Heterocyclic Free Radicals. Part 9.[1] The Single-electron Oxidation of Phenothiazine and its Methylated Derivatives by Diazonium Ions

By **John M. Bisson, Peter Hanson,*** and **Doris Slocum,** Department of Chemistry, University of York, Heslington, York YO1 5DD

In acidified acetonitrile the reaction of certain phenothiazines with diazonium ions leads to the formation of the corresponding phenothiazine cation-radicals. Kinetic investigation of the reactions between a series of methylphenothiazines and 4-methoxybenzenediazonium ion suggests a mechanism involving the rapid formation, at the heterocyclic nitrogen, of a cationic σ-complex which subsequently undergoes rate-determining homolysis. Correlations of the logarithms of the apparent second-order rate constants with the charge-transfer transition frequencies of the molecular π-complexes of the methylphenothiazines with 1,3,5-trinitrobenzene and with HMO coefficients of phenothiazine cation-radical itself, lead to conclusions concerning the nature of the rate-determining transition state.

OUR recent work has concerned the effects of substituents on the distribution of spin density in the ground states of various types of radical derived from phenothiazines.[1,2] Now, we report upon the effect of one substituent, the methyl group, on a reaction in which phenothiazine cation-radicals are formed.

The reaction between diazonium ions and phenothiazines has not been investigated previously and the only reaction reported of a comparable substrate is that of thianthrene which is oxidised to its sulphoxide upon treatment with 2-nitrobenzenediazonium ion in acetic acid, followed by aqueous work-up.[3] However, the reports that the coupling of diazonium ions with phenolate anions probably involves a radical pathway,[4] and that *NNN'N'*-tetramethylbenzene-1,4-diamine is oxidised by diazonium ions to the cation-radical, Würster's Blue,[5] were suggestive that radical formation might also be expected with phenothiazines, in appropriate circumstances, on account of their ready single-electron oxidation. This proved to be the case.

RESULTS

Reaction Conditions.—Previous work had shown that acetonitrile is a satisfactory solvent for the study of phenothiazine and its oxidation products.[6] However, it had also been found, in the absence of acidity and in the

[1] Part 8, D. Clarke, B. C. Gilbert, P. Hanson, and C. M. Kirk, *J.C.S. Perkin II*, 1978, 1103.

[2] D. Clarke, B. C. Gilbert, and P. Hanson, *J.C.S. Perkin II*, (*a*) 1977, 517; (*b*) 1976, 111; (*c*) 1975, 1078.

[3] H. Gilman and D. R. Swayampati, *J. Amer. Chem. Soc.*, 1956, **78**, 2163.

[4] N. N. Bubnov, K. A. Bilevitch, L. A. Poljakova, and O. Y. Okhlobytsin, *J.C.S. Chem. Comm.*, 1972, 1058.

[5] (*a*) K. A. Bilevitch, N. N. Bubnov, L. V. Emmanson, and O. Y. Okhlobystin, *Doklady Akad. Nauk S.S.S.R.*, 1970, 583; (*b*) B. Y. Medvedev, L. A. Poljakova, K. A. Bilevitch, N. N. Bubnov, and O. Y. Okhlobytsin, *Teor. i Eksp. Khim.*, 1972, **8**, 256.

[6] P. Hanson and R. O. C. Norman, *J.C.S. Perkin II*, 1973, 264.

presence of traces of water, that deprotonation of phenothiazine cation-radicals, unsubstituted at nitrogen, may occur leading to a complex suite of reactions.[6] To avoid this we elected to use as solvent acetonitrile with a known content of water and acidity. This was achieved by addition of aqueous fluoroboric acid to the acetonitrile in which solutions of the diazonium ions, as their fluoroborates, were to be made up.

It was found that several diazonium ions, in excess, effected the single-electron oxidation of phenothiazine at conveniently measurable rates; we chose 4-methoxybenzenediazonium ion for detailed study on account of its considerable thermal stability.[7] Solutions of 4-methoxybenzenediazonium fluoroborate (2×10^{-3} mol dm^{-3}) in acetonitrile containing 2% v/v *ca.* 40% aqueous fluoroboric acid were stable at ambient temperature over several days and we were able to use such solutions, at temperatures up to 40 °C, in kinetic runs without need for allowance for the thermolysis of the oxidant in the subsequent kinetic analysis.

Kinetic Measurements.—For kinetic measurements, thermally equilibrated solutions of a phenothiazine in acetonitrile and an excess of 4-methoxybenzenediazonium fluoroborate, in acetonitrile containing approximately 2% v/v of water and an excess of fluoroboric acid, were mixed, and the increase in absorbance in the visible part of the spectrum was monitored spectrophotometrically. Substrates of reactivity greater than phenothiazine itself exhibited increases in absorbance, due to formation of the appropriate cation-radicals, which were uniform over the full range of temperature employed (*i.e.* 278—313 K) and which were of the first order in both substrate and oxidant. Phenothiazine and 1-methylphenothiazine behaved similarly at the upper end of this temperature range, but at lower temperatures they behaved as did most 10-methylated phenothiazines over the full range, in that a rapid initial increase in absorbance was observable which levelled off in up to 100 s from the time of mixing, depending upon the temperature and the substrate, and this was followed by a subsequent slow increase of absorbance due to the formation of the cation-radical. The slower reaction was responsible for over 75% of the increase in absorbance and was of the first order in both substrate and oxidant. The behaviour of 1,10-dimethylphenothiazine was unique in that it showed the rapid initial increase in absorbance to a low value, analogous to other 10-methylated substrates, but this was not followed by any further development of colour. Scanned spectra showed that the low absorbance was not due to cation-radical but derived from a featureless tailing into the visible of a u.v. absorption band. For this substrate it was shown that the rapid initial increase in absorbance was of the first order in both the phenothiazine and the oxidant when the oxidant was in excess. For phenothiazine itself, it was also shown that the oxidation rate was independent of the acid concentration over a concentration-range of 10^2—10^3 fold that of the substrate.

Apparent second-order rate constants, k, for the oxidation were measured at a minimum of three, but usually four, temperatures in the range 278—313 K. Apparent activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were obtained from least-squares regressions of $\log(k/T)$ upon T^{-1} and these are presented in Table 1 along with ' best ' values of k for 298 K interpolated from the same regressions.

Correlations of Apparent Second-order Rate Constants.—Substituent effects in the diazonium ion. Phenothiazine is oxidised by other diazonium ions in a manner comparable with 4-methoxybenzenediazonium ion, provided the oxidant is not too electrophilic. We have employed diazonium ions with the substituents 4- and 3-MeO, 4- and 3-Me, H, and 4-PhO. The apparent second-order rate constants measured at 298 K (given in Table 2) are correlated in a Hammett plot better by σ^+ ($\rho = 1.86$; $r = 0.980$; $s = 0.133$) than by σ ($\rho = 3.04$; $r = 0.824$; $s = 0.274$). The kinetic behaviour changes, however, if substituents more electron-withdrawing than 3-MeO confer greater electrophilicity on the oxidant. If their reactions are monitored spectrophotometrically a high initial absorbance is found immediately after mixing which is due, at least in part, to the cation-radical; subsequent increase in absorbance is both slow and small and a maximum is reached, after which absorbance diminishes. This behaviour is ascribed to a change in mechanism (see Discussion section).

TABLE 1

Apparent second-order rate constants at 298 K and activation parameters for the oxidation of phenothiazines by 4-methoxybenzenediazonium ion in acidified aqueous acetonitrile [a]

Methylated positions	k/dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	Methylated positions	k/dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
0	0.122	65.3	−43	2,6	1.71	65.0	−22
1	0.135	80.1	7	2,7	4.84	51.4	−59
2	0.700	65.1	−29	2,8	2.79	64.4	−20
3	1.09	68.0	−16	3,6	2.79	64.7	−19
4	0.453	81.7	22	3,7	8.85	58.8	−29
1,3	0.953	69.1	−13	10	2.91×10^{-3}	80.9	−23
1,4	0.283	77.1	3	2,10	1.61×10^{-2}	73.8	−30
1,6	0.280	68.1	−27	3,10	1.98×10^{-2}	75.0	−26
1,7	0.796	66.2	−24	4,10	1.02×10^{-2}	84.0	−1
1,8	0.435	68.5	−22	2,7,10	7.94×10^{-2}	68.8	−35
2,3	5.14	61.3	−25	3,7,10	0.117	78.4	0
2,4	1.48	55.5	−55				

[a] Estimated errors in k are 5%; in $\Delta H^{\ddagger}$, ± 2 kJ mol^{-1} and in $\Delta S^{\ddagger}$ ± 8 J mol^{-1} K^{-1}.

TABLE 2

Apparent second-order rate constants for 298 K for the oxidation of phenothiazine by substituted benzenediazonium ions

Substituent	k/dm^3 mol^{-1} s^{-1}
H	5.01
3-Me	2.69
4-Me	1.27
3-MeO	4.53
4-MeO	0.122
4-PhO	0.869

[7] M. L. Crossley, R. H. Kienle, and C. H. Benbrook, *J. Amer. Chem. Soc.*, 1940, **62**, 1400.

Charge-transfer transition frequencies. Each of the phenothiazines employed serves as the electron-donor in a

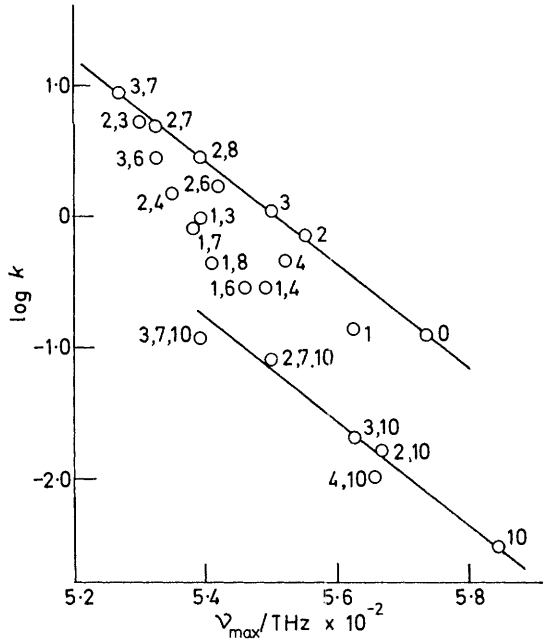


FIGURE 1 Variation of the logarithms of the apparent second-order rate constants with charge-transfer transition frequencies

molecular π-complex with 1,3,5-trinitrobenzene.[8,9] The wavelengths of maximum absorbance in the visible of these π-complexes, in solution in tetrachloromethane, were determined experimentally for solutions containing an excess of the phenothiazine. They are recorded in Table 3.

After conversion to frequency units the data were plotted against the logarithms of the apparent second-order rate constants for the oxidation of the same phenothiazines by 4-methoxybenzenediazonium ion at 298 K (Table 3 and Figure 1).

In Figure 1 data points pertaining to substrates bearing a 10-methyl group are separated from those without the nitrogen substituent; for both types of data points, those corresponding to substrates methylated on carbon atoms 2(8) and 3(7) [see structure (1)] are linearly correlated whilst those corresponding to substrates methylated at C-1(9) and C-4(6) yield points which are displaced from these correlation lines such that, in general, a 1-substituent is associated with a greater displacement than a 4(6) substituent and both displacements are in the sense that the phenothiazine concerned is oxidised less rapidly than ' expected ' from the value of its charge-transfer transition frequency.

Hückel MO coefficients. Reference to Table 1 shows that the order in which *C*-methyl substituents have their influence on rate is 3 > 2 > 4 > 1. With the exception of the 1-position, this is the same as the order of magnitudes of spin densities in the ring positions of the cation-radical of phenothiazine itself, as given by the simple Hückel MO treatment (*i.e.* 3 > 1 > 2 > 4).[10] We find linear correlations between the logarithms of the apparent second-order rate constants and the square roots of the Hückel spin densities (*i.e.* the HMO coefficients, c_i [11]) in phenothiazine cation-radical for those positions which are methylated in the substrates. Such plots are shown in Figure 2

TABLE 3

Wavelengths and frequencies of maximum absorbance of the charge-transfer transitions in π-complexes of phenothiazines with 1,3,5-trinitrobenzene and logarithms of the apparent second-order rate constants for oxidation of the phenothiazines by 4-methoxybenzenediazonium ion

Methylated positions	$\lambda_{max.}$/nm [a]	$\nu_{max.}$/THz × 10^{-2}	log *k*
0	523	5.735	−0.914
1	533	5.625	−0.870
2	540	5.552	−0.155
3	545	5.501	0.038
4	543	5.521	−0.344
1,3	556	5.392	−0.021
1,4	546	5.491	−0.548
1,6	549	5.461	−0.553
1,7	557	5.382	−0.099
1,8	554	5.411	−0.361
2,3	565	5.306	0.711
2,4	560	5.353	0.170
2,6	553	5.421	0.233
2,7	563	5.325	0.685
2,8	553	5.392	0.446
3,6	563	5.325	0.446
3,7	569	5.269	0.947
10	513	5.844	−2.536
1,10	505	5.937	
2,10	529	5.667	−1.793
3,10	533	5.625	−1.703
4,10	530	5.657	−1.991
2,7,10	545	5.501	−1.100
3,7,10	556	5.392	−0.932

[a] Wavelength measurements accurate to ±2 nm.

where the choice of log k/k_0 as ordinate relates the effect of methylation upon rate to the reaction rate of phenothiazine itself and the use of Σc_i as abscissa permits the correlation of multiply substituted substrates. Thus, for the phenothiazine substituted at C-3, $\Sigma c_i = c_3$ whilst for that substituted at positions 3 and 7, which are equivalent in

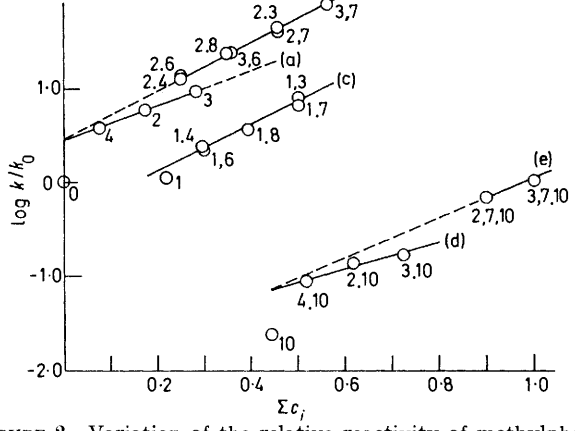


FIGURE 2 Variation of the relative reactivity of methylphenothiazines with HMO coefficients of phenothiazine cation-radical for positions methylated in the substrates.

phenothiazine [see structure (1)], $\Sigma c_i = 2c_3$; for both the substrates substituted at C-2 and C-3 and at C-2 and C-7,

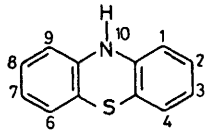
[8] R. Foster and P. Hanson, *Biochem. Biophys. Acta*, 1966, **112**, 482.

[9] C. J. Fritchie and Benes L. Trus, *Chem. Comm.*, 1968, 833.

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

[11] F. Gerson, ' High Resolution E.S.R. Spectroscopy,' Wiley, New York, 1970, p. 35.

respectively, $\Sigma c_i = c_2 + c_3$, and so forth. Hückel spin densities, orbital coefficients, and derived Σc_i values are given in Table 4.



(1)

Various points are immediately apparent from Figure 2. 10-Methylphenothiazine is almost a thousandfold less reactive than ' predicted ' by the extrapolation, to the Σc_i

TABLE 4

HMO and relative reactivity data for phenothiazines

Methylated positions (i)	Hückel spin density, ρ_i [a]	Hückel MO coefficient $c_i = \rho_i^{\frac{1}{2}}$	Σc_i	log k/k_0 [b]
0			0	0
1	0.049	0.221	0.221	0.044
2	0.031	0.176	0.176	0.759
3	0.080	0.283	0.283	0.952
4	0.006	0.077	0.077	0.570
1,3			0.504	0.893
1,4			0.298	0.366
1,6			0.298	0.361
1,7			0.504	0.815
1,8			0.397	0.553
2,3			0.459	1.625
2,4			0.253	1.084
2,6			0.253	1.147
2,7			0.459	1.599
2,8			0.352	1.360
3,6			0.360	1.360
3,7			0.566	1.861
10	0.195	0.442	0.442	−1.622
2,10			0.618	−0.879
3,10			0.725	−0.789
4,10			0.519	−1.077
2,7,10			0.901	−0.186
3,7,10			1.008	−0.018

[a] From ref. 10. [b] Log k values from Table 3.

value appropriate to the HMO coefficient at nitrogen, of line (a) which correlates three other monomethylated phenothiazines. Alternatively, it is clear that *N*-methylation of any phenothiazine *reduces* the rate at which it is oxidised by approximately two orders of magnitude. Also, the reactivity of 1-methylphenothiazine is almost an order of magnitude less than ' predicted ' by line (a), and 1-methylation, generally, gives substrates a reactivity lower than expected by a similar amount [*cf.* the vertical displacement of line (c) from line (b)]. In contrast to *N*- and 1-methylation, other *C*-methylation increases the reactivity of the phenothiazine nucleus in a manner characteristic of the extent of methylation, as shown by the finding of separate lines [(a) and (b)] for the respective mono- and di-*C*-substituted families. In the case of multiple *C*-methylation, it is immaterial for the influence on reaction rate whether both substituents are in the same or in different rings. The variation of log k/k_0 with Σc_i is of the form $\log k/k_0 = p + q\Sigma c_i$ for the correlations of Figure 2; the least-squares values of p and q are given in Table 5. It may be seen that lines (a) and (b) have a common intercept at 0.5 and characteristic slopes. Although the intercept is different for line (c), its slope, 2.4, is the same, within experimental error, as that for line (b). If line (d) is referred to 10-methylphenothiazine as origin instead of to phenothiazine, its intercept is close to 0.5. Comparable values of p are thus obtained for *C*-methylation of both phenothiazine and 10-methylphenothiazine, at other than position 1. Line (e), for which data are lacking, is arbitrarily drawn to a common intercept with line (d), relative to 10-methylphenothiazine, so that their behaviour together resembles that of lines (a) and (b).

TABLE 5

Least-squares values of slopes and intercepts of the regressions of Figure 2

Line	Methylated positions	p	q
(a)	i; $i \neq 1$ or 10	0.53	1.24
(b)	i, j; $i, j \neq 1$ or 10	0.52	2.37
(c)	1, i; $i \neq 10$ or 0	−0.38	2.43
(d)	10, i; $i \neq 1$	−1.78 (0.46) [a]	1.39
(e)	10, i, j; $i, j \neq 1$	*b*	*b*

[a] For reaction relative to 10-methylphenothiazine. [b] Insufficient data.

DISCUSSION

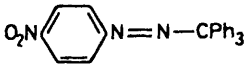
Evidence of a Pre-equilibrium.—The kinetic behaviour observed is consistent with the formation of a complex between the reactants before the rate-determining step which gives rise to products. For the 10-methylated substrates and for the less reactive of those without the nitrogen substituent at low temperatures, there is a rapid change immediately upon mixing reactants. The evidence from 1,10-dimethylphenothiazine, the only substrate where this rapid initial reaction is conveniently amenable to investigation, is that it involves both reactants and does not yield products directly. We extrapolate from this single substrate to all and suggest prior complex formation in each case. The observed enthalpies of activation are consistent with the validity of this hypothesis: they are too small to represent simple enthalpies of activation. For example, the single-step bimolecular (S_N2) reaction of ethyl halides with OH^- has, typically, an activation energy of 96.6 kJ mol^{-1} (23 kcal mol^{-1}); [12] the ready unimolecular heterolysis of benzenediazonium ion has an enthalpy of activation of 110.83 kJ mol^{-1} (26.49 kcal mol^{-1}).[13] The maximum enthalpy determined in this work is 84 kJ mol^{-1} and the mean is but 69 kJ mol^{-1}. These values are thus comparable with those found, for example, for base-catalysed hydrolysis of ethyl acetate (60 kJ mol^{-1}, *i.e.* 14.1 kcal mol^{-1}) [14] which is characterised by an exothermic prior complex formation ($B_{Ac}2$ mechanism). Observation of a negative mean apparent entropy of activation is also consistent with an associative step in the overall process.

The fact that the initial rapid change which we deduce to be the formation of a complex is, nevertheless, observably slow eliminates π-complex formation between the reactants from consideration for, although there is precedent for the formation of π-complexes by both

[12] G. H. Grant and C. N. Hinshelwood, *J. Chem. Soc.*, 1933, 258.
[13] D. F. De Tar and A. R. Ballentine, *J. Amer. Chem. Soc.*, 1956, **78**, 3916.
[14] H. H. Humphries and L. P. Hammett, *J. Amer. Chem. Soc.*, 1956, **78**, 521.

types of reactant,[8,15] it occurs at very fast rates [16] and would appear ' instantaneous ' under the conditions of the present experiments. It is inferred, therefore, that the complex which forms is a σ-complex and, further, it is assumed that the diazonium ion reacts to form this, as usual, through its β-nitrogen atom. Also, since nitrogen is the atom of greatest electron-donor capacity in the phenothiazine molecules, it is suggested that it is the site in the heterocycle which participates in σ-complex formation. There is precedent for this in the formation of triazenes from other amines and diazonium ions.[17] We shall show later that the relatively low reaction rates associated with methyl substituents in the 1-position are also consistent with nitrogen as the position of attachment in the σ-complex.

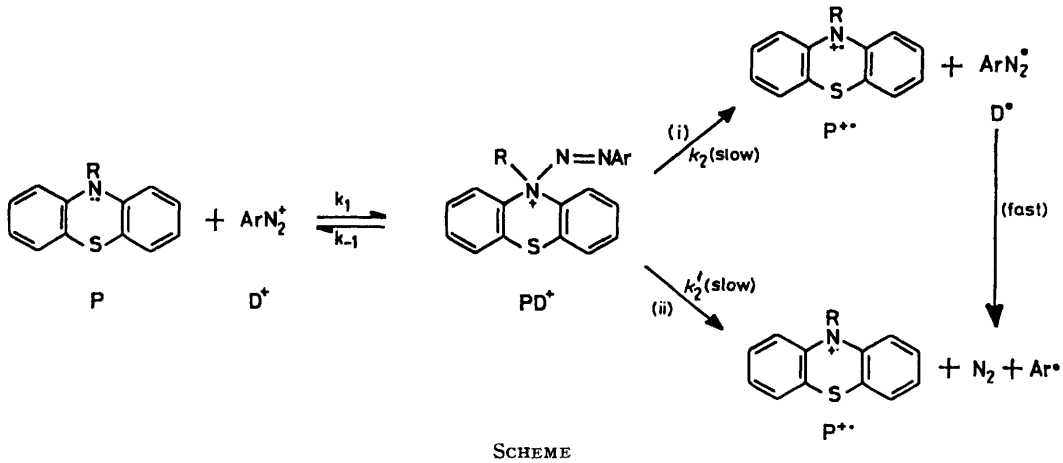
Mechanism.—In the overall reaction the phenothiazines are oxidised to their respective cation-radicals. The N–N bond inferred to be formed in the σ-complex is not, therefore, retained in the products; we suggest its homolysis constitutes the rate-determining step in the reaction. Now homolysis of the σ-complex could conceivably occur in two ways: the one with and the other without the simultaneous formation of a molecule of nitrogen (Scheme). We believe that route (i) is the most probable rate-determining step on the following grounds. Seltzer has shown, on the basis of a study of isotope effects in the thermolysis of azo-compounds, that unsymmetrical homolyses similar to route (i) of the Scheme are followed if the organic radicals which would be produced by the alternative pathway (ii) differ greatly in resonance energy.[18] The phenothiazine



(2)

cations and the phenyl radical are of such differing stability that the unsymmetrical pathway (i) is by far the most likely. Also, (2) has been shown to exhibit different degrees of internal return from radicals in solvents of differing viscosity.[19] Internal return is conceivable only from the geminate radical pair $O_2NC_6H_4N_2^{\bullet}$ and $Ph_3C^{\bullet}$ and not from $O_2NC_6H_4^{\bullet} + N_2 + Ph_3C^{\bullet}$; phenothiazine cation-radicals are of a stability comparable with $Ph_3C^{\bullet}$.

The failure to observe any dependence of the overall reaction rate upon acidity for phenothiazine itself implies that, whilst in principle possible, deprotonation of the σ-complex does not constitute a kinetically significant process, in the range of acidity examined, for those substrates which carry a proton at nitrogen. The reaction path represented in the Scheme with route (i) for the slow step is suggested, therefore, for substrates both with and without the 10-methyl group (*i.e.*, R = H and Me). In general, with the notation given in the



SCHEME

Scheme, by application of the steady-state approximation to $[PD^+]$ we find the relationship shown in (1).

$$d[P^{+\cdot}]/dt = k_2k_1[P][D^+]/(k_{-1} + k_2) \qquad (1)$$

Equation (1) describes the kinetics observed for the majority of the phenothiazines: the reaction is of the first order in each reactant; the experimental second-order rate constant, k, is composite *i.e.* $k = k_2k_1/(k_{-1} + k_2)$; no intermediate species is seen (*i.e.* $[PD^+]$ is small and in steady state). This latter point derives from the assumption that $k_1 \ll k_{-1}$; the dissociation of triazenes into amines and diazonium ions in comparably acid conditions is a known process.[20]

The cases where the rapid initial formation of σ-complex is observed are accounted for in terms of the relative magnitudes of k_1, k_{-1}, and k_2. For these substrates, k_2 has its smallest values thus equation (1) tends to

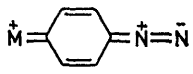
$$k = k_1k_2/k_{-1} = Kk_2 \qquad (2)$$

equation (2) where K is the equilibrium constant for the formation of the σ-complex from reactants. The

[15] S. Koller and H. Zollinger, *Helv. Chim. Acta*, 1970, **53**, 78.
[16] R. Foster, ' Organic Charge-Transfer Complexes ', Academic Press, London, 1969, p. 106.
[17] (*a*) V. Beránek and M. Večeřa, *Coll. Czech. Chem. Comm.*, 1970, **35**, 2402; (*b*) M. Remeš, J. Diviš, V. Zvěřina, and M. Matrka, *ibid.*, 1973, **38**, 1049.
[18] (*a*) S. Seltzer, *J. Amer. Chem. Soc.*, 1961, **83**, 2625, (*b*) *ibid.*, 1963, **85**, 14; (*c*) S. Seltzer and F. T. Dunne, *ibid.*, 1965, **87**, 2628.
[19] W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, 1967, **89**, 1741.
[20] K. Clausius and H. R. Weisser, *Helv. Chim. Acta*, 1952, **35**, 1524.

rapid initial change is thus the establishment of this pre-equilibrium and, furthermore, for cases where the pre-equilibrium lies relatively to the right, the standing concentration of σ-complex is relatively increased and has the greater likelihood of being observed. It is consistent that it is 10-methylated substrates which characteristically show a noticeable concentration of σ-complex: *N*-methylation increases the nucleophilicity of the donor nitrogen, *i.e.* it increases k_1 relative to k_{-1} or, alternatively, it increases K.

The effect of variation in the substituent in the diazonium ion is also understandable in terms of the above kinetic analysis. Since, to a first approximation, $k = Kk_2$ [equation (2)], the observed value of 1.86 for ρ is the sum of separate values for the substituent-dependence of K and k_2. The rate-determining step would reasonably have a small positive ρ, it being a *homolysis* with the charge of the reacting σ-complex remaining in the unsubstituted product moiety. This being the case, the substituent effect in K should dominate the experimental value of ρ. The moderately large and positive value found thus sensibly reflects the greater values of K for the more electrophilic diazonium ions with consequent higher concentrations of the kinetically active σ-complex; the need to utilise σ^+ for the substituents reflects the sensitivity of the pre-equilibrium to their $+M$ effects which are particularly effective in stabilising the diazonium ions themselves [see (3)].



(3)

When highly electrophilic diazonium ions are used, the mechanism changes: high initial absorbance is observed which derives from a high concentration of σ-complex together with product cation-radical. The absorbance ultimately declines, probably owing to further oxidation of the cation-radical to the sulphoxide which is colourless (*cf.* oxidation of thianthrene to sulphoxide by 2-nitrobenzenediazonium ion [3]). At intermediate times, the rate of increase in absorbance is apparently slow because the absorbing species, the cation-radical, is consumed almost as fast as it is formed.

The Relationship of the Substitution Pattern of the Phenothiazines to Reactivity.—N-*Methylation.* A surprising aspect of the results shown in Table 1 is the difference in magnitude of the apparent second-order rate constants when a substrate methylated at nitrogen is compared with its counterpart without the *N*-substituent. Intuitively, an increase in rate on *N*-methylation is expected; the opposite is found. It has been noted in the past that *N*-methylation of phenothiazine increases its ionisation potential.[21] Taking charge-transfer transition frequencies as functions of the ionisation potentials,[22] we find effectively, in Figure 1, correlations between reactivity and ionisation potential. It is reasonable to suppose, therefore, that the factor which raises ionisation potential upon methylation also reduces the reactivity. Malrieu and Pullman attempted to explain the increase in ionisation potential by calculations in which different geometries were assumed at the heterocyclic nitrogen for the methylated and unmethylated molecules.[23] Subsequent crystallographic work confirms their inference of a fold in the heterocycle [24,25] but disproves their suggestion of different preferred configurations at nitrogen. We suggest that the difference in ionisation potential derives essentially from an enthalpy difference between the radicals produced on ionisation, rather than between the parent species, and that differing degrees of fold *in the radicals* are sufficient to explain this enthalpy difference. The more folded is a phenothiazine cation-radical about an axis close to the N–S axis, the less effective is the dispersal of charge and spin into the flanking carbocycles since such fold is equivalent to twist in the N–C and S–C bonds. In Part 8 we showed that the e.s.r. properties of phenothiazine cation-radicals are consistent with *N*-substituents imposing characteristic folds on the heterocycle, spin and charge being less well delocalised when the cation-radical bears an *N*-substituent.[1] This, we suggest, explains the intrinsic stability difference between the two types of cation-radicals and underlies both the differences in ionisation potential and in reactivity. It is noteworthy that the apparent enthalpies of activation determined in the present work are always greater for *N*-methylated substrates than for the corresponding substrates without the *N*-substituent, which is consistent with our suggestion, on the assumption that the differences between the determined apparent enthalpies of activation reflect those between the actual enthalpies of activation. This is probable for if, as was suggested earlier [see (b) above], σ-complex formation is facilitated by *N*-methylation, the actual activation enthalpy of an *N*-methylated substrate will be more compensated by the enthalpy of formation of the σ-complex than will that of the corresponding substrate without the *N*-substituent. Differences between the actual activation enthalpies will, therefore, be greater than those between the apparent enthalpies of activation.

C-*Methylation.* The correlations of Figure 1 imply that the apparent free energies of activation for the oxidation of phenothiazines by 4-methoxybenzenediazonium ion are proportional to the ionisation potentials of the phenothiazines. If the variation in the apparent free energies of activation reflects that in actual free energies, the correlations equally imply that the rate-determining transition states resemble the products of the oxidation reaction. Involvement of the lone pair of the heterocyclic nitrogen in the σ-bond of the intermediate complex and the accompanying

[21] C. Bodea and I. Silberg, *Adv. Heterocyclic Chem.*, 1968, **9**, 321.
[22] See ref. 16, pp. 42—50.
[23] J-P. Malrieu and B. Pullman, *Theoret. Chim. Acta*, 1964, **2**, 293.
[24] (*a*) D. Feil, M. H. Linck, and J. J. H. McDowell, *Nature*, 1965, **207**, 285; (*b*) J. J. H. McDowell, *Acta Cryst.*, 1976, **B32**, 5.
[25] S. S. C. Chu and D. van der Helm, *Acta Cryst.*, 1974, **B30**, 2489.

necessary increase in the fold of the heterocycle will both serve to insulate the nitrogen atom from the π-systems of the heterocycle. Any electronic influence of the methyl groups upon the formation of the σ-complex will, therefore, be essentially inductive and will be comparably small from any position. It thus seems reasonable to infer that the variation in apparent free energies of activation with *C*-methylation does indeed reflect that in the actual free energies and their proportionality to a function of ionisation potential implies the corresponding transition states do resemble the radical products of the reaction. This being the case, the data points corresponding to substrates with 1- and 4(6)-methyl substituents, which lie displaced from the correlation lines of Figure 1, show that these substituents are not as effective in promoting reaction as they are in decreasing ionisation potential. Now there is no reason to suppose that substituents in the 1- or 4(6)-position might perturb the formation of π-complexes between phenothiazines and 1,3,5-trinitrobenzene in a way that renders the charge-transfer transition frequency invalid as a function of ionisation potential. Thus the displacements of the points from the correlation lines of Figure 1 are consistent with methyl substituents, particularly in the 1-position but also in the 4-position, impeding the oxidation reaction sterically.

The correlations of Figure 2 support these conclusions in most respects. If radical character is well developed in the transition states, as inferred above, the transition state energies would be expected to respond to methyl substituents in a manner which reflects the ability of the methyl group to interact with the highest occupied molecular orbital (HOMO) of the developing radical. Now the HOMO of a π-radical is that which contains the unpaired electron; the proportionalities in Figure 2 of the reactivity function, log k/k_0, with the coefficients of the HOMO of phenothiazine cation-radical confirm this expectation, therefore, provided the phenothiazine cation-radical itself is an adequate model for the actual radicals produced in the oxidation reaction. This is reasonable: our earlier work has shown that methyl groups in the 2- and 3-positions, at least, perturb but little the distribution of spin and charge in the phenothiazine cation-radical.[2a] We were initially surprised to find correlations involving the Hückel coefficients themselves, and not their squares, with an energy function. There is precedent, however, in the work of Bralsford, Harris, and Price,[26] elaborated by Streitwieser,[27] and theoretical justification in the work of Dewar.[28]

The finding of essentially the same slopes for lines (b) and (c) in Figure 2 implies that the capacity of the 1-methyl group to interact electronically with the HOMO of the developing radicals is not in any sense diminished. The vertical displacement of line (c) from line (b) is thus confirmation that the substituent effect of a 1-methyl group must involve an impediment, presumably steric, as well as electronic promotion of the reaction. It is interesting that Figure 2 implies no hindering role for a 4-methyl group, unlike Figure 1. Since the slopes q of the correlations of Figure 2 represent the π-electronic effects of the methyl substituents, it is tempting to interpret the positive intercept of lines (a) and (b) in terms of the inductive influence of methylation upon reaction rate. In support of this is the observation that the ratio q/p for line (a) (*i.e.* 2.34) approaches the ratio σ_R/σ_I (*i.e.* $-0.11/-0.04 = 2.75$) for the methyl group for three of Taft's ranks of σ_R.[29]

The failure of 1,10-dimethylphenothiazine to react represents the combination of both deactivating substitutions. It is likely that the effects are not merely additive, however. That 1- and 10-methyl groups interact sterically in the parent heterocycle is shown by ^{13}C n.m.r. spectroscopy;[30] thus this phenothiazine is probably more highly folded than others substituted at nitrogen. The attendant reduction in its π-electron donor-capacity is evident in Table 3. From the foregoing discussion it is clear that a similar increased fold in the radical would raise the activation energy for the reaction and this presumably occurs to the point of preventing it.

The Rate-determining Transition States.—In the rate-determining transition states, as the azo-radical departs, the fold-angle of the heterocycle will widen markedly from the high degree of fold in the σ-complex, imposed by tetrahedral nitrogen, to the values which characterise the cation-radicals, which have trigonal nitrogen and which are more nearly planar than their parent heterocycles.[1] Simultaneously, charge is redistributed from being localised on nitrogen in the σ-complex to being delocalised, almost equally between nitrogen and sulphur, in the cation-radicals.[2a,10] The charged atom is rather inaccessible to solvent in the σ-complex, especially in 10-methylated substrates which are unable to hydrogen-bond, but both charged atoms are more accessible in the cation-radicals. An increase in solvation of the phenothiazine moiety is likely, therefore, on passage to a transition state which resembles the appropriate cation-radical. We suggest that 1- and 4-methyl groups exert their hindering effect on the reaction by impeding this solvation process. The larger hindering effect of the 1-methyl group relative to the 4-methyl group probably reflects the greater spatial requirements of the groups appended at nitrogen, by comparison with the lone pairs on sulphur.

The apparent activation parameters are in harmony with this suggestion. By and large, substrates with hindering groups, particularly the 1-methyl group, are associated with large apparent enthalpies of activation: for substrates with no nitrogen substituent, the mean enthalpy found is 66 kJ mol^{-1}; all substrates with a 1-substituent show apparent enthalpies greater than or

[26] R. Bralsford, P. V. Harris, and W. C. Price, *Proc. Roy. Soc.*, 1960, **A258**, 459.
[27] A. Streitwieser, *Progr. Phys. Org. Chem.*, 1963, **1**, 1.
[28] M. J. S. Dewar, *J. Amer. Chem. Soc.*, 1951, **74**, 3341, 3345, 3350, 3353.
[29] S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, 1973, **10**, 1.
[30] P. Hanson, unpublished work.

equal to this value. For both phenothiazine and 10-methylphenothiazine, introduction of a 4-methyl substituent increases the apparent enthalpy. Additional non-hindering substituents tend to mask the influence on enthalpy of a 4-methyl group, however. It is more difficult to discern consistent trends in the entropies of activation, no doubt partly on account of the errors in them.[31] Nevertheless, a tendency for more positive apparent entropies of activation to be associated with hindering substituents is present. The mean apparent entropy is -22 J mol^{-1} K^{-1}; eight out of eleven substrates with hindering 1- and 4-methyl groups show entropies more positive than this whilst only three out of twelve substrates without hindering groups do so. The association of higher apparent enthalpies with more positive apparent entropies is consistent with less electrostriction of the solvent by the hindered substrates on passage to the transition state, by comparison with unhindered substrates.

EXPERIMENTAL

Materials.—Phenothiazine itself was a commercially available material (Cambrian). Other phenothiazines were synthesised by established routes;[2a] all but seven were known materials. The new phenothiazines were characterised by analysis and by spectroscopic methods; all the phenothiazines were characterised by their ^{13}C n.m.r. spectra. Details of synthesis and characterisation will be presented, more appropriately, elsewhere.

Diazonium fluoroborates, prepared by a well established method,[32] were washed with ethanol and diethyl ether after precipitation, air dried, and stored under refrigeration until required.

Acetonitrile was purified by distillation from P_4O_{10} followed by fractionation.

Charge-transfer Transitions.—Wavelengths of maximum visible absorbance were determined for solutions in tetrachloromethane of the phenothiazines with 1,3,5-trinitrobenzene. Concentrations were arbitrary but with the phenothiazines in excess.[8] Wavelengths were measured to ± 2 nm using a Unicam SP 8000 spectrophotometer.

Kinetics.—Solutions of phenothiazines were made up in acetonitrile at concentrations of 2×10^{-4} mol dm^{-3} and solutions of diazonium fluoroborates (2×10^{-3} mol dm^{-3}) were made up in acetonitrile containing aqueous fluoroboric acid such that the water content was 1.5—2% v/v and the concentration of fluoroboric acid variable according to circumstances.

For kinetic measurements, the above solutions were thermally equilibrated at the temperature of interest and then 1 cm^3 of the phenothiazine solution was mixed with 2 cm^2 of the diazonium fluoroborate solution. The cell concentrations upon which the principal absorbance measurements were made were thus typically: phenothiazine, 6.7×10^{-5} mol dm^{-3}; diazonium fluoroborate, 1.3×10^{-3} mol dm^{-3}; [HBF_4], 6.7×10^{-2} mol dm^{-3}; [H_2O], *ca.* 6.7×10^{-1} mol dm^{-3}. The temperatures at which the kinetics were measured were held to ± 0.2 °C using a Grant Instruments type LB50 thermostatted bath to provide circulation to the cell block of the SP 8000 spectrophotometer. The wavelengths of measurement were in the region 500—550 nm where each of the radicals produced exhibits a maximum of absorbance. Kinetic measurements were made in duplicate; the two apparent second-order rate constants normally agreed within 2.5% when solutions were used in common. The variation was somewhat greater if different solutions were used to determine the same constant. The estimated error in the second-order rate constants is taken as 5% leading to estimated errors [31] of ± 2 kJ mol^{-1} in $\Delta H^{\ddagger}$ measurements and ± 8 J mol^{-1} K^{-1} in $\Delta S^{\ddagger}$.

We thank the York College of Arts and Technology for leave of absence which enabled J. M. B. to participate in this work.

[8/217 *Received*, 9*th February*, 1978]

[31] R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Amer. Chem. Soc.*, 1961, **83**, 3819.

[32] A. Roe, *Organic Reactions*, 1949, **5**, 205, method IIB.