

The Structure of Promaziniumyl Free Radical Cation Tetrachlorocuprate Salt,* (C₁₇H₂₁N₂S)⁺[CuCl₄]⁻

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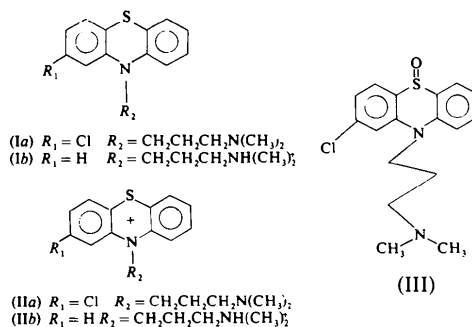
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Abstract. $M_r = 490.8$, monoclinic, $P2_1/c$, $a = 7.548$ (6), $b = 14.613$ (23), $c = 18.271$ (23) Å, $\beta = 91.69$ (8)°, $V = 2014.4$ Å³, $Z = 4$, D_m (floatation in CCl₄/hexane) = 1.607 (3), $D_x = 1.619$ Mg m⁻³. The structure was solved by the heavy-atom method and refined to residuals of $R = 0.070$ and $R_w = 0.072$ for the 2345 non-zero reflections available from a twinned crystal collected with Cu K α radiation on an automated diffractometer. Those reflections with $|h| = 1, 6$ and 7 were not used due to twin overlap. The CuCl₄²⁻ anion is a flattened tetrahedron with an average Cu–Cl distance of 2.25 (4) Å and two sets of Cl–Cu–Cl angles with two at 133.2 (1) and four at 99 (3)°. The cation is the monoprotonated promaziniumyl free radical. This tricyclic system is nearly flat with r.m.s. deviations of 0.08 Å for the 14 atoms, and the cations form two stacks along the a axis. The most likely site for the unpaired electron is the S atom; the two C–S distances, 1.714 (6) Å, are much shorter than found in neutral phenothiazines, 1.767 Å. All other bonds in the tricyclic system are normal C–C and C–N aromatic bonds. The cation is protonated at the terminal dimethylamino group.

Introduction. Derivatives of phenothiazine are an extremely important class of drugs, some of which are useful in the treatment of severe psychiatric disorders. The best known derivative is chlorpromazine, CPZ (Ia), which was first introduced into clinical psychiatry by Delay, Deniker & Harl (1952) for the treatment of schizophrenia. From an investigation of the enzymatic oxidation of CPZ, Cavanaugh (1957) proposed the existence of a stable red intermediate free radical, CPZ⁺ (IIa), which upon further oxidation gave the inactive product CPZ sulfoxide (III). It was suggested by Piette, Bulow & Yamazaki (1964) that this radical cation was responsible for the activity of this tranquilizer and Ohnishi & McConnell (1965) found that CPZ⁺ intercalates in both DNA and RNA. However, more recently the psychotic activity of these drugs has been shown to involve the binding of non-radical molecules or ions to two dopamine receptors (Kebabian & Calne,

1979) which is in accord with the current hypothesis linking dopamine and schizophrenia (Carlsson & Lindqvist, 1963).



The interest in free radical CPZ⁺ has now focused on its responsibility for the occasional side effects of long-term treatment by CPZ. Free radicals of CPZ⁺ are thought to cause skin photosensitivity, melanin deposition, retinal damage and ocular opacity in some patients (Zelickson & Zeller, 1964; Blois, 1965) and the damage apparently occurs because the CPZ⁺ radical is an electron donor (to form CPZ²⁺) or an electron acceptor (Forrest, Forrest & Berger, 1958; Lee, Akera & Brody, 1976). However, it may also scavenge other free radicals thus accounting for its anti-inflammatory action (Mahood, Packer, Searle, Willson & Wolfenden, 1980; Bahnmann & Asmus, 1980). The CPZ⁺ and other phenothiazine free radicals are quite easily formed. Borg & Cotzias (1962) reported oxidation of phenothiazines by various transition-metal ions (Fe³⁺, Co³⁺, Mn³⁺) and other mild oxidizing agents in aqueous acid solution. They are also quite stable; salts of various phenothiazine free radicals have been prepared (Ortiz, Gonzalez & Fernandez-Alonso, 1981; Merkle, Discher & Felmeister, 1964), although they do decay slowly in aqueous solutions (Felmeister, Schaubman & Howe, 1965).

Our interest in the phenothiazine free radicals is somewhat more serendipitous; we wanted to confirm the coordination of Cu²⁺ by CPZ or promazine (PZ) proposed by Huang & Gabay (1974). They obtained crystalline products from reactions of CPZ.HCl or

* 10-(3-Dimethylammoniopropyl)phenothiaziniumyl tetrachlorocuprate(II).

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PZ.HCl (Ib) with CuCl_2 in ethanol and based their hypothesis upon interpretation of various spectra (IR, UV-VIS, MS, NMR and ESR) for the CPZ product. However, they also noted some evidence for CPZ^+ free radicals in its aqueous solutions. We examined the crystalline product obtained by reacting PZ.HCl and CuCl_2 in ethanol; the absence of the chlorine substituent would avoid isomerization problems (*i.e. cis vs trans*) in any anticipated copper complex. We found that Cu^{2+} under these conditions (strong acid) did not coordinate with promazine but instead formed the salt promaziniumyl tetrachlorocuprate ($\text{PZH}^{2+} \cdot \text{CuCl}_4^{2-}$) where PZH^{2+} is the doubly charged promaziniumyl radical cation (IIb) protonated at the terminal dimethylamino group, and it is probable that the CPZ-Cu complex reported by Huang & Gabay is the similar salt $\text{CPZH}^{2+} \cdot \text{CuCl}_4^{2-}$. As crystallization of free radical cations is relatively rare and this free radical is pharmacologically significant we now describe this important structure.

Experimental. Crystals of $\text{PZH}^{2+} \cdot \text{CuCl}_4^{2-}$ were prepared according to the procedure described by Huang & Gabay (1974). Precession photographs revealed $2/m$ Laue symmetry and the systematic absences $h0l, l = 2n + 1; 0k0, k = 2n + 1$ that uniquely correspond to the space group $P2_1/c$. The crystals were invariably twinned along (001). A refinement of the setting angles for 10 reflections ($7.7^\circ \leq 2\theta \leq 56.6^\circ$) from one twin member on a Syntex PI diffractometer using Cu $K\alpha$ radiation gave the crystal data listed in the *Abstract*.

The diffraction intensities for 3830 reflections accessible with the diffractometer ($2\theta \leq 140^\circ$) were collected from one twin member of a small plate crystal ($0.008 \times 0.18 \times 0.42$ mm) with graphite-monochromated Cu $K\alpha$ radiation. A $2^\circ \text{ min}^{-1} 2\theta-\theta$ scan speed was used over $\pm 1.0^\circ$ about the $\alpha_1 - \alpha_2$ doublet with a background count of 0.125 of the scan time at each end. The intensities of four check reflections showed little variation during the data collection. The intensities were corrected using techniques described previously (Post, Von Dreele & Buseck, 1982) and an analytical absorption correction (de Meulenaer & Tompa, 1965) was applied for $\mu = 7.514 \text{ mm}^{-1}$ ($0.210 \leq A \leq 0.866$) to yield 2345 unique non-zero reflections. The reflections with $|h| = 1, 6$ and 7 were not included in this list because of overlap by reflections from the other twin.

The structure was solved by standard heavy-atom techniques.* The final model with anisotropic thermal parameters was refined by large-block least squares

(226 parameters in four blocks) using the scattering factors for $\text{Cu}^0, \text{Cl}^0, \text{S}^0, \text{N}^0, \text{C}^0$ and H^0 and including the anomalous-scattering factors for Cu, Cl and S (*International Tables for X-ray Crystallography*, 1974) to give the residuals $R = 0.070$ and $R_w = 0.072$ for the 2345 non-zero reflections. The reflections with $h = 0$ were assigned a separate scale factor since both twins contribute to those reflections. All H atoms were placed at their idealized positions.*

Discussion. As indicated in the *Introduction*, the compound reported by Huang & Gabay (1974) is not a coordination complex of Cu^{2+} and promazine but is the CuCl_4^{2-} salt of the promaziniumyl free radical cation. The atom coordinates with their equivalent isotropic thermal parameters for this salt are listed in Table 1 and bond distances and angles for both the cation and the anion are given in Table 2. Fig. 1 shows a perspective view of the promaziniumyl radical cation and Fig. 2 is a stereoscopic view of the unit cell and its contents.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38133 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Fractional coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\times 10^3 \text{ \AA}^2$)

The estimated standard deviations are in parentheses.

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}^*
Cu	2255.2 (1.2)	1333.0 (0.6)	3213.6 (0.5)	38
Cl(1)	1862.9 (2.5)	761.2 (1.1)	4335.3 (0.8)	50
Cl(2)	2629.7 (2.0)	-60.9 (1.0)	2653.6 (0.8)	40
Cl(3)	169.6 (2.3)	2400.6 (1.1)	3119.1 (0.9)	47
Cl(4)	4468.2 (2.6)	2097.8 (1.3)	2710.7 (1.4)	62
S(1)	7960.4 (2.6)	4040.9 (1.2)	4313.5 (0.8)	44
C(2)	8018 (8)	3366 (4)	5084 (3)	34
C(3)	8495 (10)	2461 (5)	4974 (4)	47
C(4)	8595 (10)	1861 (5)	5555 (4)	52
C(5)	8250 (10)	2167 (5)	6256 (4)	48
C(6)	7805 (9)	3062 (5)	6377 (4)	44
C(7)	7669 (8)	3686 (4)	5794 (3)	34
N(8)	7152 (7)	4600 (3)	5921 (3)	35
C(9)	7210 (8)	5291 (4)	5400 (3)	37
C(10)	6962 (10)	6221 (4)	5602 (4)	46
C(11)	6982 (11)	6893 (5)	5080 (5)	55
C(12)	7271 (11)	6702 (5)	4365 (4)	56
C(13)	7570 (10)	5829 (5)	4146 (3)	46
C(14)	7573 (8)	5105 (4)	4663 (3)	36
C(15)	6550 (8)	4844 (4)	6668 (3)	35
C(16)	8124 (10)	5106 (5)	7162 (3)	45
C(17)	7648 (10)	5674 (5)	7830 (4)	53
N(18)	6442 (7)	5221 (4)	8349 (3)	37
C(19)	5844 (11)	5920 (6)	8887 (4)	57
C(20)	7182 (12)	4437 (6)	8746 (5)	65

* $U_{\text{eq}} = (U_1 U_2 U_3)^{1/3}$ where U_1, U_2, U_3 are the principal axes of the thermal ellipsoid.

* From this point on all calculations were performed using the CRYSTALS package of computer programs (Rollett & Carruthers, 1974) adapted for the Univac 1110 and Amdahl 470B/7V computers.

Table 2. Bond distances (Å) and angles (°)

Estimated standard deviations are given in parentheses.

Cu—Cl(1)	2.241 (2)	Cu—Cl(3)	2.219 (2)
Cu—Cl(2)	2.301 (2)	Cu—Cl(4)	2.230 (2)
Cl(1)—Cu—Cl(2)	95.62 (7)	Cl(2)—Cu—Cl(3)	133.15 (5)
Cl(1)—Cu—Cl(3)	102.75 (7)	Cl(2)—Cu—Cl(4)	99.04 (7)
Cl(1)—Cu—Cl(4)	133.19 (6)	Cl(3)—Cu—Cl(4)	98.85 (7)
C(2)—C(3)	1.388 (9)	C(9)—C(14)	1.409 (7)
C(3)—C(4)	1.377 (10)	S(1)—C(2)	1.717 (6)
C(4)—C(5)	1.390 (10)	S(1)—C(14)	1.710 (6)
C(5)—C(6)	1.369 (9)	N(8)—C(7)	1.413 (7)
C(6)—C(7)	1.404 (8)	N(8)—C(9)	1.389 (7)
C(7)—C(2)	1.412 (8)	N(8)—C(15)	1.495 (6)
C(14)—C(13)	1.418 (8)	C(15)—C(16)	1.520 (9)
C(13)—C(12)	1.359 (10)	C(16)—C(17)	1.527 (9)
C(12)—C(11)	1.360 (11)	C(17)—N(18)	1.490 (8)
C(11)—C(10)	1.369 (10)	N(18)—C(19)	1.497 (8)
C(10)—C(9)	1.422 (8)	N(18)—C(20)	1.459 (9)
C(2)—C(3)—C(4)	120.3 (6)	C(13)—C(14)—S(1)	115.2 (4)
C(3)—C(4)—C(5)	119.9 (6)	C(9)—C(14)—S(1)	125.0 (4)
C(4)—C(5)—C(6)	120.6 (6)	C(6)—C(7)—N(8)	120.3 (5)
C(5)—C(6)—C(7)	120.8 (5)	C(2)—C(7)—N(8)	121.6 (5)
C(6)—C(7)—C(2)	118.1 (5)	C(7)—N(8)—C(9)	124.1 (4)
C(7)—C(2)—C(3)	120.3 (5)	C(10)—C(9)—N(8)	120.7 (5)
C(14)—C(13)—C(12)	120.1 (6)	C(14)—C(9)—N(8)	121.7 (5)
C(13)—C(12)—C(11)	120.5 (6)	C(7)—N(8)—C(15)	117.9 (4)
C(12)—C(11)—C(10)	121.8 (6)	C(9)—N(8)—C(15)	118.0 (4)
C(11)—C(10)—C(9)	120.1 (6)	N(8)—C(15)—C(16)	110.4 (6)
C(10)—C(9)—C(14)	117.6 (5)	C(15)—C(16)—C(17)	114.4 (6)
C(9)—C(14)—C(13)	119.8 (5)	C(16)—C(17)—N(18)	115.4 (6)
C(3)—C(2)—S(1)	115.4 (5)	C(17)—N(18)—C(19)	108.4 (5)
C(7)—C(2)—S(1)	124.3 (4)	C(17)—N(18)—C(20)	115.7 (5)
C(2)—S(1)—C(14)	102.5 (2)	C(19)—N(18)—C(20)	109.2 (5)

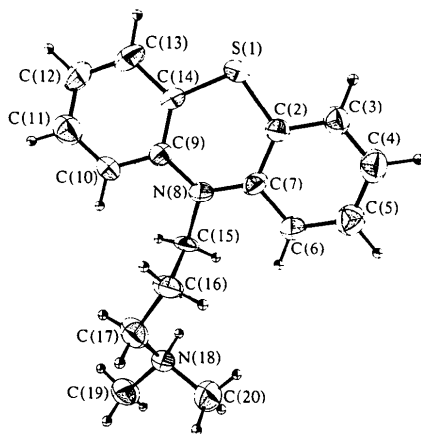
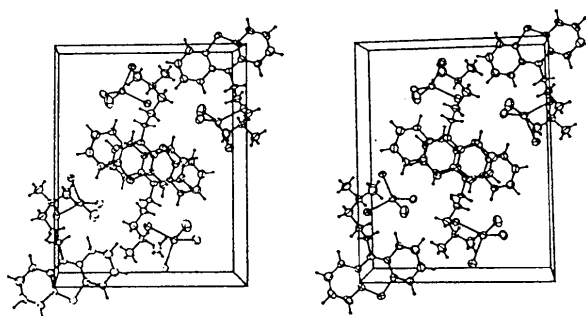
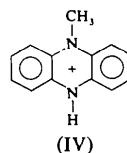


Fig. 1. Perspective representation of the promaziniumyl cation.

The promaziniumyl ion is a doubly charged cation arising from protonation of the dimethylamino group on the side chain and abstraction of an electron from the tricyclic ring system. This oxidation results in a molecular geometry that is markedly different from that of the non-radical phenothiazines. This phenothiazine group is quite flat; the 14 atoms in the tricyclic system are coplanar with r.m.s. deviations from the best plane of 0.08 Å. The slight nonplanarity is best

Fig. 2. A stereodiagram of the unit cell and its contents. The unit cell is viewed along the *a* axis with the *b* axis vertical and the *c* axis horizontal.

described as a folding (dihedral angle = 172.7°) about the S...N line; the two C₆NS groups have r.m.s. deviations of 0.012 and 0.017 Å from their best planes. Non-radical phenothiazines are butterfly shaped with dihedral angles between the two sides ranging from a minimum of 134.4° to a maximum of 158.5° (McDowell, 1976). Theoretical calculations (Pullman, 1968) indicate that the radical cation should be flat while the neutral molecule is folded. These calculations also indicate that the unpaired electron and cation charge should reside in the S atom. This appears to be borne out by this structure; the C—S bonds, 1.714 (6) Å ave., are considerably shorter than those found in normal phenothiazines, 1.767 Å (McDowell, 1976). The CSC angle in the cation is thus somewhat larger than expected for a normal phenothiazine, 98.7°, in order to accommodate the planar tricyclic system. The remaining bonds are more nearly normal; the N—C bonds average to 1.410 Å which is slightly shorter than found in average phenothiazines, 1.411 Å, and the benzene C—C bonds are identical, 1.390 (23) Å, to the average, 1.389 Å, for phenothiazines. A comparison with the *N*-hydro-*N'*-methylphenaziniumyl radical cation (HMP⁺) (IV) (Morosin, 1978) further supports the idea that the unpaired electron is primarily on the S atom; in (IV) it must be on the N atoms and thus the C—N distances are much shorter, 1.385 Å, than found in the present case.

As can be seen from Fig. 2, the planar tricyclic cations stack in two columns parallel to the *a* axis, one at (*y*, *z*) = (0, 0) and the other at (*y*, *z*) = ($\frac{1}{2}$, $\frac{1}{2}$). Along a

column the cations alternate with inversion centers so the cation planes in a column are exactly parallel, and there are two different interplanar spacings, 3.73 and 3.60 Å, in each column. The cation planes in one column are nearly parallel to those in the other; they are tilted 13.9° from the *a* axis in nearly opposite directions so that the angle between the set of planes in one column and that in the other is 23.7°. The tricyclic groups in a stack are arranged so that the center C₄NS ring is directly above and below the C(9)–C(14) benzene ring and *vice versa*; the C(2)–C(7) ring protrudes from either side of the stack. The different electronic environments seen by the two benzene rings result in some slight differences (0 to 4σ) in equivalent bonds in the two rings. The stacking of planar radical cations has also been observed in other systems; in HMP⁺.ClO₄⁻ (Morosin, 1978) the HMP⁺ ions form two stacks which are tilted at a much larger angle, 72.7°, with respect to each other. In that case the interplanar separation is only 3.26 Å and the tricyclic groups are staggered so that all three rings interact in the stack. In addition, a number of phenothiazine free radical salts of ClO₄⁻ and Br⁻ are known (Ortiz, Gonzalez & Fernandez-Alonso, 1981), all of which are presumed to have stacked radical cations. Apparently the adduct between CPZ and 7,7,8,8-tetracyano-*p*-quinodimethane (CPZ–TCNQ) reported by Metzger, Thiessen, Hopkins & Simpson (1974) does not contain radical CPZ⁺ cations. The cation probably is the CPZH⁺ cation; the tricyclic groups for the two non-equivalent cations in that structure are butterfly shaped with dihedral angles of 143.1 and 147.2° and are similar to neutral phenothiazines (Metzger, 1982). However, the TCNQ⁻ ions do form a stack in that structure and the cations are arranged in the spaces between the stacks. Both cation and anion radicals can also form mixed stacks such as are found in HMP⁺.TCNQ⁻ (Morosin, 1976, 1978).

The CuCl₄²⁻ ion is a flattened tetrahedron and is very similar to that found in many such salts (Harlow, Wells, Watt & Simonsen, 1975; Battaglia, Corradi, Marcotrigiano, Menabue & Pellacani, 1979). The average Cu–Cl bond is 2.25 (4) Å and the two largest Cl–Cu–Cl angles average to 133.2 (1)°.

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