Electron Spin Resonance Study of the Influence of the Nitrogen Substituent on the Conformation and Spin Density Distribution of Phenothiazine Derivatives

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The cation radicals of promethazine, isothiazine, and diethazine have been studied by e.s.r., and the results compared with those of other *N*-substituted phenothiazine derivatives. These results indicate that a position of the terminal amino centre closer to the ring system induces a cationic charge and spin density displacement in the heterocycle from nitrogen to sulphur. For short-chain derivatives with γ-branching, both electronic and steric effects can affect the spin density distribution. The correlation between the hyperfine couplings a_N and $a(H_{i,j})$ found in these species is interpreted as a modification of the relative weights of different resonant structures.

The biological activity of the *N*-substituted phenothiazines and their pharmacological potency are strongly influenced by the nature of the 10- and 2-R substituents in the tricyclic system (Table 1). Although the phenothiazine nucleus plays a generic role, the diverse pharmacological properties of the derivatives with varying 10-R indicate that this side-chain constitutes a specific molecular entity with pharmacological repercussions probably by a combined topographic and electronic effect.

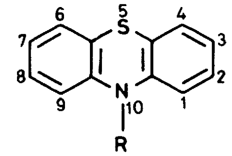
Different experimental observations[1–10] have prompted several workers[7–12] to suggest that the cation radical forms of some phenothiazine drugs can play a decisive role in neuroleptic activity. Independently of the validity of such a hypothesis, some electronic effects of the side-chain on the ring system in the neutral and cation radical forms can be correlated. Thus an e.s.r. study of the different cation radicals of phenothiazine derivatives of pharmacological interest could provide important information.[13]

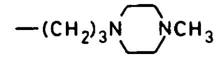
Although some e.s.r. studies have been made,[14–16] a large number of components of this family of drugs has not been analysed with enough resolution.[17–21] In previous work[22–27] we have studied several cation radicals of phenothiazine derivatives in different conditions (liquid solution, frozen solution, powder, and single crystal), to obtain information on the e.s.r. parameters related to the conformational and electronic characteristics. In this work, we have extended the study to three other monosubstituted derivatives, promethazine (PRMTZ), isothiazine (ISTZ), and diethazine (DTAZ), with a shorter, branched, or unbranched side-chain. An overall analysis of our results allows us to discuss the effects of the side-chain 10-R on the molecular conformation and the unpaired spin distribution in the ring system for several compounds with pharmacological interest.

Experimental

The different phenothiazines, as hydrochlorides were supplied by Rhône Poulenc Pharma, Madrid. The generation of their cation radicals, the preparation of samples in different conditions for recording the e.s.r. spectra, the computer programs for spectral simulation, and the e.s.r. equipment employed were all as previously described.[22–24]

Table 1. Monosubstituted phenothiazine drugs



Compound	R	Action
Phenothiazine (PTAZ)	H	Vermicide
Diethazine (DTAZ)	$-(CH_2)_2N(C_2H_5)_2$	Antiparkinson
Promethazine (PRMTZ)	$-CH_2\underset{\underset{CH_3}{\vert}}{C}HN(CH_3)_2$	Antihistamine, tranquilizer
Isothiazine (ISTZ)	$-CH_2\underset{\underset{CH_3}{\vert}}{C}HN(C_2H_5)_2$	Antiparkinson
Promazine (PRMZ)	$-(CH_2)_3N(CH_3)_2$	Tranquilizer
Perazine (PRAZ)		Tranquilizer
Alimemazine (ALMZ)	$-CH_2\underset{\underset{CH_3}{\vert}}{C}H\,CH_2N(CH_3)_2$	Tranquilizer

Results

(a) *Samples in Liquid Sulphuric Acid Solution.*—The e.s.r. spectra of the three radicals $PRMTZ^+$, $ISTZ^+$, and $DTAZ^+$ were recorded at several temperatures between 233 and 333 K. For each sample, the spectra obtained at different temperatures can be simulated using an unique set of hyperfine splitting constants (h.f.s.c.) and changing the linewidth. These h.f.s.c. values, measured from the spectra at the temperature giving the best resolution, are presented in Table 2, together with the h.f.s.c. values measured by us using other phenothiazine cation radicals under similar conditions. The linewidth values at different temperatures are shown in Table 3. The overall aspect of the spectra can be described as a main structure of four groups of lines for $ISTZ^+$ and $PRMTZ^+$ radicals and of seven groups for $DTAZ^+$.

(b) *Powder Spectra.*—The powder spectrum of $DTAZ^+$ in the perchlorate salt shows an orthorhombic signal with g_{xx} 2.0074, g_{yy} 2.0061, and g_{zz} 2.0022; these values were checked by computer simulation. For $ISTZ^+$ and $PRMTZ^+$ no powder spectra could be obtained, since isolation of the corresponding ClO_4^- salts (following Merkle's method) was unsuccessful. This is due probably to the instability of radicals with a short side-chain and branching at the γ-carbon.[20]

(c) *Samples in Frozen Sulphuric Acid Solution.*—The spectra of the dissolved radicals strongly immobilized at 77 K have been

Table 2. Experimental hyperfine splittings (10^{-4} T) of *N*-substituted phenothiazine cation radicals in liquid solution

Cation radical	T/K	a_N	a_N^{NH}	$a_{\beta H_1}$	$a_{\beta H_2}$	$a_{H_{3,7}}$	$a_{H_{2,8}}$	$a_{H_{1,9}}$	$a_{H_{4,6}}$	$a_N/a_{H_{3,7}}$	g_o	Ref.
PTAZ$^+$	253	6.52	7.36			2.58	0.48	1.26	0.46	2.53	2.0052	25
DTAZ$^+$	273	6.70		3.42	3.42	1.80	1.08	0.62	0.38	3.72	2.0054	This work
PRMTZ$^+$	273	6.40		2.62	7.30	1.30	1.24	0.48	0.46	4.92	2.0052	This work
ISTZ$^+$	253	6.46		2.64	7.36	1.30	1.24	0.48	0.46	4.97	2.0052	This work
PRMZ$^+$	295	7.08		3.52	3.52	1.96	0.92	0.80	0.40	3.61	2.0053	24
PRAZ$^+$	295	7.06		3.52	3.52	2.00	0.96	0.80	0.40	3.53	2.0054	26
ALMZ$^+$	295	7.08		1.96	5.48	1.96	1.04	0.96	0.24	3.61	2.0053	22

Table 3. Variation of linewidth ΔH_{pp} (10^{-4} T) with temperature

T/K	233	253	273	295	313	333
PRMTZ$^+$	0.84	0.48	0.30	0.38	0.42	0.60
ISTZ$^+$	0.82	0.32	0.36	0.38	0.40	0.60
DTAZ$^+$	0.90	0.50	0.28	0.32	0.38	0.46

used to determine the values of the hyperfine tensor $\hat{A}^N$ corresponding to the heterocyclic nitrogen atom (N-10). As in the case of other PTAZ-type radicals[23–25] the g_{zz} values can be estimated from the spectra by visual inspection, while in order to evaluate the other principal g values, necessary for computer simulation, we have used the g_o values measured in the liquid solution spectra and calculated the sum $g_{zz} + g_{yy} = 3g_o - g_{zz}$. The values of this sum are close to those obtained for other phenothiazine derivatives already studied; the individual g_{zz} and g_{yy} values, as well as the precise g_{zz} value, were then obtained by computer simulation of the spectra. A similar procedure was used to calculate the principal values of the $\hat{A}^N$ tensor. The values of the g and A parameters yielding the best simulations are presented in Table 4. In the case of DTAZ$^+$, the same set of g values that gives the best fit to the strongly immobilized experimental spectrum can also fit the spectrum of its salt in powder form.

Discussion

To our knowledge, no e.s.r. study has been previously published on ISTZ$^+$ and DTAZ$^+$, while the spectrum of PRMTZ$^+$ in liquid solution at room temperature has been studied by other authors. Clarke *et al.*[14] and Lagerkrantz[21] have recorded low-resolution spectra of this radical, observing the four groups of lines, but they could not calculate the h.f.s.c. values. Fenner[18] has presented a more detailed study, but he did not consider the possible non-equivalence of the β-protons for his analysis. As previously reported for ALMZ$^+$,[22] this type of non-equivalence can explain the fact that the number of main groups of lines is different to that of other *N*-substituted phenothiazine cation radicals without γ-branching.[19–24] The liquid-solution spectrum of DTAZ$^+$, with a main structure of seven groups of lines, can be interpreted as due to the coupling with two equivalent β-protons, whose h.f.s.c. are close to half of the corresponding value for the nitrogen atom N-10.

Table 4. E.s.r. parameters of strongly immobilized cation radicals at 77 K

Cation radical	A^N_{xx}	g_{xx}	A^N_{yy}	g_{yy}	A^N_{zz}	g_{zz}
PRMTZ$^+$	1.3	2.0072	1.3	2.0060	16.6	2.0024
ISTZ$^+$	1.7	2.0072	1.7	2.0060	16.0	2.0024
DTAZ$^+$	1.6	2.0074	1.6	2.0061	16.9	2.0022

$\hat{A}^N$ tensor components are expressed in 10^{-4} T.

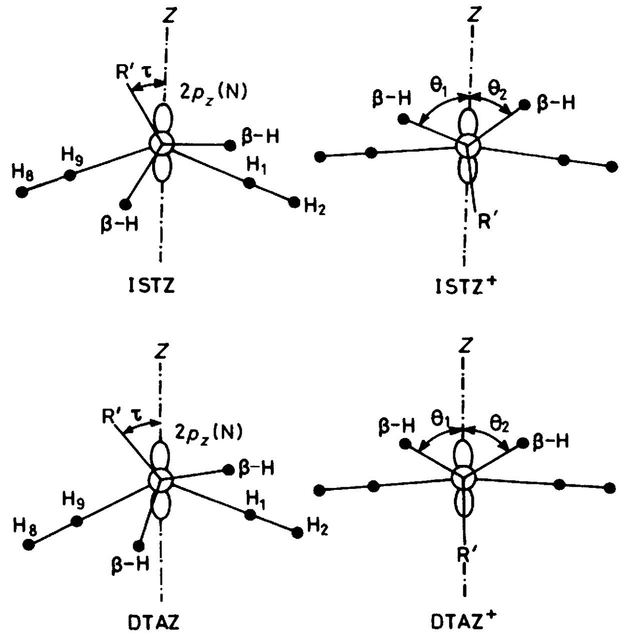


Figure 1. Conformational effects of the oxidation in branched and unbranched phenothiazine derivatives

(a) *Overall Conformation of the Radicals.*—The absence of significant variations of the h.f.s.c. with temperature indicates that, in the studied range, these cation radicals do not present interconversion between (as far as e.s.r. is concerned) noticeably different conformers. Using McConnell's expression (1) and assuming $C_o \simeq 0$ together with a relation between θ_1 and θ_2, it is possible, as in previous work,[24] to calculate the constant C and the angle θ formed by the $2p(\pi)$ axis of the nearly planar[27] N-10 atom and the plane defined by the position of atoms N-10, β-C, and β-H, which gives information on the conformation of the side-chain (Figure 1). The results of *X*-ray diffraction studies for similar cation radicals[27,28] indicate that the two β-protons are placed at the same side of the molecular plane; in such a way assuming in a first approximation a regular tetrahedral symmetry for the bonds to the β-C atom we would have $|\theta_1| + |\theta_2|$ *ca.* 120°. Using the values obtained for the h.f.s.c. $a_{\beta H_1}$ and $a_{\beta H_2}$ and considering the value obtained from equation (2) as an approximation of ρ^{π}_N (π spin density at the nitrogen atom) we have roughly estimated the values of $|\theta_1|$, $|\theta_2|$, and C which are presented in Table 5, together with the absolute value of the pseudoangle of torsion τ (S···N-β-C-γ-C) of the side-chain around the N-10–β-C bond (Figure 1).

$$a_{\beta H} = \rho^{\pi}_N C \cos^2\theta + C_o \qquad (1)$$

$$c_p^2 = T^N_{zz}/2\,B_o = (A^N_{zz} - a_N)/34 \qquad (2)$$

Table 5. Electronic and conformational parameters of *N*-substituted phenothiazine cation radicals calculated from e.s.r. data

	Cation radical (e.s.r.)							Neutral form (*X*-ray)	
Compound	T_{zz}^{N}	c_p^2	C	$\lvert\theta_1\rvert$ (°)	$\lvert\theta_2\rvert$ (°)	$\lvert\tau\rvert$(°)[a]	Ref.	τ(°)	Ref.
DTAZ	10.2	0.30	47	60	60	0(180)	This work	38	28
PRMTZ	10.2	0.30	64	68	52	8(172)	This work	32	37
ISTZ	9.5	0.28	68	68	52	8(172)	This work	32	28
PRMZ	10.4	0.31	46	60	60	0(180)	24	−34, 5	38, 39
PRAZ	10.4	0.31	46	60	60	0(180)	26		
ALMZ	8.5	0.25	56	69	51	9(171)	22		

[a] The e.s.r. experimental results do not allow us to distinguish between these two possibilities. T_{zz}^{N} and C values are expressed in 10^{-4} T.

In the DTAZ$^+$ radical the side-chain adopts a symmetrical arrangement in relation to the ring system; however it shows some deviation in the ISTZ$^+$ and PRMTZ$^+$ radicals (Figure 1). A comparison of the values of these deviations with those obtained by XRD for the corresponding neutral forms (Table 5) shows that the oxidation of the molecule has affected the conformation of its side-chain in a similar way to that presented in a previous study on chlorpromazine.[27] The oxidation opens the folded plane of the tricyclic system and relaxes the steric repulsion between the β-protons and 1- and 9-H, producing a significant change in the conformation of the chain that can take now a more symmetric position in relation to the aromatic part of the molecule.

(b) *Influence of the Length of the Side-chain.*—The data presented in Table 2 indicate that the values of a_N increase with n [where n is the number of methylene groups separating the N-10 atom from a polar substituent X, *i.e.*, 10-R = $(CH_2)_nX$]. The ISTZ$^+$, PRMTZ$^+$, and DTAZ$^+$ radicals with $n = 2$ have a_N values smaller than ALMZ$^+$, PRMZ$^+$, and PRAZ$^+$, which have longer side-chains. This result is in agreement with the work of Hanson *et al.*[29] who conclude that an across-bond polarizability effect for the polymethylene chain, together with a through-space electrostatic field effect for polar terminal substituents, define the electronic influence of 10-R upon the ring system. The first effect increases with n, the second decreases with n and Taft's inductive substituent constant σ_I jointly, reflecting the diminution with distance of the inductive effect of the polar group. The closer position of the terminal amino centre induces a cationic charge and spin density displacement in the heterocycle from nitrogen to sulphur. Although several of the cation radicals of Table 2 show γ-branched side-chains and differences in the terminal group, the length of the $(CH_2)_n$ chain seems to exert a predominant influence on the a_N value. The minor but singular effect of γ-branching will be discussed below.

The variation of the linewidth with temperature observed in liquid solution shows systematically an asymmetric **U**-shaped curve with the minimum corresponding to the temperature, T_m, of best resolution. Comparison of the different T_m values shows a direct correlation with the size of the 10-R substituent expressed by the number n (Figure 2). The **U**-shaped curve can be explained by considering the existence of two relaxation mechanisms. Remembering that for a hydrodynamically spherical molecule of radius a the inverse of the relaxation times corresponding to both mechanisms is $T_2^{-1} \sim \eta a^3/T$ (spin-orbit) and $T_2^{-1} \sim T/\eta\, a^3$ (spin-rotational)[30,31] we can see that, the higher the a value, the greater the contribution of the first mechanism, and the smaller that due to the second (for a given temperature and the same solvent with a viscosity coefficient η). The composition of both curves for each radical shows a shift of the minimum towards higher temperatures with increasing a values (with η approximately constant, $T_m \sim a^3$). This behaviour is roughly in agreement with the experimental results as shown in Figure 2. The radicals with higher n, which are probably those with higher a, have a larger value of T_m. The PTAZ$^+$, cation radical without a side-chain, presents the lowest T_m value.

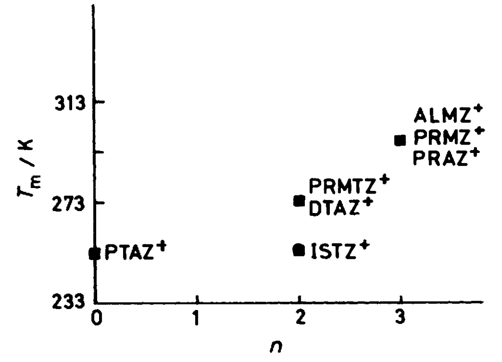


Figure 2. Temperature of best resolution *versus* number of methylene groups separating the N-10 atom from the terminal amino group for different *N*-substituted phenothiazine cation radicals

(c) *Effect of Branching of the Side-chain at the γ-Carbon Level.*—The fact that the side-chain of the radical with γ-branching keeps a certain degree of torsion, even in spite of the oxidation effect, can be interpreted as due either to steric repulsions between the side-chain and the ring system or to molecular interactions with the environment by a direct or indirect effect of the methyl group as substituent in the γ-carbon. The difference of 6° between the torsion angle values[32,33] for DATZ and ISTZ in the neutral form has been attributed just to the presence of the CH_3 group that differentiates them, and can be compared with the 8° value estimated by us using e.s.r. results for the cationic forms.

A comparison of the results presented here with those for other similar radicals shows that the branching of the side-chain at the γ-C atom has a clear influence on the e.s.r. spectra. Radicals having this type of branching, with the γ-C atom as chiral centre, have non-equivalent β-protons and the side-chain shows a certain deviation from the symmetrical conformation presented by the unbranched radicals at the γ-C level. This torsion around the N-10–β-C bond seems to be a consequence of the γ-branching. The estimated magnitude of this effect, equal to 8° for the pair DTAZ$^+$–ISTZ$^+$ as previously indicated, is

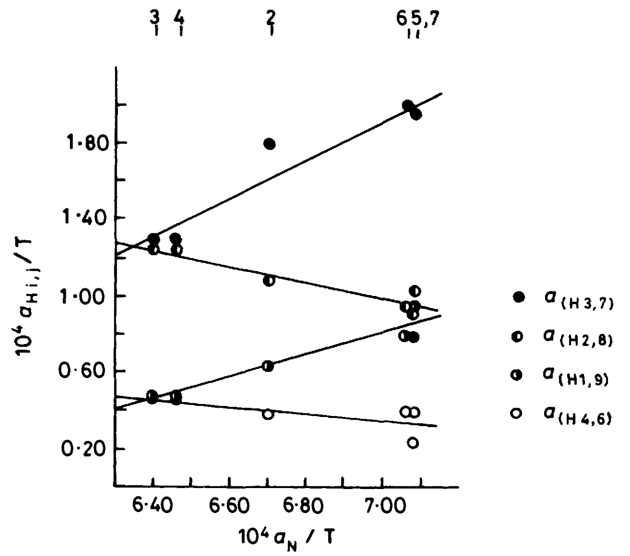


Figure 3. Variation of $a_{H_{i,j}}$ with a_N for *N*-substituted phenothiazine cation radicals (see Table 2)

similar to that obtained for the pair PRMZ$^+$-ALMZ$^+$ [22,24] which has a longer polymethylene chain (a higher *n*-value).

The influence of γ-branching on the spin density distribution in the ring system shows singular characteristics. Thus, though such influence is negligible for radicals with long side-chains ($n = 3$; ALMZ$^+$ *versus* PRMZ$^+$), a reduction in the size of the alkylamine chain causes important changes on the h.f.s.c. of the protons in the tricyclic system ($n = 2$; ISTZ$^+$ *versus* DTAZ$^+$). This shows that both structural factors, length of the side-chain and γ-branching, interfere. A possible explanation is as follows: when the side-chain is long, the terminal amino group is far from the ring system and the conformational change forced by γ-branching is irrelevant to interaction between both parts of the radical. With reduction of the distance by shortening the side-chain, the influence of the supplementary CH_3 group changes, by an indirect mechanism, the electronic and/or steric interaction between the amino group and the ring system, which causes appreciable changes in the h.f.s.c. In a similar way, the influence of branching on the nitrogen h.f.s.c. is higher for $n = 2$ than for $n = 3$.

The observed decrease in the a_N value by effect of the γ-branching can be related with a possible increase in the electrostatic repulsion of the cationic charge (and concomitant spin density) on N-10 by the probably protonated amino centre.[6,34] If, as indicated by Clark *et al.*,[14] the $a_N/a_{H_{3,5}}$ ratio is a measure of the degree of molecular folding, the increase observed in this ratio value (ISTZ$^+$ *versus* DTAZ$^+$; see Table 2), can be interpreted as related to an increase of the folding as a direct or indirect consequence of γ-branching. Then, both electronic and steric effects can contribute to the overall influence of γ-branching on the spin density distribution in phenothiazine cation radicals *N*-substituted by a short side-chain.

(d) *Spin Density Distribution in the Ring System.*—The analysis of the data corresponding to the h.f.s.c. values of the different magnetic nuclei of the tricyclic system (Table 2) shows the existence of defined correlations between them. In Figure 3 the h.f.s.c. values of protons of the lateral rings are plotted against the nitrogen hyperfine splittings a_N for the different radicals studied in this and previous work. Figure 3 shows that $a_{H_{i,j}}$ has a positive correlation with a_N for the equivalent proton pairs $i,j = 3,7$ and 1,9, and a negative correlation for 2,8 and 4,6. Fitting the values of Table 2 by the least-mean-squares method, expressions (3)—(6) are obtained. These correlation are fulfilled, to a good approximation, by the values obtained by other authors for the h.f.s.c. of similar phenothiazine derivatives. For comparison, several experimental data reported in the literature are plotted in Figure 4 together with the lines corresponding to equations (3)—(6). The quality of the predictions is variable, being higher for the phenothiazine radicals whose side-chain has a terminal polar group with $\sigma_I > 0$ (see refs. 14 and 29). Other factors, such as the use of different solvents or different steric interaction between the side-chain and the ring system, can contribute to these deviations.

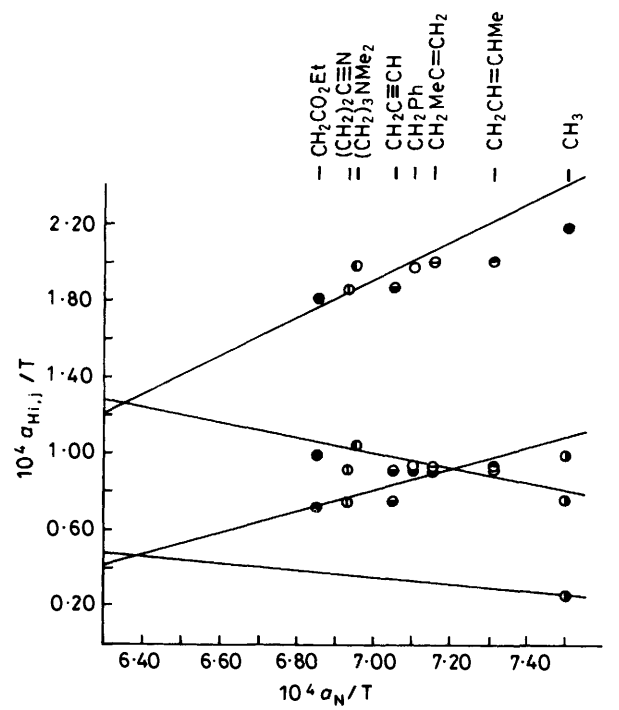


Figure 4. Comparison between our experimental equations for $a_{H_{i,j}}$ and a_N and the points corresponding to other *N*-substituted cation radicals (see refs. 14, 16, and 17)

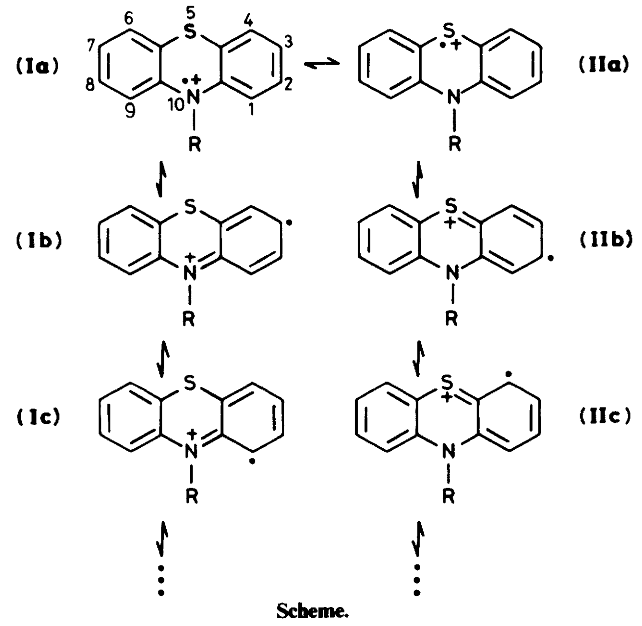
$$a_{H_{3,7}} = \quad 1.00a_N - 5.08 \; |r| = 0.961 \qquad (3)$$

$$a_{H_{2,8}} = -0.40a_N + 3.82 \; |r| = 0.945 \qquad (4)$$

$$a_{H_{1,9}} = \quad 0.58a_N - 3.27 \; |r| = 0.955 \qquad (5)$$

$$a_{H_{4,6}} = -0.17a_N + 1.55 \; |r| = 0.678 \qquad (6)$$

Small differences in the folding angle can also be the origin of the variation of the values used to obtain equations (3)—(6). The smaller value of $|r|$ in (6) is, probably, connected with errors in the experimental determination of the smallest h.f.s.c. The anomalous behaviour of the unsubstituted phenothiazine cation radical PTAZ$^+$, which has been ignored in obtaining equations (3)—(6), remains unexplained. A similar situation has been reported by Clark *et al.* for this radical in studies of correlation between a_N and σ_I in a family of radicals for *N*-substituted phenothiazine derivatives.[14] These authors explain it as due to important differences in molecular planarity. It is also our opinion that the degree of folding could be a relevant factor, because of its influence on the spin density distribution; however, as was indicated previously,[25] the probable existence



Scheme.

of significant radical–solvent interactions for PTAZ$^+$, modifying the electronic influence of N-10 upon the ring system, can be another casual factor. In any case, Figure 4 also shows that the h.f.s.c. values $a_{H_{2,8}}$ will be higher than those $a_{H_{1,9}}$ only when $a_N < 7.20 \times 10^{-4}$ T. The inversion in the relative magnitude of these h.f.s.c. at $a_N \simeq 7.20 \times 10^{-4}$ T invalidates the procedure often followed in the past[17,24] for the assignment of the $H_{2,8}$ and $H_{1,9}$ splittings based in the results of theoretical studies of a derivative such as 10-methyl-PTAZ,[16] since this latter has $a_N \simeq 7.50\ 10^{-4}$ T, *i.e.* a value beyond the crossover of the corresponding lines of Figure 4.

An overall analysis of the correlations (3)—(6) indicates clearly that the effect of the lateral chain 10-R on the charge and spin distribution in the tricyclic system can be interpreted as a modification of the relative weights of the resonant structures of types (**I**) and (**II**) (Scheme), each type being characterized by localization of the positive charge in the nitrogen and the sulphur atoms, respectively. By considering the relative magnitude of the h.f.s.c. observed experimentally, we can establish the following relation between the weights: *p*(**Ib**) > *p*(**IIb**) > *p*(**Ic**) > *p*(**IIc**) which indicates that the structures of type (**I**) predominate over those of type (**II**). As the S^{16} nucleus with $I = 0$ is not magnetic, it is impossible to extend the empirical comparison to the structures (**Ia**) and (**IIa**). However, the results obtained for the other weights suggest that possibly *p*(**Ia**) > *p*(**IIa**); this is equivalent to saying that the spin density in N-10 is higher than that on the sulphur atom, in agreement with the results of spin densities obtained through theoretical calculations for some radicals of the phenothiazine derivatives.[16,35,36]

An analysis of the slopes m_i in equations (3)—(6) also reveals a well defined order in their absolute values: $|m_3| > |m_5| > |m_4| > |m_6|$, indicating that position 3 in the ring system is the most sensitive to changes in the cationic charge and spin density on the heterocyclic nitrogen atom; on the other hand, position 2, among those bearing the unpaired electron in type (**II**) resonant structures, is the most sensitive to these changes, but now with opposite sign, which suggests a correspondingly large positive correlation with the (not measurable) charge and spin density on the sulphur atom. The 1 and 4 positions, with a lower spin density, are also less sensitive to changes, respectively, in the situation of the nitrogen and sulphur atoms. Therefore, it seems that the presence of the charge and unpaired electron on each of the heteroatoms affects their respective *ortho-* and *para-*positions of the lateral cycles, in a way similar to the influence of first-order substituents on the activation of the carbon atoms placed in the same positions in a benzene ring.

From the practical point of view, equations (3)—(6) allow us to estimate the value of the h.f.s.c. $a_{H_{i,j}}$ for similar phenothiazine derivative radicals once the a_N values are known; these values, because of their larger magnitude, should be easily measurable even in ill resolved spectra.

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