Heterocyclic Free Radicals. Part 8.[1] The Influence of the Structure and the Conformation of the Side-chain on the Properties of Phenothiazine Cation-radicals substituted at Nitrogen

By **David Clarke, Bruce C. Gilbert, Peter Hanson,* and Christopher M. Kirk,** Department of Chemistry, University of York, Heslington, York YO1 5DD

In 10-substituted phenothiazine cation-radicals the extent of variation in nitrogen hyperfine splitting is greatest for purely hydrocarbon substituents and is reduced on introduction of polar functions into the alkyl group. It is concluded that the substituent effect is mainly a through-bond inductive effect of the classical kind. Substituents greater than methyl show strong preferences for particular conformations about the N–C bond. Variations in the ratio a(N) : a(3-H) are interpreted in terms of changes in the fold angle of the radicals occurring in response to changes of substituent type. Chiral substituents, as found in certain phenothiazine drugs, have characteristic effects on the e.s.r. spectra of the derived cation-radicals: two non-equivalent proton splittings arise from the β-CH_2 group.

EARLIER Parts have dealt with the influence of substituents in the 2- and 3-positions of phenothiazine on the distribution of spin density in its derived radicals, including cation-radicals,[1] and with conformational and substituent effects in the 10-aryl substituted cation-radicals of phenoxazine and phenothiazine.[2] The present investigation extends this work to cation-radicals of phenothiazine with aliphatic side-chains attached to nitrogen. Besides the intrinsic interest of these radicals there is possible additional value in their study since the therapeutically useful phenothiazines usually bear an alkylamino side-chain attached to nitrogen. Whilst cation-radicals themselves are not necessarily involved in the phenothiazines' pharmacological activity, it is probable that inferences may be drawn about the conformational behaviour in solution of the drug molecules by relating it to that of derived and similar radicals. There has been considerable interest in ascertaining the conformational preferences of phenothiazine drugs either by computation[3] or by crystal structure determination[4,5] but little is known of their conformational properties in solution.

TABLE 1

Experimental hyperfine splittings (mT) of 10-substituted phenothiazine cation-radicals

Substituent	a(N)	a(β-H)	a(1-H)	a(2-H)	a(3-H)	a(4-H)	a(N) : a(3-H)	g
Bu^tCH_2	0.778	0.360	0.119	0.060	0.210	0.031	3.705	2.0051
Bu^i	0.765	0.391	0.097	0.097	0.211		3.625	2.0051
Et	0.751	0.372	0.094	0.094	0.211		3.559	2.0052
$Ph[CH_2]_3$	0.750	0.389	0.088	0.088	0.207		3.623	
Me	0.749	0.724	0.098	0.073	0.212	0.024	3.533	2.0052
$Ph[CH_2]_2$	0.737	0.369	0.088	0.088	0.203	0.020	3.630	2.0052
$MeCH{=}CHCH_2$	0.732	0.378	0.093	0.093	0.201		3.642	2.0052
$CH_2{=}CMeCH_2$	0.715	0.386	0.093	0.093	0.201		3.557	2.0052
$Me_2\overset{+}{N}H[CH_2]_3$	0.715	0.361	0.089	0.089	0.198	0.039	3.611	2.0052
$PhCH_2$	0.710	0.384	0.093	0.093	0.199		3.568	2.0052
$CH{\equiv}CCH_2$	0.705	0.332	0.092	0.092	0.187		3.770	2.0053
$N{\equiv}C[CH_2]_2$	0.693	0.343	0.075	0.091	0.187		3.706	2.0053
EtO_2CCH_2	0.685	0.365	0.072	0.100	0.183		3.743	2.0053
$Me_2\overset{+}{N}H[CH_2]_3$,2-Cl	0.685	0.342	0.101	0.101	0.189		3.460	2.0055
cyclo-C_5H_9	0.782	0.202	0.115	0.059	0.202	0.029	3.871	2.0050
Pr^i	0.779	0.183	0.091	0.091	0.200		3.895	2.0050
Ph_2CH	0.714	0.280	0.092	0.069	0.182	0.024	3.923	2.0052
CO_2Me	0.638		0.059	0.117	0.184		3.467	2.0055
CO_2Et	0.632		0.060	0.117	0.186		3.398	2.0055
Ph	0.695		0.090	0.090	0.215	0.022	3.232	
		a(N-H)						
H	0.634	0.729	0.113	0.050	0.249	0.050	2.546	2.0052

RESULTS

(a) *E.s.r. Data.*—In Table 1 are presented the measured e.s.r. parameters for phenothiazine cation-radicals which were generated by treating the appropriate phenothiazines, in solution in $MeNO_2$, with $AlCl_3$, with H_2SO_4, or with $Tl(OAc)_3$.

Nitrogen hyperfine splittings, a(N), were unambiguously assignable in each case; the splitting due to the β-protons (*i.e.* those attached to the first carbon of the aliphatic side-chain), where present, were also, in general, readily assigned (*vide infra*). Splittings from the phenothiazine ring protons are assigned on the basis of molecular orbital calculations carried out on 10-methylphenothiazine,[6] on the assumption that other alkyl substitution will not greatly influence the

[1] Part 7, D. Clarke, B. C. Gilbert, and P. Hanson, *J.C.S. Perkin II*, 1977, 517.

[2] D. Clarke, B. C. Gilbert, and P. Hanson, *J.C.S. Perkin II*, (*a*) 1975, 1078; (*b*) 1976, 114.

[3] J. L. Coubeils and B. Pullman, *Theor. Chim. Acta*, 1972, **24**, 35.

[4] J. J. H. McDowell, *Acta Cryst.*, 1969, **B25**, 2175; 1970, **B26**, 954; P. Marsau, *ibid.*, 1971, **B27**, 42.

[5] M. C. Malmstrom and A. W. Cordes, *J. Heterocyclic Chem.*, 1972, **9**, 325.

[6] P. D. Sullivan and J. R. Bolton, *J. Magnetic Resonance*, 1969, **1**, 356.

distribution of spin density within the heterocycle. Most of the cation-radicals listed in Table 1 bear a purely hydrocarbon side-chain, but in some, polar groupings are introduced. Amongst these are the drugs promazine hydrochloride and chlorpromazine hydrochloride whose spectra, recorded here, represent improvements on those previously reported.[7] The 10-alkoxycarbonylphenothiazine cation-radicals have not previously been described. Table 1 also contains, for comparison, e.s.r. data on the cation-radicals of phenothiazine itself and of 10-phenylphenothiazine.[1,2]

(b) *Correlations of Nitrogen Hyperfine Splittings.*—No comprehensive set of substituent constants exists which will correlate all the a(N) values of Table 1. However, we find that by using σ_I in two ways, virtually all the results can be accommodated. The σ_I values we have preferred are, in general, those of Taft [8] and of Levitt and Widing,[9] the latter being derived either from Taft's original σ^* values [10] or from recent ionisation potential measurements.[9] For convenience, the σ_I values used are tabulated in Table 2.

TABLE 2

Substituent constants, σ_I, employed

Substituent	σ_I	Ref.	Substituent	σ_I	Ref.
Bu^t	−0.074	9	$PhCH_2$	−0.026	9
Pr^i	−0.065	9	MeCH=CH	−0.012	9
cyclo-C_5H_9	−0.065	9	Ph_2CH	−0.008	9
Bu^tCH_2	−0.062	9	$O_2N(CH_2)_2$	0.000	9
Bu^i	−0.058	9	CH_2=CH	0.05	8
Et	−0.056	9	Ph	0.10	8
Me	−0.046	9	3-$O_2NC_6H_4$	0.19	11
$Ph[CH_2]_3$	−0.044	9	N≡CCH_2	0.24	8
$Ph[CH_2]_2$	−0.038	9	4-$O_2NC_6H_4$	0.22	11
$MeCH{=}CHCH_2$	−0.034	9	CO_2R	0.30	8

In Figure 1 is plotted the variation in nitrogen hyperfine splitting with σ_I for the cation-radicals with purely hydrocarbon substituents, with the exception of CH≡CCH_2 and CH_2=$CMeCH_2$ for which no satisfactory σ_I values exist. A good linear correlation is obtained: we find the least mean

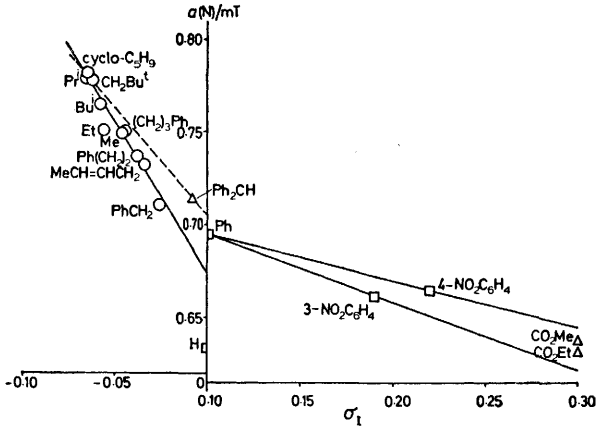


FIGURE 1 Variation of a(N) with σ_I for various 10-substituted phenothiazine cation-radicals: ○, data used in line definition; □, see refs. 1 and 2; △, data not used in definition of equation (1)

squares expression to be (1). This line is defined ignoring the results for the unsubstituted and the diphenylmethyl-substituted cation-radicals (see Discussion). For comparison are included the lines representing the variation with

$$a(\mathrm{N}) = 0.674 - 1.604\sigma_I \quad (r\ 0.958) \qquad (1)$$

substituent of the nitrogen hyperfine splittings of 10-arylphenothiazine cation-radicals.[2b] (The σ_I values for 3- and

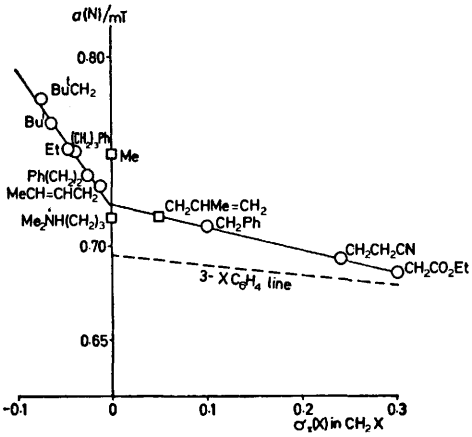


FIGURE 2 Variation of a(N) with σ_I(X) for phenothiazine cation-radicals with 10-substituents of type CH_2X ——, and 3-X-phenyl – – – – (ref. 2*b*). □, Points not used in line definition (see text)

4-nitrophenyl are taken from Charton.[11]) Extrapolations of these lines embrace the points for CO_2R groups.

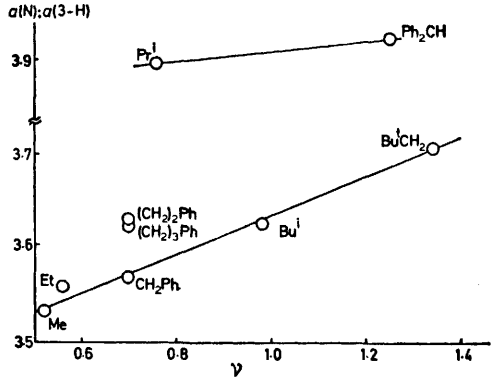


FIGURE 3 Variation of a(N) : a(3-H) with ν for 10-substituted phenothiazine cation-radicals

In Figure 2 are plotted a(N) *versus* σ_I(X) for substituents of the type XCH_2. The plot consists of two linear portions of different slopes and common intercept: a(N) is much more susceptible to change in substituent structure when σ_I(X) is negative, *i.e.* $a(\mathrm{N}) = 0.721 - 0.717\sigma_I(\mathrm{X})$ (r 0.978) than when it is positive, *i.e.* $a(\mathrm{N}) = 0.722 - 0.126\sigma_I(\mathrm{X})$ (r 0.999). It is noteworthy that the result for 10-methallylphenothiazine cation-radical is adequately correlated if σ_I for CH_2=CH is used when X is CH_2=CMe. Use of Charton's σ_I value [12] for HC≡C fails to correlate a(N) for 10-propargylphenothiazine cation-radical, however. Also, since σ_I for Me_2NH^+ is close to that for NO_2[8,12] we have assumed that σ_I for $(CH_2)_2NO_2$ (*i.e.* 0) [9] approximates the

[7] H. Fenner and H. Möckel, *Tetrahedron Letters*, 1969, 2815.
[8] S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Progr. Phys. Org. Chem.*, 1973, **10**, 1; C. D. Ritchie and W. F. Sager, *ibid.*, 1964, **2**, 323.
[9] L. S. Levitt and H. F. Widing, *Progr. Phys. Org. Chem.*, 1975, **12**, 119.
[10] R. W. Taft in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, ch. 13.
[11] M. Charton, *Progr. Phys. Org. Chem.*, 1973, **10**, 81 (appendix 1).
[12] M. Charton, *J. Org. Chem.*, 1964, **29**, 1222.

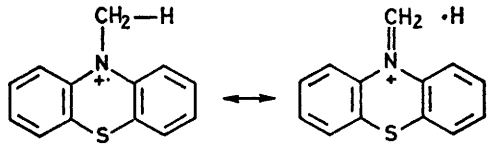
value for $(CH_2)_2\overset{+}{N}HMe_2$ and have used it to plot the result for promazine hydrochloride in Figure 2 fairly satisfactorily.

In Figure 3 is plotted the ratio $a(N) : a(3\text{-H})$ *versus* Charton's steric substituent ν for those of our data for which ν values exist.[13] Points appropriate to substituents attached by primary carbon, in general, are separated from those attached by secondary carbon. Also the five points of type XCH_2 where X is not flexible are linearly correlated (see Discussion section).

(c) *Conformational Preferences of the Side-chain.*—Examination of Table 1 shows that the splitting from the methyl protons in 10-methylphenothiazine cation-radical is similar to that of nitrogen. On the other hand, when the cation-radical possesses a methylene group attached to nitrogen the β-splitting observed is close to half the corresponding nitrogen splitting and when only a methine proton is responsible for β-splitting, the observed splitting is variable but always smaller than any of the methylene splittings. These observations are consistent with the methyl group being able to rotate freely and with other side-chains having marked conformational preferences. For a predominantly hyperconjugative mechanism of transfer of spin density from nitrogen to β-protons [see (1a and b)] at a planar nitrogen centre (see later) the β-proton splitting $a(\beta\text{-H})$ should be given by equation (2) where ρ_N is the π-

$$a(\beta\text{-H}) = \rho_N B\cos^2\theta + B_0 \qquad (2)$$

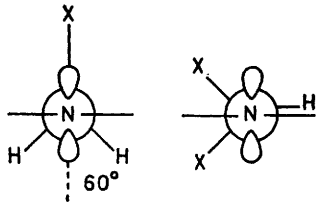
electron spin density at the heterocyclic nitrogen, θ is the dihedral angle between the nitrogen $2p(\pi)$ orbital containing the unpaired electron and the β-C–H bond, B is a constant, and B_0 a correction term added to allow for spin density transmission by spin polarisation. For β-protons in a variety of radicals, B_0 is sufficiently small to be neglected to a first approximation.[14,15]



(1a) (1b)

The fact that the methyl protons interact equivalently is evidence for free rotation about N–CH_3, with $\langle\cos^2\theta\rangle$ 0.5. Then taking Sullivan and Bolton's value, $\rho_N = 0.295$, for 10-methylphenothiazine cation-radical [6] the observed methyl proton splitting of this radical leads to a value for B of 4.9 mT. If we assume that the value of B is independent of the alkyl group attached to the nitrogen, then from measured β-H splittings we can determine the preferred conformations of these groups (*cf.* ref. 15). For example, for substituents of the type XCH_2, β-methylene splittings close to 0.36 mT correspond to θ *ca.* 60°. This indicates that the radicals adopt a preferred conformation in which the group X eclipses the singly occupied $2p(\pi)$ orbital on nitrogen [see (2)]. This is in agreement with expectation from consideration of a model which minimises steric interaction between the group X and the 1- and 9-hydrogens of the heterocycle. Sevilla and Vincow have observed comparable behaviour in the structurally related 9-methyl and 9-ethylxanthenyl radicals.[16]

Equation (2) predicts a minimum for $a(\beta\text{-}H)$ of 0.361 mT. From Table 1 it may be noted that when X is polar (*viz.* C≡CH and CH_2CN) β-splittings smaller than the predicted minimum are found. This may represent the limit of validity of the approximations made in using equation (2). In particular, constancy of B may not hold as X becomes



(2) (3)

polar. A similar observation has been made by Stock and Wasielewski on β-splitting in XCH_2-substituted nitrobenzene anion-radicals, when X is a highly polar group.[17]

The smaller values of β-H splittings observed for the three radicals bearing substituents of the type CHX_2 imply that in each case the preferred conformation has a value of θ greater than that for (2). We believe that the appropriate conformation is that with θ 90°, *i.e.* (3), the conformation which minimises interactions of the X groups with the heterocyclic 1- and 9-hydrogen atoms (*cf.* other radicals with β-CHR_2 substituents [15]). The fact that the observed splitting is not zero, as would be predicted from equation (2) with θ 90° may be explained by the contribution of other conformations (with $\theta \neq 90°$) to the weighted average.

(d) *Other Cation-radicals.*—We have studied other systems beyond those listed in Table 1. They have not been recorded there either because resolution was so poor that even the nitrogen splitting is in doubt or because chemical reaction occurred resulting in loss of the substituent.

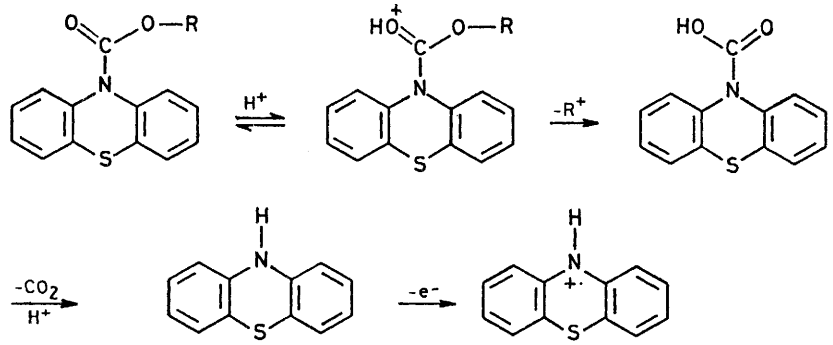
(i) *Simple alkyl groups.* Under the conditions used to generate the radicals of Table 1, the cation radicals from n-propyl- and n-butyl-phenothiazine gave spectra which were ill resolved. Although a general three-line spectral envelope was evident, no measurement, even of the nitrogen splitting could reliably be made.

(ii) *Allylic substituents.* Three phenothiazines were studied which bore allylic substituents, 10-allyl-, 10-crotyl-, and 10-methallyl-phenothiazine. Each of these, when oxidised in an acidic system (*e.g.* $AlCl_3$–$MeNO_2$ or H_2SO_4–$MeNO_2$) gave a spectrum which changed with time. The spectral envelope of the final product had four lines in the 1 : 2 : 2 : 1 pattern characteristic of a cation-radical unsubstituted at nitrogen *i.e.* $a(N) \simeq a(N\text{–H})$. Apparently the side-chain is lost. The process is slow for 10-methallyl-phenothiazine, the spectrum of the authentic 10-substituted cation-radical being obtained first. Loss of the substituent from nitrogen was proved by effecting the oxidation with D_2SO_4–$MeNO_2$. Here the final spectrum width was much narrowed on account of the derived radical being deuteriated at nitrogen. The nature of the radical ultimately produced is not known. It appears on the basis of spectrum simulation that the substituent is retained in the product and we tentatively assign it to the 1-position.

[13] M. Charton, *J. Amer. Chem. Soc.*, 1975, **97**, 1552.
[14] R. O. C. Norman and B. C. Gilbert, *Adv. Phys. Org. Chem.*, 1967, **5**, 53.
[15] D. H. Geske, *Progr. Phys. Org. Chem.*, 1967, **4**, 125.
[16] M. D. Sevilla and G. Vincow, *J. Phys. Chem.*, 1968, **72**, 3647.
[17] L. M. Stock and M. R. Wasielewski, *J. Amer. Chem. Soc.*, 1975, **97**, 5620.

Further work is needed on this point.* The change which occurs may be an artefact of acidity rather than an intrinsic property of cation-radicals with allylic substituents, for stable normal species are obtained using the non-acidic oxidant $Tl(OAc)_3$–$MeNO_2$. Unfortunately, the spectrum of 10-allylphenothiazine radical is too poorly resolved to permit measurement of either the nitrogen- or the β-splitting, when generated in this manner.

(iii) 10-*Alkoxycarbonylphenothiazine cation-radicals.* Oxidation of 10-methoxycarbonyl- and 10-ethoxycarbonylphenothiazine with acidic oxidants yielded cation-radicals whose e.s.r. characteristics are presented in Table 1. Oxidation of the corresponding isopropyl and t-butyl esters, however, resulted in the formation of the cation-radical of phenothiazine itself. A cleavage of the conjugate acid of these substrates to yield the stabilised carbonium ion and 10-carboxyphenothiazine, which would immediately decarboxylate, would account for these observations (Scheme).



SCHEME

Use of $Tl(OAc)_3$–$MeNO_2$ failed to oxidise any of the 10-alkoxycarbonylphenothiazines.

(iv) *Radicals with chiral substituents.* The drug promethazine hydrochloride was also studied. In this material the side-chain is $CH_2CHMe\overset{+}{N}HMe_2$. Oxidation of this substrate gave a poorly resolved spectrum whose envelope pattern approximated to 1 : 2 : 2 : 1. This had been noted earlier by Lagercrantz who showed also, by effecting oxidation with D_2SO_4, that total loss of alkyl side-chain does not occur.[18] Lagercrantz rationalised the observation by postulating a cleavage of the side-chain to give CH_2OH which was then supposed to adopt a rigid conformation in which the methylene protons would exhibit markedly different splittings. We have confirmed that the product radical does not have exchangeable hydrogen on the heterocyclic nitrogen but prefer to account for the observed form of the spectrum in terms of the chirality of the side-chain. Thus the β-methylene group has magnetically inequivalent protons; it is diastereotopic by virtue of the adjacent γ-chiral centre. As has been pointed out [19,20] previously for a variety of radicals (*e.g.* nitroxides, nitro radical-anions) in which a β-CH_2 group is situated between the radical centre and a chiral centre, the β-proton pattern comprises a doublet of doublets (1 : 1 1 : 1) with, in some cases, as a consequence of restricted rotation, a broadening of the middle lines. The β-proton pattern is then 1 : broad : broad : 1, with the separation between the two sharp lines equal to the sum of the two proton splittings. For the radical described here, we believe that there is a similar explanation and that $a(N) \simeq a(\beta\text{-}H_1) + a(\beta\text{-}H_2) \simeq 0.7$ mT. Since this is approximately $2 \times a(\beta\text{-H})$ for R = Et, *etc.*, a similar conformation is evidently preferred (though it is one which chirality leads to slightly different individual values of θ and hence different splittings).

Other phenothiazine drugs Trimeprazine and Aprobit, which also contain a γ-chiral centre in the side-chain, have also been found to give four-line low resolution spectra.[18,21] As confirmation of our conclusion we recorded the e.s.r. spectrum of the cation-radical from (±)-10-pentylphenothiazine. Although ill resolved, it too exhibited the expected four-line spectrum.

(e) *Attenuation of Substituent Effects with Alkyl Chain Length.*—Levitt and Widing have shown that the curve which describes the attenuation of the substituent effects of alkyl groups with increasing chain length is a rectangular hyperbola.[9] Assuming this form for the effect of substituents of the type $[CH_2]_nX$ in the phenothiazine cation-radical family, we may write equation (3) where p—r are

$$a(N)_n = p + q\left(\frac{n}{r+n}\right) \qquad (3)$$

constants. The three data we have for substituents of the type $[CH_2]_nPh$ permit evaluation of p—r for the case of X = Ph. We find equation (4). This expression predicts

$$a(N)_n = 0.621 + 0.166\left(\frac{n}{0.857+n}\right) \qquad (4)$$

$a(N) = 0.787$ mT for an infinitely long alkyl chain, which figure accords closely with the nitrogen splitting predicted by equation (1) for a substituent with $\sigma_I = 0.068\,6$, the value deduced by Levitt and Widing for an infinitely long alkyl group.[9]

DISCUSSION

Electronic Effects of Alkyl Groups.—Whilst the inductive effects of polar substituents such as CO_2R, NO_2, *etc.*, are well accounted for by the electrostatic fields set up at

* We thank a referee for drawing our attention to the report of a radical-mediated rearrangement of allylanilines possibly comparable with the change described here (N. Paillous and A. Lattes, *Tetrahedron Letters*, 1971, 4945).

[18] C. Lagercrantz, *Acta Chem. Scand.*, 1961, **15**, 1545.

[19] B. C. Gilbert, J. P. Larkin, and R. O. C. Norman, *J.C.S. Perkin II*, 1972, 1272; B. C. Gilbert and M. Trenwith, *ibid.*, 1973, 1384.

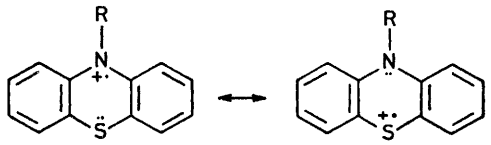
[20] C. Lagercrantz and M. Setako, *Acta Chem. Scand.*, 1974, **B28**, 619.

[21] L. Levy, T. N. Tozer, L. D. Tuck, and D. B. Loveland, *J. Medicin. Chem.*, 1972, **15**, 898.

a site of interest by the dipoles within the substituent,[22] the origin of the comparatively small substituent effects of alkyl groups has been more difficult to explain. There is little permanent separation of charge within alkyl groups, thus probably field effects are negligibly small. Because of this Ritchie and Sager suggested some years ago [8] that the σ^* values of all alkyl groups (from which σ_I may be derived) should be taken as zero. However, it has become clear that different alkyl groups do exert significantly different effects.[9] Recently, Charton attempted to show that Taft's original σ^* contains a steric element.[10,23] This view, however, has been criticised on statistical grounds [24] and, furthermore, it is difficult to reconcile recent determinations of σ_I for alkyl groups from ionisation potentials,[9] which accord well with those derived from σ^*, with any steric effect. Thus the literature values of σ_I for alkyl groups seem to represent a true measure of the electron-donating capacity of such groups, relative to hydrogen. It has been suggested for alkyl groups appended to unsaturated systems, that the electron-donation derives from hyperconjugative interactions between the site of interest and the β-C–H bonds of the alkyl group.[25] However, in the present system where the alkylated site is on an aminium radical centre, although *spin* density can be delocalised into an alkyl group by hyperconjugative interactions [see (1a and b)] the laws of valency preclude the hyperconjugative dispersal of *charge*. Thus in the phenothiazine cation-radical family, the observed correlations of experimental a(N) values by σ_I appear to relate to through-bond inductive effects (I_σ) of the classical type, deriving from the differential polarisabilities of the different alkyl groups, by comparison with hydrogen.[26] It has been shown that such classical inductive effects are real over one or two bond lengths; [27] it is reasonable, therefore, to postulate that they are significant in the present system for the substituents are attached directly to one of the principal charge-bearing atoms in it.

In our previous work on various types of phenothiazine cation-radicals we have accounted for variations in nitrogen coupling constant over a range of substitution in terms of the redistribution of spin and cationic charge-density between principal sites on the phenothiazine heteroatoms.[1,2] Again, the same mechanism appears to hold: as a(N) decreases over the present range of substitution a parallel, small but real increase in g value occurs. This is consistent with spin density on sulphur increasing as that on nitrogen decreases. Thus, the substituent effect in 10-alkylphenothiazine cation-radicals is envisaged as a perturbation of the relative weightings of structures (4a and b) by substituents R of differing polarisability: the more polarisable is R then the greater is the stability of (4a) relative to (4b) and the greater is the cationic charge and concomitant spin on nitrogen.

Polar Substituents.—That introduction of heteroatoms into alkyl groups has a marked effect on their substituent effects is demonstrated by Figure 2: as X in CH_2X



(4a) (4b)

becomes electron withdrawing relative to hydrogen, the susceptibility of the experimental observable to change with substituent character is markedly decreased. This accords well with the hypothesis that the alkyl substituent effect in phenothiazine cation-radicals is essentially a through-bond phenomenon. Introduction of a heteroatom into the alkyl group creates a dipole which has a component in the bond between the aminium centre and the β-carbon atom which is opposed to the dipole induced in the same bond by the aminium centre. The net capacity for electron-donation from the β-carbon to the aminium centre is thus reduced as observed. For comparison, in Figure 2 is reproduced the line showing the dependence, in arylphenothiazine cation-radicals, of a(N) upon the 3-substituent in the aryl ring. Here the susceptibility is further reduced no doubt partly on account of the fact that the β-carbon is now sp^2 hybridised and less polarisable than sp^3 carbon. The displacement of the point for 10-methylphenothiazine cation-radical from the lines of Figure 2 is puzzling. It is unlikely to derive from a unique geometry of the heterocycle (*vide infra*); possibly it arises from the perturbation of the distribution of spin density by the hyperconjugative interaction shown in (1a and b) which is uniquely large for the methyl group and which is reflected in the large β-H splitting of this group.

Radical Geometry.—Examination of Table 1 shows that the ratio a(N) : a(3-H) takes values characteristic of the type of substituent at nitrogen. Thus when the substituent is attached by primary carbon the value of the ratio is 3.637 ± 0.133 (the result for chloropromazine hydrochloride was not used in the evaluation of this average for this molecule is additionally substituted in the heterocyclic nucleus). When the substituent is attached by secondary carbon the value of the ratio is 3.896 ± 0.027, whilst when the substituent is an ester group the ratio falls to 3.432 ± 0.035. These figures are all greater than the values of the ratio for the phenylphenothiazine and unsubstituted cation-radicals. We believe these differences stem from geometry changes in the radicals which depend upon the type of substituent.

Reference to Table 3 shows that the angles subtended by bonds to nitrogen in reduced phenothiazines are much

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[23] M. Charton, *J. Amer. Chem. Soc.*, 1975, **97**, 3691.

[24] A-J. MacPhee and J-E. Dubois, *Tetrahedron Letters*, 1976, 2471.

[25] See, for example, Proceedings of the Conference on Hyperconjugation, Bloomington, 1958, reported in *Tetrahedron*, 1959, **5**, 105.

[26] T. L. Brown, *J. Amer. Chem. Soc.*, 1959, **81**, 3229, 3232.

[27] H. O. Hooper and P. J. Bray, *J. Chem. Phys.*, 1960, **33**, 334.

closer to the trigonal than the tetrahedral value. This being the case, it is unlikely that the local geometry at nitrogen will be other than trigonal when, upon oxidation, the nitrogen becomes an aminium centre. (This was assumed in our deductions of preferred side-chain conformations.) However, the data of Table 3 also show that the reduced heterocycles are folded about an axis

TABLE 3

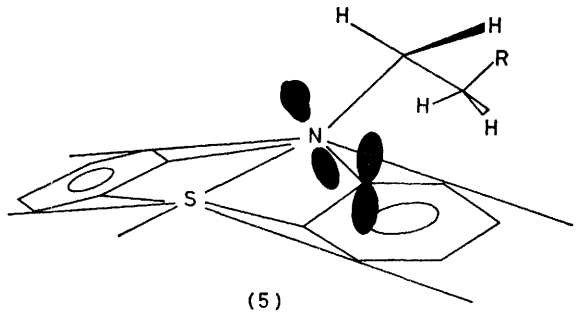
X-Ray crystal structure data for phenothiazine and some 10-substituted derivatives

Substituent	CNC (°) [a]	Fold angle (°) [b]	Ref.
H	121.5 [c]	153.3 [c]	28
	124.4 [d]	158.5 [d]	
Me	118.0	143.7	29
Et	116.7	135.0	30
Pr^i	117.4,	136.1,	31
	118.6	146.8	
$Me_2\overset{+}{N}HCHMeCH_2$	119.5	140.7	5

[a] Angle subtended at the heterocyclic nitrogen by ring carbons. [b] Dihedral angle between planes of the lateral carbocyclic rings. [c] Monoclinic crystal. [d] Orthorhombic crystal.

close to the N–S axis and that the degree of fold varies with the substituent such that the larger substituents impose the greater degree of fold. Now a fold about the N–S axis of the heterocycle is equivalent to twist in its N–C and S–C bonds. Thus if fold persists in the phenothiazine cation-radicals the delocalisation of spin and charge from the heteroatoms into the flanking carbocycles will be reduced from that expected for a planar system. The consequence will be an increased value for the ratio a(N) : a(3-H) the greater the degree of fold. Models indicate that phenothiazine cation-radicals unsubstituted at nitrogen may be planar without impediment and no doubt the necessity for charge-delocalisation impels them to be nearer planar than their parent phenothiazines; any alkyl group on nitrogen in a planar heterocycle, however, would necessitate closer than van der Waals approach of β-hydrogens to the 1- and 9-hydrogens of the heterocycle. Thus retention of a degree of fold in the alkylated radicals is expected. The relative magnitudes of the a(N) : a(3-H) ratios found for side-chains attached by primary and secondary carbons are consistent with the steric demands of these types of substituents: the more hindered the aminium centre the greater the fold induced in the heterocycle.

Equally, the displacements of the points for the unsubstituted and the 10-diphenylmethylphenothiazine cation-radicals in Figure 1 are explicable in these terms. The correlation line intersects the ordinate at a(N) 0.674 mT [equation (1)], but this does not coincide with the result for phenothiazine cation-radical a(N) 0.634 mT. The intercept represents the nitrogen splitting the unsubstituted radical would have if it had a fold comparable with the alkylated radicals. The fact that the true point is *below* the intercept is consistent with the unsubstituted radical being more nearly planar. Similarly, the displacement of the diphenylmethyl point above the correlation line is consistent with a more folded heterocycle in this cation-radical. Indeed, the characteristic value for the a(N) : a(3-H) ratio for radicals with a side-chain attached by secondary carbon implies that they all lie on a line whose slope and intercept are different from those for alkyl side-chains attached by primary carbon (broken line in Figure 1). We have insufficient data to be certain that this is so. Although Figure 1 shows no curvature which would denote a continuous variation in fold angle with substituent size as is observed in the solid phase for reduced phenothiazines, Figure 3 implies that, nevertheless, such variation is real. Charton's parameter ν is interpolated from van der Waals radii.[13] The linear variation of the ratio a(N) : a(3-H) with ν for radicals with side-chains attached by primary carbon and of comparable conformational properties implies that we may be detecting such steric dependence of the fold angle in the cation-radicals also. In general our conclusions about the shapes of alkylated phenothiazine cation-radicals accord well with the prediction, (5), of Coubeils and Pullman.[3]



(5)

Comparisons between Phenothiazine Cation-radicals.— The ratio of a(N) : a(3-H) for 10-phenylphenothiazine cation-radical implies that the heterocycle is nearer to planar in this radical than in the alkylated cation-radicals. This is reasonable in view of the geometry deduced for the aryl-substituted radicals [2] where the planes of the phenyl ring and the trigonal nitrogen subtend a dihedral angle of *ca.* 65°. It is, therefore, at first sight surprising that a(N) for 10-phenylphenothiazine cation-radical (0.695 mT) is greater than the intercept value (0.674 mT) from Figure 1. Since σ_I for Ph is positive, a 10-phenylphenothiazine cation-radical with the *same* fold angle as the alkylated radicals would be expected to have a(N) smaller than the intercept value; if, as inferred above, the actual 10-phenylphenothiazine cation-radical is more nearly planar than the alkylated radicals, a(N) would be expected to be smaller still. Confirmation of this reasoning comes from equation (3) which predicts a nitrogen splitting of 0.621 mT for a 10-phenylphenothiazine cation-radical (*i.e.* n 0), having the fold angle of an alkylated phenothiazine cation-radical.

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[29] S. S. C. Chu and D. van der Helm, *Acta Cryst.*, 1974, **30B**, 2489.
[30] S. S. C. Chu and D. van der Helm, *Acta Cryst.*, 1975, **31B**, 1179.
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We suggest mesomeric interaction between the phenyl ring and the aminium centre is responsible for the ' high ' a(N) observed for 10-phenylphenothiazine cation-radical. Despite the high twist angle of *ca.* 65° in the *N*-phenyl bond, mesomerism is not negligible as witnessed by the observation of proton splittings from the phenyl group.[2] In Part 6 we showed the influence of $+M$ substituents in the phenyl ring is to perturb the distribution of spin and charge between the heterocyclic nitrogen and sulphur such than spin density on nitrogen increases.[2b] This comparison of 10-phenylphenothiazine cation-radical with alkylated radicals implies that mesomeric donation from the unsubstituted phenyl group is also significant in determining its a(N) value. Even cross-conjugation of the π-electrons of the phenyl ring with nitro substituents does not reduce a(N) below the hypothetical value of 0.621 mT.

The proximity of the points in Figure 1 for 10-alkoxycarbonylphenothiazine cation-radicals to the correlation lines for 10-arylphenothiazine cation-radicals indicates a similarity between the two types of radical. In both the side-chain is attached by sp^2 carbon with the C–N bond having a high twist angle. The fact that the a(N) : a(3-H) ratios imply the acylated radicals to be more folded than the arylated radicals accords with the steric requirements of the two side-chains. The observation of very *low* a(N) for the acylated radicals must, therefore, be a consequence of the electronegative nature of the ester groups which repels cationic charge and necessarily also spin from nitrogen to sulphur. This is confirmed by the observation of a high g value.

EXPERIMENTAL

Materials.—We are indebted to May and Baker Ltd. for gifts of promethazine hydrochloride and chlorpromazine hydrochloride and to John Wyeth and Brother Ltd. for a gift of promazine hydrochloride.

Alkylphenothiazines were prepared by treating the conjugate base of phenothiazine (generated in dimethyl sulphoxide by treatment of the heterocycle with a slight excess of sodium hydride–mineral oil suspension),[32] with an excess of an appropriate alkyl halide. The mixture was stirred under nitrogen for 1 h at 60°, after which the solution was poured into ice–water acidified with HCl. The crude product, if solid, was isolated and dried; occasionally the product was an oil, in which case, after precipitation, it was extracted into chloroform, dried over

TABLE 4

Physical data for 10-substituted phenothiazines

Substituent	M.p. or b.p. (°C)	Lit. m.p. or b.p. (°C)	Ref.	N.m.r. data (τ) [a,b]
Me	100—101	101—103	33*a*	6.71 (3 H, s, CH_3)
Et [c]	103—104	103—104.5	33*b*	6.21 (2 H, q, *J* 7 Hz, CH_2), 8.57 (3 H, t, *J* 7 Hz, CH_3)
Pr	50—51	49—50	33*b*	6.24 (2 H, t, *J* 7 Hz, NCH_2), 8.19 (2 H, m, *J* 7 Hz, CH_2), 9.00 (3 H, t, *J* 7 Hz, CH_3)
Pr^i [c]	59—60	59—60	33*b*	5.83 (1 H, m, *J* 7 Hz, CH), 8.42 (6 H, d, *J* 7 Hz, CH_3)
Bu	143—146 (0.15 mmHg)	226—230 (15 mmHg)	34	6.25 (2 H, t, *J* 7 Hz, NCH_2), 8.0—9.4 (7 H, m, C_3H_9)
Bu^i	127—129 [d]			6.46 (2 H, d, *J* 7 Hz, CH_2), 7.84 (1 H, m, *J* 7 Hz, CH), 9.04 (6 H, d, *J* 7 Hz, CH_3)
cyclo-C_5H_9	100—101 [d]			5.60 (1 H, m, *J* 8 Hz, CH), 7.6—8.8 (8 H, m, ring H)
Bu^tCH_2 [c]	152—153 [d]			6.13 (2 H, s, CH_2), 9.13 (9 H, s, CH_3)
(±)-C_5H_{11}	44—46 [d]			6.48 (2 H, m, CH_2), 7.8—9.4 [9 H, m, $CH(CH_3)CH_2CH_3$]
CH_2=$CHCH_2$	156—160 (0.2 mmHg)	187—195 (1 mmHg)	33*c*	3.8—4.5 (1 H, m, =CH), 4.7—5.2 (2 H, m, $=CH_2$), 5.6—5.9 (2 H, m, CH_2)
MeCH=$CHCH_2$	216—220 (0.2 mmHg) [d]			4.3—4.6 (2 H, m, $=CH_2$), 5.76br (2 H, s, CH_2), 8.43br (3 H, s, CH_3)
CH_2=$CMeCH_2$	53—55	50	35	5.06br (1 H, s, with allylic splitting, =CH), 5.20br (1 H, s, =CH), 5.80br (2 H, s, CH_2), 8.22 (3 H, s, CH_3)
CH≡CCH_2	93—95	95—96	36	5.52 (2 H, d, *J* 2.5 Hz, CH_2), 7.59 (1 H, t, *J* 2.5 Hz, ≡CH)
Ph[CH_2]$_3$	97—99 [d]			6.27 (2 H, t, *J* 6 Hz, NCH_2), 7.33 (2 H, t, *J* 7 Hz, $PhCH_2$), 7.95 (2 H, m, CH_2)
Ph[CH_2]$_2$	72—73 [d]			5.8—6.2 (2 H, m, NCH_2), 6.8—7.2 (2 H, m, $PhCH_2$)
$PhCH_2$ [c]	90—91	90—92	33*d*	5.10 (2 H, s, CH_2)
Ph_2CH	182—184 [d]			3.50 (1 H, s, CH)
N≡C[CH_2]$_2$ [e]	158—159	158—159	36	5.73 (2 H, t, *J* 7 Hz, NCH_2), 7.12 (2 H, t, *J* 7 Hz, CH_2CN)
Et_2OCCH_2	103—104	102	33	5.63 (2 H, s, NCH_2), 5.77 (2 H, q, *J* 7 Hz, OCH_2), 8.76 (3 H, t, *J* 7 Hz, CH_3)
CO_2Me	92—93 [d]			6.23 (3 H, s, CH_3)
CO_2Et	116—117	109—110	37	5.75 (2 H, q, *J* 7 Hz, CH_2), 8.78 (3 H, t, *J* 7 Hz, CH_3)
CO_2Pr^i	135—137 [d]			4.98 (1 H, m, *J* 7 Hz, CH), 8.78 (6 H, d, *J* 7 Hz, CH_3)
CO_2Bu^t	108—110 [d]			8.54 (9 H, s, CH_3)

[a] Phenothiazine aromatic protons resonate in the region of *ca.* τ 3. Neither they nor other aromatic proton resonances are tabulated. [b] Shifts relative to Me_4Si in $CDCl_3$ unless otherwise indicated. [c] In CCl_4. [d] Satisfactory elemental analysis obtained. [e] In [$^2H_6$]acetone.

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[37] N. Fraenkel, *Chem. Ber.*, 1885, **18**, 1845.

$MgSO_4$, and the solvent removed *in vacuo* to give the crude material as a viscous oil. Solid products were purified by column chromatography [alumina; light petroleum (b.p. 40—60°)] followed by recrystallisation from ethanol. Oils were purified by distillation under reduced pressure.

10-Cyanoethylphenothiazine was prepared by reaction of phenothiazine with acrylonitrile catalysed by Triton B[38] and 10-ethoxycarbonylmethylphenothiazine was prepared from the heterocycle and ethyl bromoacetate in refluxing nitrobenzene in the presence of copper bronze and potassium carbonate.[39] 10-Alkoxycarbonylphenothiazines were precared by treatment of phenothiazine-10-carbonyl chloride (Aldrich) with the appropriate alkoxide in the parent alcohol. After pouring into water the materials were isolated, and recrystallised from ethanol or ethanol–benzene. Physical data for the phenothiazines used are given in Table 4.

Nitromethane used as solvent for the cation-radicals was refluxed over calcium hydride for 1 h, distilled, and stored over Type 4A molecular sieve. Granular aluminium chloride (Fisons), thallium acetate sesquihydrate (Emanuel), and sulphuric acid (H_2SO_4 and D_2SO_4) were used as supplied.

E.s.r. Measurements.—The generation of cation-radicals, the conditions for the observation of their e.s.r. spectra, and the spectrum simulation program employed were all as previously described.[1,2]

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