Heterocyclic Free Radicals. Part 7.[1] Substituent Effects on the Distribution of Spin Density in the Cation, Neutral, and Nitroxide Radicals of Phenothiazine

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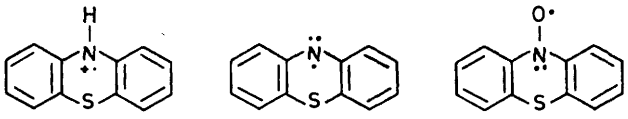
The influence of 2-and 3-substituents in the cation, neutral, and nitroxide radicals of phenothiazine is rationalised in terms of the distribution of spin density between heteroatoms and its response to the electronic effect of the substituents. Mesomeric effects predominate in the cation and neutral radicals but are more important in the former than in the latter. Inductive effects in both families are manifested to a greater extent in the 3-substituted than in the 2-substituted series. In nitroxide radicals, mesomeric effects dominate the 3-substituted series whereas inductive effects dominate the 2-substituted series. Halogen substituents have strikingly different effects in the 3-substituted series of the three families of radicals. This is accounted for in terms of the nature and magnitude of the charge carried by nitrogen in these three radical families.

RECENTLY we have reported an investigation of how aryl substituents influence the distribution of spin density in cation-radicals derived from 10-phenylphenoxazine and 10-phenylphenothiazine.[1] Now we present the results of a study of how substituents in the 2 and 3 positions of the heterocycle influence the distribution of spin density in three further families of radicals derived from phenothiazine. These are the cation (1), neutral (2), and nitroxide (3) radicals.



(1) (2) (3)

There is a two-fold interest in the cation-radicals: the major tranquillising drugs derived from phenothiazine usually bear a 2-substituent and their cation-radicals have been implicated in their behaviour *in vivo*.[2] It is also of interest to compare the effects of substituents in the cation-radicals (1) with those in their conjugate bases, the neutral radicals (2), to assess the influence of charge in otherwise ostensibly very similar radical species. The nitroxides (3) are included as a further comparison since they are readily available from the same starting material as the other radicals and the effects of substituents on e.s.r. parameters in simpler aromatic nitroxides have been reported.[3]

As before we seek to correlate variations in coupling constants induced by substitution using various Hammett-type substituent constants.[1] There is precedent for the application in phenothiazine chemistry of substituent constants properly defined for benzenoid systems: thermodynamic [4,5a] and kinetic properties [5b] ($E_{\frac{1}{2}}$ and radical disproportionation rates, respectively) have been correlated by their use.

RESULTS

(a) *Variations in Nitrogen Hyperfine Splittings.*—In Table 1 are presented the nitrogen hyperfine splittings for monosubstituted phenothiazine cation, neutral, and nitroxide radicals with g values for selected examples; in Table 2 are presented similar results for symmetrically disubstituted cation and neutral radicals. In both Tables the Δa_N values represent the changes in a_N, relative to the appropriate unsubstituted parent radical, which are induced by the substitution. It may be seen in both cation and neutral radicals which bear substituents in position 2, or 2 and 8, that the electron-donating groups ($+M$) serve to decrease a_N relative to the corresponding parent radical and electron-withdrawing groups to increase a_N. By contrast, in cation and neutral radicals substituted in the 3, or 3 and 7, positions, overall electron-donating groups serve to increase a_N and

[1] Part 6, D. Clarke, B. C. Gilbert, and P. Hanson, *J.C.S. Perkin II*, 1976, 114.
[2] I. S. Forrest, F. M. Forrest, and M. Berger, *Biochim. Biophys. Acta*, 1958, **29**, 441.
[3] E. G. Janzen, *Accounts Chem. Res.*, 1969, **2**, 279.
[4] J.-P. Billon, *Ann. Chim.* (*France*), 1962, **7**, 183.
[5] (*a*) T. N. Tozer, L. D. Tuck, and J. Cymerman Craig, *J. Medicin. Chem.*, 1968, **12**, 294; (*b*) T. N. Tozer and L. D. Tuck, *J. Pharm. Sci.*, 1965, **54**, 1169.

electron-withdrawing groups to decrease a_N. It is noteworthy, however, that in the 3- or 3,7-substituted series the influence of halogens is of different character between the cationic and neutral radical families: in cation-radicals halogens behave as electron-donors and increase a_N whilst in the neutral radicals they diminish a_N like electron-withdrawing substituents. Further significant points are that in 2- and 2,8-substituted series the substituent effects in cation-radicals are greater than in neutral radicals; 3- and 3,7-substituted cation-radicals are the only series to show, over the range of substitution studied, increases in a_N which exceed decreases; for other series, and especially for the family of neutral radicals, increases in a_N are small by comparison with decreases; in disubstituted cation and neutral radical families the effect of the second substituent is virtually to double the effect of the first (see Figure 1).

Both 2- and 3-substituted series of nitroxides show an increase in a_N values for electron-donating and a decrease for electron-withdrawing substituents. For the set of substituents studied, the range of decreased a_N values is larger than the range of increased values in both series, and the 3-substituted series shows the largest overall variation in a_N. In the 2-substituted series both F and Cl diminish a_N like electron-withdrawing substituents but in the 3-substituted series F behaves as a weak electron donor and marginally increases a_N whilst Cl behaves as an electron acceptor and decreases a_N.

TABLE 1

Nitrogen hyperfine splittings for 2- and 3-substituted phenothiazine radicals

	Cation (1)			Neutral (2)			Nitroxide (3)		
	a_N/mT	Δa_N/μT	g	a_N/mT	Δa_N/μT	g	a_N/mT	Δa_N/μT	g
H	0.634	0	2.005 2	0.705	0	2.004 6	0.945	0	2.005 7
2-OMe	0.550	−84	2.005 3	0.663	−42	2.004 8			
2-Me	0.621	−13		0.698	−7		0.948	3	
2-F	0.602	−32		0.685	−20		0.924	−21	
2-Cl	0.608	−26		0.690	−15		0.925	−20	
2-COMe	0.662	28	2.005 2	0.712	7	2.004 6	0.935	−10	
2-CF_3	0.650	16		0.709	4		0.927	−18	
2-CN	0.650	16		0.708	3		0.923	−22	
2-NO_2				0.706	1		0.913	−32	
3-OMe	0.676	42	2.004 8	0.718	13	2.004 6	0.968	23	
3-Me	0.650	16		0.710	5		0.955	10	
3-F	0.671	37		0.701	−4		0.950	5	
3-Cl	0.649	15		0.695	−10		0.925	−20	
3-CF_3	0.613	−21		0.677	−28		0.900	−45	
3-CN	0.607	−27		0.663	−42		0.877	−68	
3-NO_2	0.596	−38	2.005 5	0.645	−60	2.004 9	0.854	−91	

TABLE 2

Nitrogen hyperfine splittings of 2,8- and 3,7-disubstituted phenothiazine radicals

	Cation (1)			Neutral (2)		
2,8-X_2	a_N/mT	Δa_N/μT	g	a_N/mT	Δa_N/μT	g
H	0.634	0	2.005 2	0.705	0	2.004 6
OMe	0.494	−140	2.005 5	0.638	−67	2.004 8
Me	0.600	−34	2.005 2	0.693	−12	2.004 6
F	0.565	−69	2.005 5	0.662	−43	2.004 7
Cl	0.588	−46	2.005 6	0.679	−26	2.004 6
COMe	0.669	35	2.005 1	0.721	16	2.004 6
CN	0.661	27	2.005 2	0.714	9	2.004 6
3,7-X_2						
OMe	0.705	73	2.004 7	0.733	28	2.004 5
Me	0.656	22	2.005 0	0.712	7	2.004 5
F	0.704	70	2.005 1			
Cl	0.657	23	2.005 6	0.692	−13	2.005 2
NO_2	0.577	−57	2.005 8	0.614	−91	2.004 8

[6] S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Progr. Phys. Org. Chem.*, 1973, **10**, 1.

[7] H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, 1964, **86**, 5168; F. W. Baker, R. C. Parish, and L. M. Stock, *ibid.*, 1967, **89**, 5677.

(b) *Correlation of Variations in Nitrogen Hyperfine Splittings.*—In Table 3 are presented the results of a statistical analysis of variation in Δa_N for the different families of radicals in terms of dual parameter expressions such as equation (1) where σ_I is Taft's inductive substituent constant,[6] which has been shown [7] to be a good measure of the

$$\Delta a_N = \rho_I \sigma_I + \rho_R \sigma_R = \rho_I(\sigma_I + \lambda\sigma_R) \qquad (1)$$

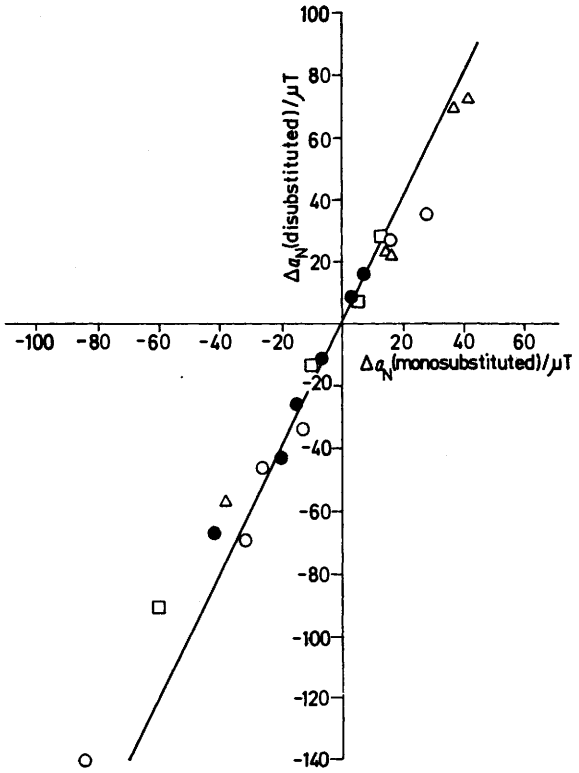


FIGURE 1 Δa_N(disubstituted) *versus* Δa_N(monosubstituted) for neutral and cation-radicals: ○ 2,8 *versus* 2 cation; △ 3,8 *versus* 3 cation; ● 2,8 *versus* 2 neutral; □ 3,7 *versus* 3 neutral. The line has slope 2

field effects exerted by polar and dipolar substituents at a site of interest, and σ_R represents, in turn, each of Taft's ranks of mesomeric substituent parameter,[6] *i.e.*, σ_R(BA), σ_R^0, σ_R^-, and σ_R^+. ρ_I and ρ_R are, respectively, the susceptibilities of the Δa_N values to variation, separately, with the inductive and mesomeric effects of the substituents.

The definition of the parameter f is the ratio of s to the root mean square of the values of the dependent variable *i.e.*, Δa_N. Taft suggests that $f \leqslant 0.1$ be taken as the criterion of the goodness of fit of a dual parameter expression to a set of experimental data.[6] It may be seen from Table 3 that this obtains only for equation (7); for all the other ' best '

TABLE 3

Statistical results for correlations by dual parameter expressions $\Delta a_N = \sigma_I\rho_I + \sigma_R\rho_R = \rho_I(\sigma_I + \lambda\sigma_R)$

Family	Series	n [a]	σ_R	ρ_I/μ_T	ρ_R/μ_T	s [b]	r_I [c]	r_R [d]	R [e]	f [f]	λ	
	2	7	σ_R(BA)	16.446	123.776	12.759	0.159	0.966	0.970	0.334	7.526 2	
	2	7	σ_R^0	11.793	152.402	14.330	0.159	0.960	0.962	0.375	12.922 6	
	2	7	σ_R^-	14.827	93.492	22.327	0.159	0.902	0.905	0.584	6.305 4	
Cation (1)	2	7	σ_R^+	**−0.192**	**88.263**	**6.625**	**0.159**	**0.992**	**0.992**	**0.173**	**−459.0 3**	$\simeq -\infty$
	3	7	σ_R(BA)	−31.029	−95.129	7.404	0.522	0.959	0.982	0.248	3.065 8	
	3	7	σ_R^0	−23.819	−121.722	5.529	0.522	0.977	0.990	0.185	5.112 8	
	3	7	σ_R^-	**−13.549**	**−82.520**	**4.287**	**0.522**	**0.990**	**0.994**	**0.144**	**6.090 6**	
	3	7	σ_R^+	−23.859	−64.489	11.998	0.522	0.939	0.952	0.402	2.702 9	
	2	8	σ_R(BA)	−1.663	54.385	−4.915	0.204	0.968	0.968	0.277	−32.711 7	
	2	8	σ_R^0	−3.922	66.224	5.872	0.204	0.952	0.954	0.331	−16.884 4	
	2	8	σ_R^-	−4.294	28.528	9.302	0.204	0.870	0.880	0.525	−8.972 2	
Neutral (2)	2	8	σ_R^+	**−7.493**	**39.437**	**2.313**	**0.204**	**0.988**	**0.993**	**0.130**	**−5.268 0**	
	3	7	σ_R(BA)	−60.103	−59.275	7.048	0.747	0.844	0.976	0.232	0.986 2	
	3	7	σ_R^0	−55.438	−76.307	6.113	0.747	0.877	0.982	0.201	1.376 4	
	3	7	σ_R^-	**−48.247**	**−52.755**	**3.823**	**0.747**	**0.920**	**0.993**	**0.126**	**1.093 4**	
	3	7	σ_R^+	−55.520	−40.335	9.062	0.747	0.853	0.960	0.298	0.726 5	
	2	7	σ_R(BA)	−47.540	0.170	2.323	0.985	0.104	0.985	0.116	-3.576×10^{-3}	$\simeq 0$
	2	7	σ_R^0	−47.586	0.451	2.323	0.985	0.152	0.985	0.116	-9.478×10^{-3}	$\simeq 0$
	2	7	σ_R^-	−47.473	−0.142	2.323	0.985	0.212	0.985	0.116	2.991×10^{-3}	$\simeq 0$
Nitroxides (3)	2	7	σ_R^+	−47.630	0.425	2.323	0.985	0.184	0.985	0.116	-8.923×10^{-3}	$\simeq 0$
	3	7	σ_R(BA)	−89.006	−103.102	11.271	0.713	0.871	0.977	0.238	1.158 4	
	3	7	σ_R^0	−80.908	−132.693	9.121	0.713	0.902	0.985	0.192	1.640 0	
	3	7	σ_R^-	**−68.190**	**−92.034**	**2.363**	**0.713**	**0.945**	**0.999**	**0.050**	**1.349 7**	
	3	7	σ_R^+	−81.584	−69.436	15.678	0.713	0.870	0.955	0.330	0.851 1	

[a] Number of data sets. [b] Standard deviation of the estimate. [c] Correlation coefficient of Δa_N on σ_I. Correlation coefficient of Δa_N on σ_R. [e] Multiple correlation coefficient. [f] See text and ref. 6.

' Best ' correlations for any series (bold-faced in Table 3) are judged as those for which the standard deviation of the estimate s is the smallest, the multiple correlation coefficient R is the largest, and for which Taft's parameter f[6] is the smallest. The large magnitude of $|\lambda| = \rho_R/\rho_I$ obtained in the best correlation of the data for 2-substituted cation-radicals implies that here the variation in Δa_N is virtually independent of the inductive (field) effects of the substituents. (Taft has suggested that $|\lambda| > 10$ is equivalent to $|\lambda| = \infty$ for practical purposes.[6]) Conversely, the very small values of λ obtained using any σ_R for 2-substituted nitroxides implies that here the variations in their Δa_N are independent of resonance effects and depend only upon the inductive (field) effects. The ' best ' statistical results are summarised in equations (2) to (7) [Figure 2 compares graphically equations (2) and (3)].

Cation-radicals

2-Series $\Delta a_N = 88.26\sigma_R^+$ (2)

3-Series $\Delta a_N = -13.55\sigma_I - 82.52\sigma_R^-$ (3)

Neutral radicals

2-Series $\Delta a_N = -7.49\sigma_I + 39.44\sigma_R^+$ (4)

3-Series $\Delta a_N = -48.25\sigma_I - 52.75\sigma_R^-$ (5)

Nitroxides

2-Series $\Delta a_N = -47.55\sigma_I$ (6)

3-Series $\Delta a_N = -68.19\sigma_I - 92.03\sigma_R^-$ (7)

correlations we find $0.1 < f < 0.2$. We believe this lack of precision in the correlations to be significant and shall return to it later.

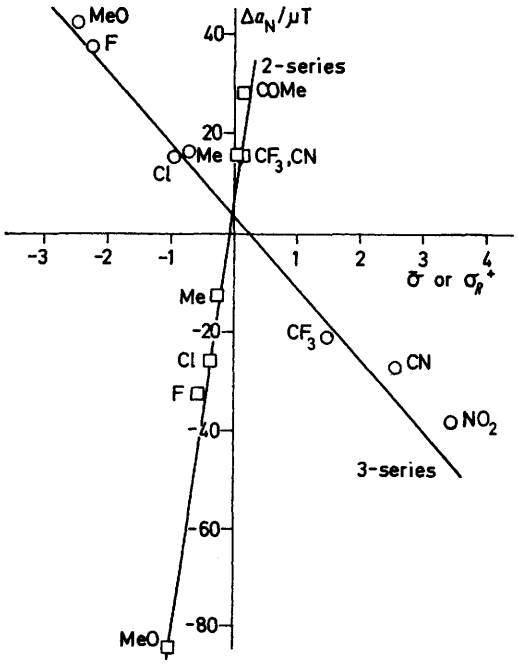


FIGURE 2 Comparison of substituent effects on Δa_N in the two series of cation-radicals. The lines correspond to equations (2) and (3)

TABLE 4

(a) Experimental hyperfine splittings (mT) of the cation-radicals from 2,8-disubstituted phenothiazines; calculated splittings in parentheses

X	a(N)	a(N-H)	a(1-H)	a(3-H)	a(4-H)	a(X)	g
OMe [a]	0.494	0.583	0.057	0.257	0.039	0.019	2.005 5
	(+0.541)	(−0.576)	(−0.033)	(−0.296)	(+0.065)		
F	0.565	0.643	0.057	0.233	0.019	0.233	2.005 5
Cl	0.588	0.675	0.070	0.240			2.005 6
Me	0.600	0.686	0.089	0.257	0.044	0.089	2.005 2
	(+0.608)	(−0.648)	(−0.090)	(−0.272)	(+0.071)		
H	0.634	0.729	0.113	0.249	0.050	0.050	2.005 2
	(+0.670)	(−0.713)	(−0.157)	(−0.251)	(+0.078)	(−0.024)	
CN	0.661	0.755	0.138	0.216	0.035		2.005 2
COMe	0.669	0.764	0.143	0.230	0.045		2.005 1

(b) Experimental hyperfine splittings (mT) of the cation-radicals from 3,7-disubstituted phenothiazines; calculated splittings in parentheses

X	a(N)	a(N-H)	a(1-H)	a(2-H)	a(4-H)	a(X)	g
OMe	0.705	0.777	0.135	0.069	0.069	0.069	2.004 7
	(+0.696)	(−0.741)	(−0.168)	(−0.078)	(+0.103)		
F [b]	0.704	0.780	0.149	0.065	0.065	0.704	2.005 1
Cl	0.657	0.757	0.099	0.049	0.049	0.049	2.005 6
Me	0.656	0.743	0.128	0.065	0.065	0.315	2.005 0
	(+0.676)	(−0.720)	(−0.160)	(−0.032)	(+0.083)		
H	0.634	0.729	0.113	0.050	0.050	0.249	2.005 2
	(+0.670)	(−0.713)	(−0.157)	(−0.024)	(+0.078)	(−0.251)	
NO_2	0.577	0.667	0.105		0.027	0.052	2.005 8
	(+0.587)	(−0.625)	(−0.100)	(−0.006)	(−0.030)		

[a] Complex spectrum—tentative assignment of splittings. [b] Splittings from ^{19}F and ^{14}N probably not equivalent, but small difference not resolved owing to broad linewidths, *ca.* 40 μT.

Statistical data are not presented for disubstituted radical families, numbers of data sets being insufficient in some series. On the other hand we have been able to analyse completely the e.s.r. spectra of the disubstituted radicals studied. This was not attempted for monosubstituted series where the substituent destroys the symmetry of the radical.

(c) *MO Calculations and Assignment of Splittings for Disubstituted Cation-radicals.*—Tables 4a and b contain, respectively, details of the analyses of the e.s.r. spectra of some 2,8- and 3,7-disubstituted phenothiazine cation-radicals, together with results for the parent radical. Assignments of splittings to protons at different positions are based on the results of Hückel–McLachlan MO calculations. For phenothiazine cation-radical itself we have chosen parameters employed previously [8] for calculations of hyperfine splittings in this and related radicals (h_N1.5, k_{CN}1.0, h_S1.25, k_{CS}0.57, $\lambda = 1.2$; Q_{CH}^H −2.7 mT, Q^N 2.78 mT, Q_{NH}^H −2.96 mT, $Q^S = 3.34$ mT) and we have incorporated a simple modification to simulate the perturbing effect of the substituent: we have chosen simply to vary h_C for the carbon atoms to which substituents are attached. This is the basis of the so-called ' Inductive Model ' employed to simulate the effect of alkyl groups on electron distribution in π-systems.[9]

Figures 3 and 4 describe the changes in calculated splittings for 2,8- and 3,7-disubstituted phenothiazine cations as a function of h_C. Comparison of these results with the analyses presented in Tables 4a and b shows that if our assignments of splittings and signs are indeed correct, then agreement with the observed overall trends is obtained. For example, for the 2,8-disubstituted series, the effect of decreasing $h_{C(2,8)}$ to simulate the role of overall electron-releasing groups is to lower a_N, to render a(1-H) less negative and a(4-H) less positive, and to make a(3-H) more negative, as is observed. For the 3,7-disubstituted cation-radicals the opposite trends are predicted: as $h_{C(3,7)}$ is reduced to

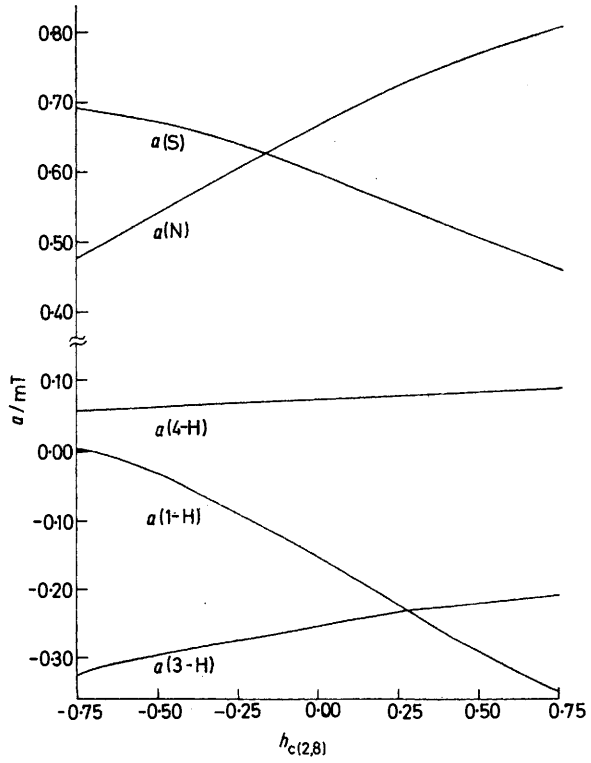


FIGURE 3 Variation of calculated coupling constants for the phenothiazine cation-radical as a function of the value of $h_{C(2,8)}$ taken

simulate the effect of electron-releasing groups, a(1-H) and a(2-H) become more negative and a(4-H) becomes more positive. For most substituents these predictions are

[8] M. F. Chiu, B. C. Gilbert, and P. Hanson, *J. Chem. Soc.* (*B*), 1970, 1700.

[9] A. Streitwieser in ' Molecular Orbital Theory for Organic Chemists,' Wiley, New York, 1967, p. 133.

borne out in practice and good agreement is obtained in both series of disubstituted cation-radicals for $h_O^{Me} = -0.2$ and $h_O^{OMe} = -0.5$; in the 3,7-disubstituted series nitro-substitution is well accommodated by $h_O^{NO_2} = 0.5$ (calculated values are included in Tables 4a and b).

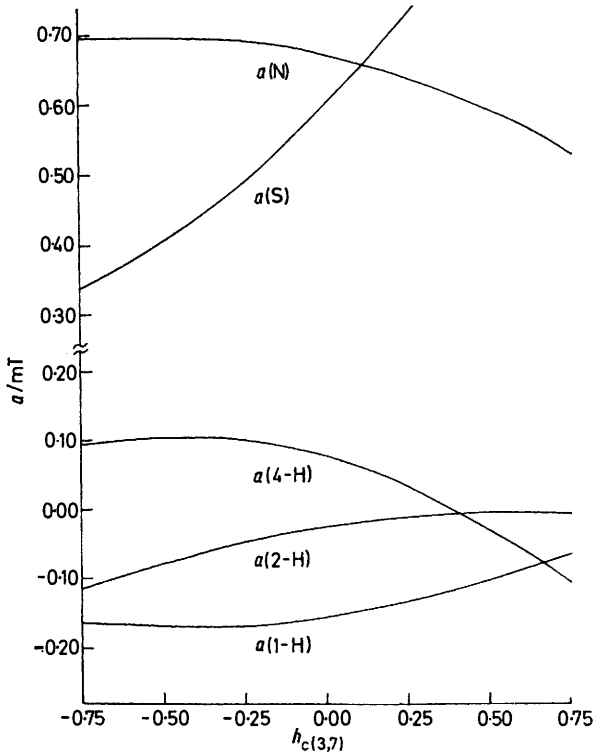


FIGURE 4 Variation of calculated coupling constants for the phenothiazine cation-radical as a function of the value of $h_{C(3,7)}$ taken

TABLE 5

(*a*) Experimental hyperfine splittings (mT) of the neutral radicals from 2,8-disubstituted phenothiazines [a]

X	*a*(N)	*a*(1-H)	*a*(3-H)	*a*(4-H)	*a*(X)	*g*
OMe	0.638	0.191	0.382	0.093	0.012	2.004 8
F	0.662	0.235	0.377	0.095	0.188	2.004 7
Cl	0.679	0.263	0.376	0.096		2.004 6
Me	0.693	0.257	0.376	0.100	0.070	2.004 6
H	0.705	0.285	0.366	0.095	0.095	2.004 6
CN	0.714	0.310	0.356	0.096		2.004 6
COMe	0.721	0.300	0.352	0.097		2.004 6

(*b*) Experimental hyperfine splittings (mT) of the neutral radicals from 3,7-disubstituted phenothiazines [a]

X	*a*(N)	*a*(1-H)	*a*(2-H)	*a*(4-H)	*a*(X)	*g*
OMe	0.733	0.282	0.050	0.101	0.050	2.004 5
Me	0.712	0.282	0.073	0.103	0.404	2.004 5
H	0.705	0.285	0.095	0.095	0.366	2.004 6
Cl	0.692	0.293	0.041	0.109	0.079	2.005 2
NO_2	0.614	0.175	0.019	0.089	0.175	2.004 8

[a] Ring proton splittings assigned by comparison of experimental splittings with those calculated for the *cation*-radical series, see text.

(d) *Assignment of Splittings for Disubstituted Neutral Radicals.*—Tables 5a and b contain, respectively, our assignment of splittings for the 2,8- and 3,7-disubstituted neutral radicals. The assignment of ring proton splittings is made by comparison with the calculations reported for *cation*-radicals above. Our earlier calculations [8] had indicated that *a*(1-H) is slighly greater than *a*(3-H) in the parent neutral radical. However, we have now shown experimentally that the reverse is the case. The e.s.r. spectrum of the neutral radical from [3-^{2}H]phenothiazine shows, when compared with that from the undeuteriated heterocycle, that the splitting from one of the pair of protons with the largest hyperfine splitting value is removed. We thus conclude that the order of magnitudes of splittings in the neutral radical resembles that in the cation, *i.e.* $|a(3\text{-H})| > |a(1\text{-H})| > |a(2\text{-H})| \simeq |a(4\text{-H})|$.

DISCUSSION

Janzen has argued that normal substituent constants will serve to correlate variations in the distribution of spin density in radicals providing the substituent does not acquire a large proportion of the spin.[3] This is consistent with a substituent participating essentially only in the displacements of electrons in pairs. He has termed *valid* those substituents which, in a particular radical system, behave in this way. In valence-bond terms the effect of a substituent is to influence, by dipolar mechanisms, the relative weightings of, usually, two principal structures. In Part 6 [1] we were able to account for the variation of nitrogen hyperfine splitting with aryl substituents in cation-radicals from 10-arylphenoxazines (4; X = O) and 10-arylphenothiazines (4; X = S) in

(4a) (4b)

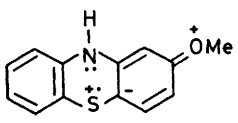
terms of principal structures which place spin on N or X, the relative weightings varying with the substituents. Our rationale for the behaviour of the radicals studied in the present work is similar.

(a) *Cation-radicals.—Mesomeric effects.* Earlier calculations and experiment imply that sulphur and nitrogen represent the major sites of spin density in phenothiazine cation-radicals.[1,8] We interpret the influence of substituents in the present family to be essentially to redistribute spin density between these heteroatoms. In accord with this is the observation that substituents in either the 2- or the 3-position which cause a diminution in a_N, relative to the parent unsubstituted cation-radical, also produce an increase in *g* value consistent with transfer of spin to sulphur, and *vice versa* (see Tables 1 and 2). In qualitative terms, we may rationalise the influence of electron-donating 2-substituents in decreasing a_N through contributions such as (5), for 2-MeO; Tables 1 and 2 show that for 2-substituents the substituent effect follows the normal mesomeric order *i.e.*, MeO > F > Cl > Me. For the mesomerically donating substituents in the 3-position which *increase* a_N, relative to the parent cation-radical, we visualise contributions from structures such as (6), for 3-MeO. Again the trend is essentially in order of mesomeric effects.

The influence of mesomerically electron-withdrawing

groups in the two series of cation-radicals is understood in terms of structures (7) and (8) which show the contributions of the CN substituent serving to increase a_N from the 2-position and to decrease it from the 3-position.

It is conceivable that *d*-orbital participation by sulphur might be significant in cationic species,[10] in particular in those where the effect of the substituent is to increase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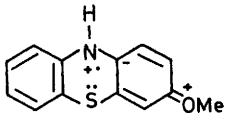
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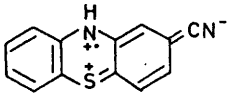
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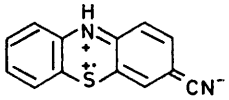
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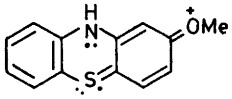
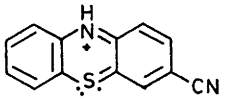

(9)


(10)

positive charge density on divalent sulphur above that in the parent radical, *e.g.*, as for 2-MeO and 3-CN. Contributions from structures such as (9) and (10), which invoke *d*-orbital participation at sulphur in dispersing high dipolar charges, might account for the greater magnitude of the substituent effect of MeO from the 2-position than from the 3-position and the converse for CN.

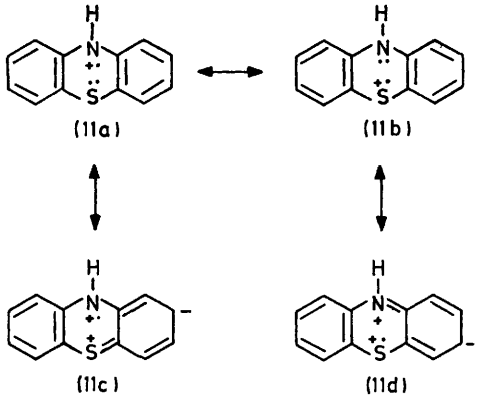
Turning to the statistical results for phenothiazine cation-radicals, the finding that the best correlation for the 2-substituted series involves σ_R^+ [equation (2)], is in harmony with the dominant influence of $+M$ groups (Table 1), and the suggested contributions from structures like (5) and (9). The finding of a best correlation involving σ_R^- for the 3-substituted series of cation-radicals [equation (3)], is at first sight surprising. A σ_R^- correlation is perhaps reasonable for $-M$ substituents [*cf.* the role imputed to structures like (8)], but since the distribution of Δa_N values about zero is approximately symmetrical (Table 1) it is not obvious why the statistics imply a $-M$ dominance of the data. In explanation, we first note a difference in character between the present radicals and those for which, previously, hyperfine splittings have been correlated using substituent constants.[1,3] In earlier cases where the substituents' effects have been to redistribute spin density between two primary sites, only one of these was able to interact directly with the substituents. In phenothiazine radicals a substituent in either the 2- or the 3-position is necessarily conjugated with one of the heteroatoms and simultaneously '*meta*' within the heterocycle to the other. Consequently, neither primary residence of spin density is free from interaction with a substituent in either position. Furthermore, a redistribution of spin density occurring over a range of substitution might be correlated for the conjugated heteroatom by σ_R^+, σ_R^-, or σ_R(BA) but for the '*meta*'-heteroatom by σ_R° (σ_R° is defined for the type of electronic interaction which obtains in the *meta*-relationship of a substituent to a site of interest.[6,11] Now since for a selection of substituents involving all electronic types (what Taft has termed a basis set [6]), σ_R° is not a linear function of any other rank of σ_R, it is not generally to be expected that a precise correlation of substituent effects should emerge from a statistical treatment using a single σ_R value. We believe this is the reason for the general lack of precision, by Taft's $f \leqslant 0.1$ criterion, of the best correlations drawn from Table 3 by comparison with other systems for which the bisected substituent constant treatment is successful.

Returning now to the particular instance of the 3-substituted cation-radicals, the precision of equation (3) is, by Taft's criterion, the poorest of the 'best' correlations and, furthermore, we note that correlation by σ_R° is but marginally poorer (Table 3). It is consistent with what has gone before that a redistribution of electron density over the range of substitution which is relatively poorly correlated by a mesomeric parameter appropriate to conjugation *i.e.*, σ_R^+, σ_R^-, or σ_R(BA), should be almost as well correlated by σ_R°: the redistribution of electron density is 'seen' from the 3-substituent as a change at sulphur almost as much as it is a change at nitrogen. We conclude, therefore, that the mesomeric substituent effect in the 3-substituted cations is complex being correlated in part by σ_R° and by σ_R^- for $-M$ groups. Since for three out of the four donor groups used, σ_R° is numerically the same as σ_R^-,[6] the dual parameter statistics give an apparent best, though relatively imprecise, correlation which involves σ_R^- overall.

Inductive effects. Equation (2) implies that the substituent effect on a_N in phenothiazine cation-radicals is independent of the inductive effects of 2-substituents, and the negative value for ρ_I in equation (3) implies that spin density on nitrogen decreases as the 3-substituents' $-I$ effects become greater in magnitude (*i.e.* σ_I becomes more positive). This in turn means that as the substituents become inductively more electron-withdrawing, positive charge accumulates on sulphur, the *nearer* heteroatom. This is contrary to expectation from a model which would merely redistribute positive charge (and concomitant spin) from the nearer to the further heteroatom under the influence of the electrostatic fields of the substituents, as was found for cation-radicals from arylphenothiazines.[1] To account for the facts we suggest an alternative polarisation of the radicals in the electrostatic fields of the substituents. Canonical forms (11a and b) are the principal contributors to the structure of phenothiazine cation-radical; (11c and d) are minor contributors obtained by delocalising the lone-pair on

[10] W. G. Salmond, *Quart. Rev.*, 1968, **22**, 253.
[11] R. W. Taft, S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Amer. Chem. Soc.*, 1959, **81**, 5352.

sulphur and nitrogen in (11a and b), respectively, into the flanking rings. They are minor, for in them dipolar charges are separated and positive charge is accumulated in the central ring. The polarisations in (11c and d) will be enhanced by the $-I$ effect of substituents in either the 2- or the 3-position, but if we assume that the weighting of structures of type (11d) is somewhat greater than that of type (11c) throughout both ranges of substitution the experimental observations can be accounted for. Accumulation of net negative charge at position 3, relative to the parent, involves migration of spin from nitrogen to sulphur. 3-Substituents will stabilise, by their $-I$ effects, negative charge at the 3-position, thus the suggested polarisation is in accord with the experimental findings of a negative ρ_I for 3-substituted cation-radicals. A positive ρ_I might seem indicated for 2-substituted cation-radicals for they should most effectively stabilise negative charge at the substituted position. If, however,



charge accumulation at position 3 is intrinsically easier than at position 2 [*i.e.*, the implication of greater weighting for type (11d) structures], 2-substituents might increase negative charge density at position 3 with an effectiveness comparable with that at position 2. The effects on spin distribution of the alternative polarisations are mutually cancelling; the observation of the independence of variation in Δa_N values from inductive effects requires that they are exactly so, within the errors of experiment. The apparent capacity of the system to delocalise the lone-pair on nitrogen better than that on sulphur is consistent with the observation that, in comparable environments, nitrogen is the more powerful electron-pair donor, *cf.* all ranks of σ_R for amino-functions and MeS,[6] and also reactivities and properties of pyrrole and thiophen.[12]

The very simple MO approach to the description of substituent effects in phenothiazine cation-radicals, the 'Inductive Model' which merely modifies the electronegativity parameters of the substituted carbons,[9] gives very adequate account of the trends in both nitrogen and proton hyperfine splitting. The success in describing the trends in proton splittings is noteworthy, *e.g.* the prediction, paralleling observation, that a(3-H) increases whilst a(1-H) decreases with decreasing a_N in 2-substituted cation-radicals. This is unexpected on the basis of a simple 'benzylic' model for transmission of spin density from nitrogen into the flanking rings.

The success of the simple MO description reinforces our understanding of the nature of substituent effects in phenothiazine cation-radicals as outlined above. The descriptive valence bond treatment and the MO calculation are concordant in essentials: that spin density is redistributed mainly between the heteroatoms over the ranges of substitution studied and that spin acceptance by substituents is so insignificant that neither approach takes account of it.

(b) *Neutral Radicals.*—The detail of earlier Hückel–McLachlan calculations on the phenothiazine neutral radical [8] has been called into question by the finding that the relative magnitudes of proton hyperfine splitting are not correctly predicted [see Results section (d)]. Despite this, we suggest that the implication of the MO treatment, that spin density is distributed much less equally between nitrogen and sulphur in neutral radicals than in cation-radicals, is true. In valence-bond terms, structure (12b) involving separated charges would be expected to make the minor contribution. The findings of the present work are consistent: Tables 1 and 2 show that any increases in a_N brought about by substitution are small by comparison with decreases, implying that the intrinsic capacity for redistribution of spin from sulphur to nitrogen is small.

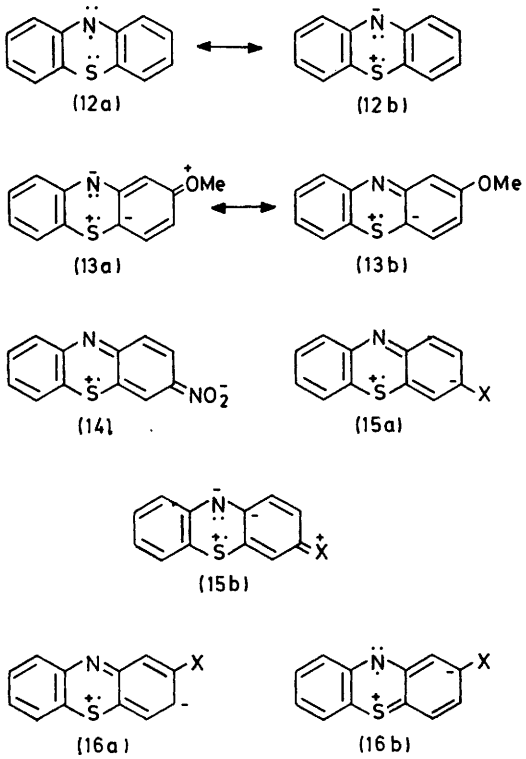
For all series of neutral radicals the data of Tables 1 and 2 are readily interpreted: the variation in a_N for the 2-substituted series is consistent with $+M$ substituents increasing the weighting of (12b) relative to (12a) by comparison with the parent radical, *e.g.* structures (13a and b), for 2-MeO. That high electron demand is made upon $+M$ substituents is further evidenced by fluorine having a greater donor effect than chlorine. The finding that the best σ correlation for 2-substituted neutral radicals involves σ_R^+ [equation (4)] reflects the dominant role implied for $+M$ groups by the skew distribution of Δa_N values about zero.

For 3-substituted neutral radicals the dominant role of $-M$ groups and the finding of a σ correlation involving σ_R^- [equation (5)] is consistent with large contributions like (14), for 3-NO_2. It is noteworthy in this series of radicals that halogens are electron withdrawing with chlorine having the greater effect. It would seem therefore, that for halogens structures such as (15a), which would decrease a_N relative to the parent, dominate (15b) where the effect would be opposite. This significant role of inductive effects is reflected by equation (6) having a large negative ρ_I comparable in magnitude with ρ_R, *i.e.* λ *ca.* 1.

As in the cation-radicals, the importance of inductive effects is greater in the 3-position than in the 2-position and again we suggest the reason is the greater intrinsic capacity of the system to delocalise a nitrogen lone-pair

[12] R. M. Acheson in 'An Introduction to the Chemistry of Heterocyclic Compounds,' Wiley, New York, 1967, 2nd edn., p. 141.

than a sulphur lone-pair. This is consistent with the finding of a negative ρ_I value for the 2-substituted



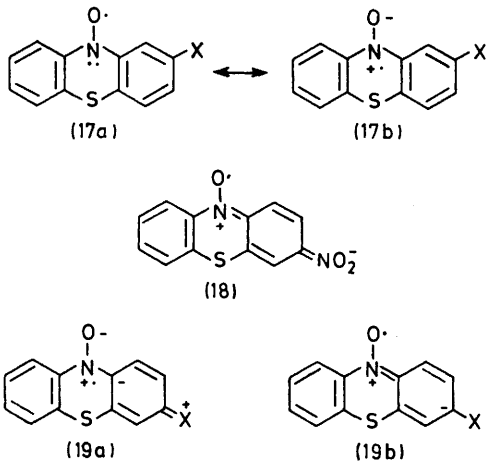
neutral radicals which suggests that structure (16a) outweighs structure (16b) under the influence of the electrostatic field of any substituent X.

(c) *Nitroxides.*—For this family of radicals the effect of substituents is not to perturb the distribution of spin between nitrogen and sulphur but between nitrogen and oxygen. In this respect the phenothiazine nitroxides resemble simpler nitroxides more than they resemble the other familes of radicals discussed above.

We conclude that the effects of 2-substituents on a_N in nitroxides depend only on their inductive effects [equation (6)]. The results require the extent of dipolar charge separation in the nitroxide function to decrease as the $-I$ effects of 2-substituents increase. In the heterocycle the positive end of the nitroxide dipole on nitrogen is always closer to the substituted carbon than is the negative end on oxygen. The response of the dipolar charge separation to substitution is thus as expected on purely electrostatic grounds: as X becomes more electron-withdrawing the weighting of (17b) relative to (17a) decreases.

The 3-substituted phenothiazine nitroxides parallel the behaviour of *para*-substituted phenyl nitroxides.[3] The effect of $-M$ substituents is to reduce a_N, relative to the parent radical, by contributions such as (18), for 3-NO_2. Our finding of a σ_R^- correlation is in harmony with $-M$ substituents dominating the data and parallels the σ^- relationship for phenyl nitroxides reported by Janzen.[3] The negative ρ_I value found implies a mechanism of response of the nitroxide dipole to the field effects of 3-substituents similar to that suggested for their 2-substituted analogues. The precision of the best correlation for 3-substituted nitroxides, [equation (7)], meets Taft's $f \leqslant 0.1$ criterion.[6] We note that in this instance, only one of the primary sites of residence of spin density (nitrogen and not oxygen) interacts with substituents in the phenothiazine ring, which is the condition outlined earlier for high precision of correlation.

It is interesting to compare the substituent effects of fluorine and chlorine in 3-substituted nitroxides with those in the foregoing 3-substituted cation and neutral radicals. In the nitroxides fluorine is a donor as are both halogens in the cation-radicals but chlorine is electron withdrawing as are both halogens in the neutral radicals. For an *overall* electron-donating halogen, structure (19a) would dominate (19b) whereas for an overall electron-accepting halogen the reverse would be true. In the dipolar nitroxides the demand for electrons made by the nitrogen on the halogen will be less than in the cations; the system evidently distinguishes the relatively greater capacity of fluorine to donate mesomerically despite the fact that it has a more powerful inductive effect than chlorine (*cf.* donor : acceptor capacity as measured by the ratio $\sigma_R^+ : \sigma_I$ for the two halogens, F $-0.57 : 0.50$; Cl $-0.36 : 0.46$). In the dipolar structure (12b) of neutral radicals, nitrogen is negatively



charged and thus makes no demand for electron density on either halogen; to the contrary, both act as electron acceptors.

EXPERIMENTAL

(a) *Phenothiazines.*—Phenothiazine and its 2-chloro, 2-methoxy, and 2-trifluoromethyl derivatives were commercially available materials. We are indebted to Professor J. I. G. Cadogan for the gift of [3-^{2}H]phenothiazine.

The remaining phenothiazines used were synthesised by established routes: A, thionation of appropriately substituted diarylamines; B, Smiles rearrangement of suitable 2-acylaminodiaryl sulphides; C, nitrene mediated rearrangement of suitable 2-nitrodiaryl sulphides; and D, elaboration from an existing phenothiazine. The diarvl-

amine precursors were obtained by Ullmann reaction of aryl iodides with anilides followed by hydrolysis and the diaryl sulphide precursors were made by reaction of 2-nitroaryl chlorides with appropriate thiols.

TABLE 6

Source and m.p. data for the substituted phenothiazines

Substituent	Position	Source [a]	M.p. (°C)	Lit. m.p. (°C)	Ref.
OMe	3	C	158—160	158—160	13
	2	Aldrich [b]	179—180	179—180	14
Me	3	C	177—178	166—168	13
	2	C	191—193	187—188	13
F	3	A	175—176	176—177	15
	2	C	200—201	199	13, 19
Cl	3	B	203—204	199	16
	2	Aldrich [b]	196—197	196—197	17
COMe	2	D [c]	191—192	192—193	18
CF_3	3	B	215—217	217—218	19
	2	Aldrich [b]	190—193	188—189	20
CN	3	D [d]	182—184		
	2	D [d]	207—208	202—203	21
NO_2	3	B	216—217	218	17
	2	B	169—173	174—175	22
OMe	3,7	A	193—195	194—196	23
	2,8	A	170—173	174—175	24
Me	3,7	C	224—226	226—228	13, 23
	2,8	C	250—252		
F	3,7	A	164—166	165—167	25
	2,8	A	222—224 [e]	198	25
Cl	3,7	D [f]	220—223	227	26
	2,8	A	275—276	267.5	27
COMe	2,8	D [c]	265—267	249—251	28
CN	2,8	D [d]	280—290 [g]		
NO_2	3,7	D [h]	320 (decomp.)	286—287	29

[a] A, Thionation; B, Smiles rearrangement; C, nitrene route; D, modification of existing phenothiazine. [b] Material purified by chromatography; SiO_2–benzene. [c] Friedel–Craft reaction on 10-acetylphenothiazine. [d] Cyanation of chlorophenothiazine using CuCN in quinoline. [e] Material has satisfactory elemental analysis. [f] Chlorination of phenothiazine with PCl_5. [g] No elemental analysis, but material shows expected mass spectral and spectroscopic properties. [h] Oxidative nitrosation of phenothiazine.

All the phenothiazines but three are known compounds; indications of source, m.p. characteristics, and relevant references are given in Table 6.

(b) *Cation-radicals.*—All the cation-radicals investigated were generated as stable species by addition of a granule of $AlCl_3$ to a solution of the heterocycle in nitromethane.[1,30]

(c) *Neutral Radicals.*—Neutral radicals were obtained by shaking solutions of the heterocycles in benzene with PbO_2.[8] The life-times of these radicals were variable but typically of the order of 1 h at the concentrations used for e.s.r. measurement.

(d) *Nitroxide Radicals.*—Nitroxide radicals were generated by treatment of solutions of the heterocycles in nitromethane with t-butyl hydroperoxide, with warming if necessary.[8] Again, life-times were variable at the concentrations employed, ranging from 0.5 h to many hours.

(e) *E.s.r. Measurements.*—All e.s.r. spectra were obtained on a Varian E3 spectrometer at ambient temperature. Hyperfine splittings were measured to within 0.005 mT by comparison with the spectrum of a solution of *p*-benzosemiquinone in aqueous ethanol [a(H) 0.236 8 $\pm$0.000 1 mT[31]] and g values were measured by comparison with an aqueous solution of Fremy's salt (g 2.005 5).[32]

Nitromethane was distilled from CaH_2 and both it and benzene (AnalaR) were stored over type 4-A molecular sieve. Solutions made using either solvent were deoxygenated with a stream of nitrogen before and during mixing.

The computer simulation of spectra used a FORTRAN IV program in which Lorentzian line-shape was assumed.[8] The multiple regression program used in the dual parameter statistical analysis was written by Dr. M. Green. All computation was executed on an ICL 4130 computer.

We thank the S.R.C. for a research studentship (to D. C.).

[6/1301 *Received*, 5*th July*, 1976]

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