6·437 (3)	7·233 (3)	*a*
	135·6	6·251 (3)	7·408 (3)	
Chlorpromazine HCl	130·8	6·74	4·88	*b*
Chloropromazine sulfoxide	159·5	4·85	6·63	*c*
1-Chlorpromazine HBr	145·7	6·574	6·353	*d*
Chlorpromazine free base	134·0	4·15	6·81	*e*
7-Hydroxychlorpromazine	138·8	6·111	6·505	*f*
Promazine HCl	140	6·09	7·39	*g*
Methoxypromazine	166	6·357	6·647	*h*
Triflupromazine HCl	136·3	6·38	6·42	*i*
	145·0	6·28	7·28	

References: (*a*) This work, (*b*) Dorignac-Calas & Marsau (1972), (*c*) Dahl, Hjorth & Hough (1982), (*d*) Martin, Hallberg, Kramer, Svensson, Bates & Ortega (1984), (*e*) McDowell (1969), (*f*) McDowell (1977), (*g*) Rogers, Horn & Kennard (1976), (*h*) Marsau & Gauthier (1973), (*i*) Phelps & Cordes (1974).

Table 3. *Selected dimethylaminopropyl torsion angles* (°)

C(12)–N(1)–C(13)–C(14)	134·9
C(12)′–N(1)′–C(13)′–C(14)′	−63·5
N(1)–C(13)–C(14)–C(15)	179·5
N(1)′–C(13)′–C(14)′–C(15)′	−171·5
C(13)–C(14)–C(15)–N(2)	166·6
C(13)′–C(14)′–C(15)′–N(2)′	−164·9

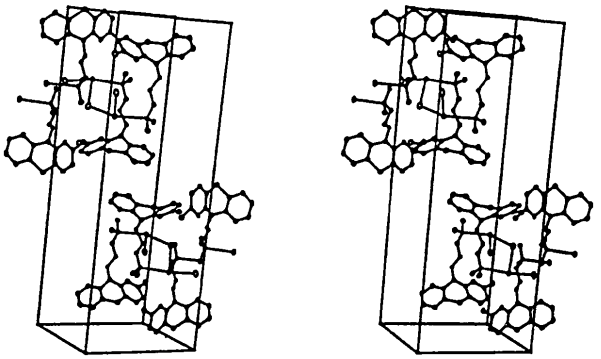

Fig. 2. Stereoscopic packing diagram of the contents of the unit cell showing the H-bond network.

There is an H-bond network involving the protonated N atoms [N(2) and N(2)′], the water molecule and the chloride ions (Cl and Cl′). There are H bonds between the chloride ions and the amine H atoms [Cl···HN(2)′, 2·021 (2) and Cl′···HN(2), 2·089 (5) Å; Cl···HN(2)′—N(2)′, 173·2 (4) and Cl′···HN(2)—N(2), 165·3 (4)°]. Additionally, Cl′ is H-bonded to the water molecule through HO(2) [Cl′···HO(2), 2·248 (6) Å and Cl′···HO(2)—O(1), 104·8 (3)°]. Fig. 2 shows the H-bonding scheme between the molecules and ions in the unit cell.

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Crystallographic Characterization of the Anticancer Drug Bisantrene* Cocrystallized with Pyridinium Chloride

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Abstract. $C_{22}H_{24}N_8^{2+}.C_5H_6N^+.3Cl^-.2H_2O$, $M_r = 623{\cdot}0$, monoclinic, $C2/c$, $a = 23{\cdot}410\ (4)$, $b = 9{\cdot}694\ (2)$, $c = 13{\cdot}745\ (3)$ Å, $\beta = 104{\cdot}76\ (2)°$, $V = 3016{\cdot}3\ (4)$ Å^3, $Z = 4$, $D_m = 1{\cdot}39$, $D_x = 1{\cdot}372$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 3{\cdot}44$ cm^{-1}, $F(000) = 1304$, $T = 293$ K, $R = 0{\cdot}045$ for 1241 unique reflections [$I \geq 3{\cdot}0\sigma(I)$]. The crystal structure consists of stacks of alternating bisantrenium and pyridinium cations. Adjacent stacks are linked by strong interstack

* 9,10-Anthracenedicarboxaldehyde bis[(4,5-dihydro-1*H*-imidazol-2-yl)hydrazone].

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