Crystal and Molecular Structure of the Alimemazine Cation Radical

Maria del Carmen Apreda, Felix H. Cano, and Concepción Foces-Foces
Instituto de Química-Física Rocasolano, C.S.I.C., Serrano 119, 28006 Madrid, Spain
Fransisco López-Rupérez, Jose C. Conesa, and Javier Soria *
Instituto de Catálisis y Petroleoquímica, C.S.I.C., Serrano 119, 28006 Madrid, Spain

The crystal structure of the alimemazine (trimeprazine) cation radical, a phenothiazine drug molecule, has been determined from three-dimensional *X*-ray diffraction data and refined by least-squares methods. Cell constants were *a* 10.674 9(4), *b* 12.741 9(5), *c* 9.509 9(4) Å, α 110.863(3), β 103.433(3), γ 66.671(4)°, $Z = 2$. The molecule is planar, the angle between the best planes for the two benzene rings being 1.9(3)°, The C–S–C angle is 102.6(4)° and S–C bonds are 1.709(11) and 1.710(7) Å in length. The side-chain is protonated at the nitrogen atom and asymmetrically placed in relation to the tricyclic system.

The pharmacological properties of phenothiazine drugs has stimulated research on their structural features in the solid state by *X*-ray diffraction[1,2] in an attempt to provide information on the structure–activity relationships in this class of drugs.[3–5] However, in spite of the biological activity of the cation radical forms[6–8] and of the interesting solid-state properties of their ion radical salts[9,10] the number of *X*-ray diffraction studies on this type of species is few.[11–13]

In previous works we have studied the alimemazine cation radical (ALMZ$^+$) [10-(3-dimethylamino-2-methylpropyl)-phenothiazine], a phenothiazine drug with a side-chain branched due to the presence of a methyl group at the level of the second carbon,[14,15] by means of e.s.r. The results showed conformational changes in solution in relation to unbranched radicals. To determine how this difference in the side-chain affects the structural characteristics of ALMZ$^+$ in the solid state, we have carried out an *X*-ray diffraction study of this radical. The results are compared with those previously reported for other phenothiazine cation radicals, mainly chlorpromazine (CPZ$^+$), because the single crystals contained the same type of counterion.

Experimental

The alimemazine sample (0.25 g), in tartrate form (Rhône Poulenc Pharma), was dissolved in perchloric acid (5 ml; 70% in H_2O). The oxidation was assisted by the addition of a drop of 30% hydrogen peroxide solution, which remarkably intensified the dark red colour of the solution.[16,17] This latter was then diluted with equal volumes first of acetone and then of ether. After cooling at −5 °C a fine crystalline precipitate was obtained, which was washed with ether and dried. From this preparation an appropriate single crystal was selected for the *X*-ray diffraction study.

Crystal Data.—The sample size was 0.08 × 0.20 × 0.27 mm and the absorption coefficient was 39.85 cm^{-1}, no correction being done. Cell constants were *a* 10.674 9(4), *b* 12.741 9(5), *c* 9.509 9(4) Å, α 110.863(3), β 103.433(3), γ 66.671(4)°, $Z = 2$. They were obtained by least-squares fitting of the setting angles for 78 reflexions with $\theta < 45°$. The species have the formula $(C_{18}H_{23}N_2S)^{2+}(ClO_4)_2^-$, the cation radical being protonated at the N(2) atom. Hereafter the formula HALMZ^{2+} for alimemazine cation radical is used.

Data Collection and Processing.—The data were collected on a Philips PW 1100 diffractometer with Cu-K_α, graphite-monochromated radiation. The 2 745 measurements were done by ω—2θ scans, up to $\theta < 55°$, giving rise to 2 032 observed reflexions [$3\sigma_c(I)$ criterion].

Table 1. Final atomic co-ordinates

Atom	*x*	*y*	*z*
S	0.113 0(2)	−0.467 4(2)	0.290 3(2)
N(1)	0.326 6(5)	−0.337 9(4)	0.448 0(6)
C(1)	0.223 5(13)	−0.252 8(10)	0.091 9(12)
C(2)	0.130 8(11)	−0.307 8(9)	0.017 5(11)
C(3)	0.100 3(11)	−0.370 8(10)	0.082 3(11)
C(4)	0.164 2(7)	−0.383 4(6)	0.225 3(8)
C(5)	0.260 2(7)	−0.328 5(6)	0.305 5(8)
C(6)	0.288 5(10)	−0.262 1(8)	0.235 7(10)
C(7)	0.212 9(7)	−0.468 3(6)	0.459 1(8)
C(8)	0.195 0(9)	−0.536 4(7)	0.536 5(11)
C(9)	0.263 1(9)	−0.540 3(7)	0.675 3(11)
C(10)	0.351 3(9)	−0.477 1(7)	0.738 9(11)
C(11)	0.372 1(8)	−0.411 5(7)	0.665 2(9)
C(12)	0.303 8(6)	−0.404 6(5)	0.521 5(7)
C(13)	0.430 8(7)	−0.280 7(6)	0.515 9(10)
C(14)	0.374 0(9)	−0.144 9(6)	0.590 1(9)
C(15)	0.316 0(8)	−0.116 7(6)	0.735 0(9)
N(2)	0.252 6(7)	0.015 5(5)	0.811 0(7)
C(16)	0.215 7(14)	0.036 8(9)	0.962 7(11)
C(17)	0.135 9(12)	0.077 4(10)	0.718 8(13)
C(18)	0.489 1(17)	−0.096 0(14)	0.615 5(18)
Cl(1)	0.370 8(2)	0.276 0(2)	−0.018 4(3)
O(1)	0.437 4(8)	0.153 5(7)	−0.062 9(13)
O(2)	0.233 2(7)	0.311 5(7)	−0.077 7(9)
O(3)	0.437 1(10)	0.348 6(10)	−0.018 1(15)
O(4)	0.369 7(9)	0.299 8(10)	0.145 2(10)
Cl(2)	0.070 8(2)	0.155 3(2)	0.342 4(3)
O(5)	0.180 0(11)	0.056 5(10)	0.345 0(15)
O(6)	−0.023 1(8)	0.182 7(7)	0.447 6(8)
O(7)	−0.000 9(16)	0.105 0(15)	0.197 3(12)
O(8)	0.089 6(17)	0.244 4(11)	0.311 4(14)

Structure Analysis and Refinement.—A non-hydrogen model was obtained by direct methods[18,19] and refined by least-squares.[20] The hydrogen atoms were located on a difference map and weights were assigned so as to give no trends in $\langle w\Delta^2\rangle$ *versus* $\langle F_o\rangle$ or $\langle \sin\theta/\lambda\rangle$. The atomic scattering factors used were taken from ref. 21. The final agreement factors were 0.083 and 0.085 (*R* and R_w, respectively), with a ratio of freedom of 5.5 reflexions per parameter (which were 372). In the final difference synthesis only one relevant peak, of *ca.* 1 e Å^{-3}, appears, near the Cl atom of a ClO_4^- group.

Results

The final atomic co-ordinates are presented in Table 1. Those for hydrogen atoms, along with the thermal parameters and observed and calculated structure factors, are available on request. Tables 2 and 3 show the main geometrical features of the title compound, the O–Cl–O angles ranging from 97.9(8) to 120.8(7)°. The numbering scheme is presented in Figure 1, which is a view of the compound with the involved hydrogen interactions, numerically described in Table 4. Figures 2 and 3 show lateral views of the cation moiety, in order to clarify the conformation of the ring system and the substituent chain. Newman projections along (N(1)–C(13) and C(13)–C(14) are presented in Figure 4; included in it are the corresponding data for the chlorpromazine cation radical case (CPZ^+).[13] Finally the most significant contacts between closest molecules in $HALMZ^{2+}$ and CPZ^+ single crystals related by the symmetry operations are compared in Table 5.

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

S–C(4)	1.709(11)	S–C(7)	1.710(7)
N(1)–C(5)	1.398(9)	N(1)–C(12)	1.392(11)
N(1)–C(13)	1.470(10)	C(1)–C(2)	1.357(19)
C(1)–C(6)	1.405(15)	C(2)–C(3)	1.336(21)
C(3)–C(4)	1.406(13)	C(4)–C(5)	1.395(11)
C(5)–C(6)	1.394(16)	C(7)–C(8)	1.408(15)
C(7)–C(12)	1.401(11)	C(8)–C(9)	1.358(14)
C(9)–C(10)	1.375(14)	Cl(1)–O(1)	1.383(8)
C(10)–C(11)	1.370(16)	Cl(1)–O(2)	1.397(7)
C(11)–C(12)	1.406(10)	Cl(1)–O(3)	1.368(15)
C(13)–C(14)	1.536(9)	Cl(1)–O(4)	1.477(10)
C(14)–C(15)	1.510(13)	Cl(2)–O(5)	1.338(10)
C(14)–C(18)	1.522(23)	Cl(2)–O(6)	1.439(10)
C(15)–N(2)	1.509(8)	Cl(2)–O(7)	1.472(13)
N(2)–C(16)	1.486(14)	Cl(2)–O(8)	1.364(18)
N(2)–C(17)	1.467(13)		
C(4)–S–C(7)	102.6(4)	C(12)–N(1)–C(13)	119.8(6)
C(5)–N(1)–C(13)	117.4(6)	C(5)–N(1)–C(12)	122.7(6)
C(2)–C(1)–C(6)	120.9(12)	C(1)–C(2)–C(3)	119.5(10)
C(2)–C(3)–C(4)	121.4(11)	S–C(4)–C(3)	114.9(7)
C(3)–C(4)–C(5)	121.0(8)	S–C(4)–C(5)	124.1(6)
N(1)–C(5)–C(4)	123.3(7)	C(4)–C(5)–C(6)	116.3(7)
N(1)–C(5)–C(6)	120.4(8)	C(1)–C(6)–C(5)	121.0(10)
S–C(7)–C(12)	124.2(6)	S–C(7)–C(8)	114.8(6)
C(8)–C(7)–C(12)	121.0(7)	C(7)–C(8)–C(9)	121.0(9)
C(8)–C(9)–C(10)	118.7(9)	C(9)–C(10)–C(11)	121.5(9)
C(10)–C(11)–C(12)	121.8(8)	C(7)–C(12)–C(11)	116.0(7)
N(1)–C(12)–C(11)	121.0(7)	N(1)–C(12)–C(7)	123.0(6)
N(1)–C(13)–C(14)	115.1(7)	C(13)–C(14)–C(18)	108.0(9)
C(13)–C(14)–C(15)	110.6(7)	C(15)–C(14)–C(18)	112.4(9)
C(14)–C(15)–N(2)	113.6(6)	C(15)–N(2)–C(17)	113.7(7)
C(15)–N(2)–C(16)	110.6(7)	C(16)–N(2)–C(17)	111.6(8)

Discussion

The experimental results indicate that only one crystallographically independent dication is present in the single crystal, having a C–S–C angle of 102.6(4)° and S–C bond lengths of 1.709(11) and 1.710(7) Å, midway between the values for a C–S single (1.81 Å) and double bond (1.61 Å). As in the case of phenothiazine cation radical ($PTAZ^+$),[12] this suggests that the π-delocalization is spread over the central ring. Although the flattening of the phenothiazine ring system does not always

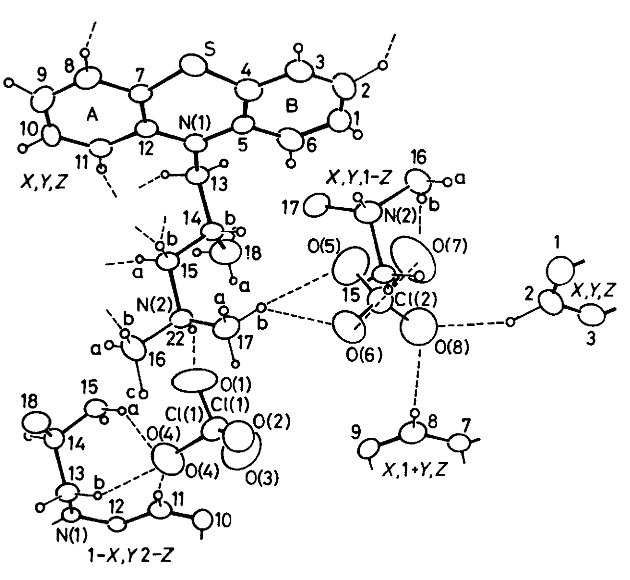

Figure 1. ORTEP view[24] of the molecular packing with atomic numbering

Table 3. Selected conformational angles (°)

C(7)–S–C(4)–C(5)	−2.9(8)	S–C(4)–C(5)–N(1)	0.9(11)
C(12)–N(1)–C(5)–C(4)	0.9(11)	C(5)–N(1)–C(12)–C(7)	0.2(11)
S–C(7)–C(12)–N(1)	−3.1(11)	C(4)–S–C(7)–C(12)	4.0(8)
C(12)–N(1)–C(13)–C(14)	−104.5(8)	C(5)–N(1)–C(13)–C(14)	79.4(9)
C(12)–N(1)–C(13)–H(13a)	141.8(53)	C(12)–N(1)–C(13)–H(13b)	18.0(61)
C(5)–N(1)–C(13)–H(13a)	−34.3(54)	C(5)–N(1)–C(13)–H(13b)	−158.0(61)
N(1)–C(13)–C(14)–C(15)	71.6(9)	N(1)–C(13)–C(14)–C(18)	−165.0(9)
N(1)–C(13)–C(14)–H(14)	−43.5(54)	H(13a)–C(13)–C(14)–C(15)	−171.2(52)
H(13a)–C(13)–C(14)–C(18)	−47.8(52)	H(13a)–C(13)–C(14)–H(14)	73.7(75)
H(13b)–C(13)–C(14)–C(15)	−52.2(60)	H(13b)–C(13)–C(14)–C(18)	71.2(61)
H(13b)–C(13)–C(14)–H(14)	−67.3(80)	C(13)–C(14)–C(15)–N(2)	−177.5(7)
C(13)–C(14)–C(15)–H(15a)	62.7(58)	C(13)–C(14)–C(15)–H(15b)	−60.9(42)
C(18)–C(14)–C(15)–N(2)	61.7(11)	C(18)–C(14)–C(15)–H(15a)	−58.1(58)
C(18)–C(14)–C(15)–H(15b)	178.3(42)	H(14)–C(14)–C(15)–N(2)	−63.4(55)
H(14)–C(14)–C(15)–H(15a)	176.8(79)	H(14)–C(14)–C(15)–H(15b)	53.2(68)
C(14)–C(15)–N(2)–C(16)	−172.0(8)	C(14)–C(15)–N(2)–C(17)	61.6(10)
C(14)–C(15)–N(2)–H(22)	−52.1(54)	H(15a)–C(15)–N(2)–C(16)	−51.1(57)
H(15a)–C(15)–N(2)–C(17)	−177.5(57)	H(15a)–C(15)–N(2)–H(22)	68.9(78)
H(15b)–C(15)–N(2)–C(16)	68.4(41)	H(15b)–C(15)–N(2)–C(17)	−58.0(41)
H(15b)–C(15)–N(2)–H(22)	−171.7(67)	C(7)–S · · · N(1)–C(13)	116.6(7)
C(7)–S · · · N(1)–C(12)	−1.4(4)	C(7)–S · · · N(1)–C(5)	177.3(4)
C(4)–S · · · N(1)–C(13)	−60.3(9)	C(4)–S · · · N(1)–C(12)	−178.3(4)
C(4)–S · · · N(1)–C(5)	0.4(4)		

Table 4. Hydrogen interactions (Å) X–H ··· Y. That marked with an asterisk is the most likely to be a bond, with N ··· O(1) distance of 2.926(13) Å, the other C ··· O distances being larger than 3 Å

X	H	Y	X–H	H ··· Y	X–H ··· Y
N(2)	H(22)	O(1)	0.91(10)	2.08(9)	154(7) *
C(15)	H(15a)	O(4)	0.95(8)	2.61(7)	149(6)
C(13)	H(13b)	O(4)	0.98(9)	2.57(9)	151(7)
C(11)	H(11)	O(4)	0.87(8)	2.58(8)	171(7)
C(17)	H(17b)	O(5)	1.13(15)	2.52(15)	160(8)
C(17)	H(17b)	O(6)	1.13(15)	2.61(12)	109(7)
C(15)	H(15b)	O(6)	1.02(8)	2.54(7)	114(3)
C(15)	H(15b)	O(7)	1.02(8)	2.64(8)	159(3)
C(16)	H(16b)	O(7)	0.95(11)	2.34(10)	160(7)
C(2)	H(2)	O(8)	1.11(13)	2.55(13)	156(7)
C(8)	H(8)	O(8)	0.92(9)	2.45(8)	151(6)

Table 5. Most significant contacts between closest molecules related by the symmetry operations*

Distances	CPZ$^+$	HALMZ^{2+}
S ··· C(11)	* 3.45(3)/3.54(2)	5.04(8)
S ··· H(14b)	* 3.00(—)/5.4(—)	6.80(48)
S ··· H(13b)	3.85(13)/5.48(13)	4.16(66)
S ··· N(1)	3.86(3)/4.07(3)	5.82(4)
N(1) ··· C(8)	* 3.27(5)/3.79(4)	4.69(10)

* *I.e.* $(1/2 - x, \pm 1/2 + y, 3/2 - z)$ in CPZ$^+$ and $(1 - x, -1 - y, 1 - z)$ in HALMZ^{2+}. For the CPZ$^+$ molecule there are two values as the molecules involved are not strictly parallel. Those contacts marked with an asterisk are just about the sum of the van der Waals radii (ref. 23), the others being much larger. The distances are expressed in Å and estimated standard deviations are in parentheses.

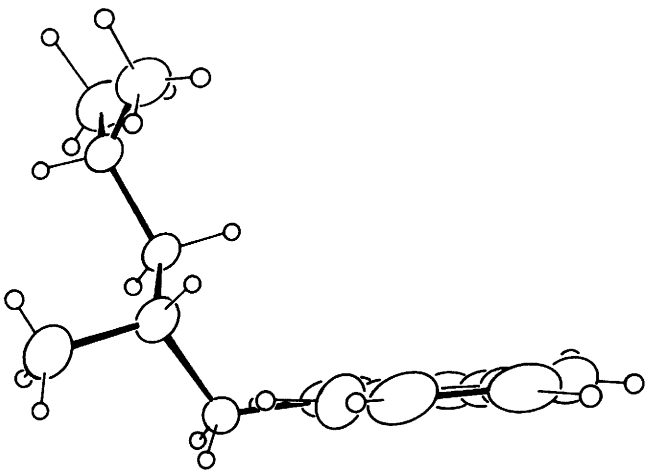

Figure 2. Lateral ORTEP view, showing the chain folding

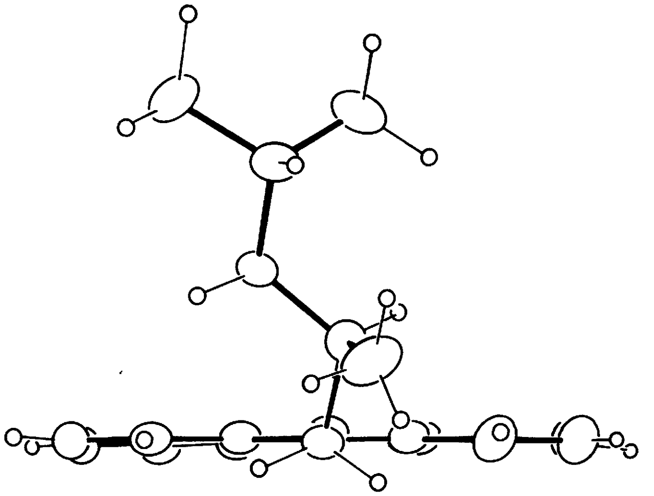

Figure 3. Lateral ORTEP view, showing the chain exit

accompany the π-delocalization,[1,2] here the system is quite planar, the angles between the two external benzene rings being 1.9(3)°. Moreover, N(1) also has a planar geometry, with angles of 122.7(6), 119.8(6), and 117.4(6)°. The N(1)–C (rings) bond lengths are in agreement with the values found in this type of compound.[1,2]

The conformation of the side-chain is described by the torsion angles (Table 3) and displayed in Figure 4. The Newman projection along the N(1)–C(13) (Figure 4a) shows that the situation of the side-chain in HALMZ$^+$ and CPZ$^+$ radicals is different. The separation of C(14) from the bisecting plane of C(5)–N(1)–C(12) [12.5(7) *versus* 1.3(16)°] is larger and consequently H(13a) and H(13b) and the theoretical atoms, a′ and b′,[22] are asymmetrically situated with respect to this bisecting plane. Around the C(13)–C(14) bond, the Newman projection shows that there is a twist of about 120° with respect to the CPZ$^+$ symmetrical conformation, where the main chain followed nearly the same direction as the methyl group follows here (Figure 4b). This twist is mainly responsible for the different orientation of the side-chain, leaving the N(2) atom asymmetrically situated with respect to the centroids of the benzene rings: 6.192(10) and 5.717(11) Å.

The branching of the side-chain seems responsible for its torsion around N(1)–C(13) bond and also for the probable '*endo*' position of H(13a) and H(13b) in relation to the folded plane of the ring system. Thus, in HALMZ^{2+}, C(5) and C(2) and H(13a) and H(13b) are placed at the same side of the plane normal to the bisecting one, while in CPZ$^+$, without branching, both pairs of atoms are on different sides (Figure 4). Although these differences are not significant in terms of the achieved precision, the distances H(13b) ··· H(11) and H(13a) ··· H(6) are shorter for HALMZ^{2+} [1.89(15); 1.99(11) Å] than for CPZ$^+$ [2.12(15); 2.09(18) Å], showing in the first case larger steric crowding in this part of the molecule. If the position of H(13a, b) atoms are really '*endo*', the repulsion between both pairs of hydrogens atoms could contribute in the HALMZ^{2+} radical to more perfect planarity of the ring system.

The crystal packs with a network of hydrogen interactions (Figure 1) and its asymmetric parts involving two ClO_4^- groups and five molecular units. Among those interactions, the most likely one to have hydrogen-bond character[23] is marked with an asterisk in Table 4. It seems that the conformation adopted by the side-chain could be due to packing require-

Table 6. Geometrical and conformational parameters of phenothiazine cation radicals

Compound	I (°)			II (Å)		III (Å)		Ref.
	C_6–C_6	C(7)–S–C(4)	C(12)–N–C(5)	S–C(4)	S–C(7)	A–N(2)	B–N(2)	
$PTAZ^+$-$Ni(tfd)_2^-$	172.2	102.8	121	1.74(1)	1.72(1)			11
$PTAZ^+$-$SbCl_6^-$	175.8	104	127	1.71(2)	1.71(2)			12
CPZ^+-ClO_4^-	169.9(11)	99.6(9)	125.5(12)	1.776(13)	1.773(22)	6.62(2)	6.62(2)	13
$HALMZ^{2+}$-$(ClO_4^-)_2$	1.9(3)	102.6(4)	122.7(7)	1.709(11)	1.710(7)	5.72(1)	6.19(1)	This work

I, Dihedral angles between the best planes for the benzene rings and bond angles to heteroatoms. II, Comparison of bond distances in the central ring. III, Distances of the terminal nitrogen atom N(2) from the lateral ring centres. Estimated standard deviations in parentheses.

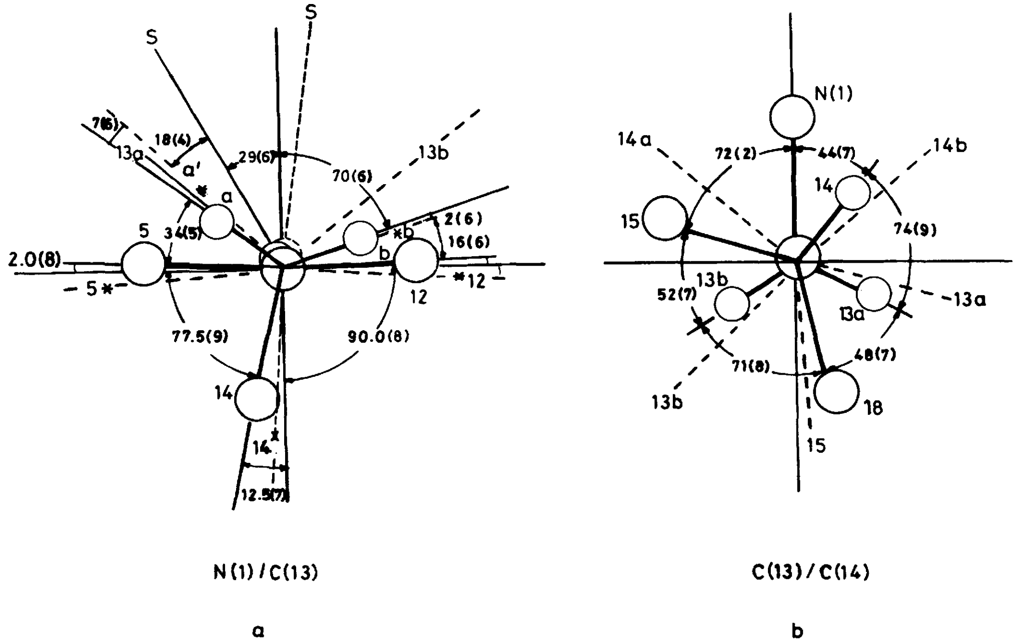

Figure 4. Newman's projections along (a) N(1)–C(13) and (b) C(13)–C(14). Dashed lines show the C–H(13) bonds corresponding to the CPZ^+ case. a' and b' refer to the H(13a) and H(13b) calculated.[22] The plane bisecting the C(5)–N(1)–C(12) angle and its orthogonal one are used as the reference frame. The first one is supposed to contain the z-axis of the N(1) $2p(\pi)$ orbital. S marks the direction of the sulphur atom position, partially hidden by the N and C atoms

ments. The results in Table 5 indicate that, even with the same counterion, the crystal packings of $HALMZ^{2+}$ and CPZ^+ are very different. In the first case, the distance between the planes corresponding to different molecules in the unit cell is greater and the molecules are laterally displaced. This result can be related to the protonation of N(2), present in $HALMZ^{2+}$ but not in CPZ^+. A different distribution of the electrostatic charge on the side-chain can be an important factor responsible for the different ion arrangements observed in the crystal structure.

Table 6 reports some geometrical and conformational parameters for phenothiazine cation radicals. For unsubstituted phenothiazine radical ($PTAZ^+$) differences in the type of counterions modify the packing and some molecular angles as C_6–C_6 or C(12)–N(1)–C(5). For CPZ^+ and $HALMZ^{2+}$ radicals, as the perchlorate salt, some differences are observed for the C_6–C_6 and C(7)–S–C(7) angles and S–C(4) and S–C(7) bond lengths; the angles increasing and the bonds becoming shorter on going from CPZ^+ to $HALMZ^+$. These results agree well with greater participation of the sulphur atom in the molecular conjugation in the case of $HALMZ^{2+}$ and can explain the differences between the g values of $HALMZ^{2+}$ and CPZ^+ radicals observed in the solid state by e.s.r. The principal values of the $\hat{g}$ tensor, measured for single crystals in previous work,[13,15] show the following relations: $g_{xx}(HALMZ^{2+}) > g_{xx}(CPZ^+)$ [2.0076(1) *versus* 2.0071(1)]; $g_{yy}(HALMZ^{2+}) > g_{yy}(CPZ^+)$ [2.0061(1) *versus* 2.0058(1)]; and $g_{zz}(HALMZ^{2+}) = g_{zz}(CPZ^+)$ [2.0022(1)] and can be justified, in agreement with X-ray diffraction results, assuming a larger contribution for $HALMZ^{2+}$ to the unpaired electron wavefunction of the orbitals of the sulphur atom, whose spin–orbit coupling constant is larger than that of nitrogen (365 cm^{-1} *versus* 78 cm^{-1}).

Acknowledgements

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