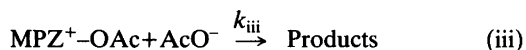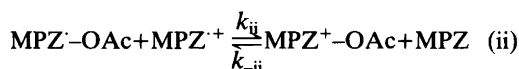# The Kinetics and Mechanisms of the Reactions of Cation Radicals of Phenothiazine Derivatives with Acetate Ion and Water in Acetonitrile

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The kinetics of the reaction of the cation radical of N-methylphenothiazine (MPZ) with acetate ion in aqueous acetonitrile were observed to be consistent with mechanism (i)−(iii) and rate law (iv).

$$MPZ^{\cdot+}+AcO^- \overset{K_i}{\rightleftharpoons} MPZ^{\cdot}-OAc \qquad (i)$$

$$MPZ^{\cdot}-OAc+MPZ^{\cdot+} \underset{k_{-ii}}{\overset{k_{ii}}{\rightleftharpoons}} MPZ^+-OAc+MPZ \quad (ii)$$

$$MPZ^+-OAc+AcO^- \overset{k_{iii}}{\longrightarrow} Products \qquad (iii)$$

$$Rate=2k_{iii}K_iK_{ii}[MPZ^{\cdot+}]^2[AcO^-]^2/([MPZ]+k_{iii}/k_{-ii}[AcO^-]) \qquad (iv)$$

The reaction orders in $MPZ^{\cdot+}$, MPZ, and AcO^- were observed to be 2, −0.5 and 1.5, respectively, at $[H_2O]$ equal to 2.78 M. The reaction was observed to be inhibited by both acetic acid and water due to the deactivation of acetate ion by hydrogen bonding. No deuterium kinetic isotope effect was observed when reactions were carried out in the presence of D_2O. Under comparable conditions the reactivity of chlorpromazine cation radical was observed to be about 10^2 times than for $MPZ^{\cdot+}$.

The phenothiazine cation radicals are among the most stable ion radicals known. The ease with which these cation radicals can be studied, as compared to more reactive ones, has led to numerous studies of their properties and reactions.[1-19] We have recently [1] commented on the mechanism of the reactions of chlorpromazine (1) cation radical in aqueous buffers. The


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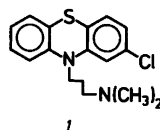
reaction had previously been examined by McCreery and coworkers [2,3,5] and the product was observed to be the oxide (2). The sulfurane

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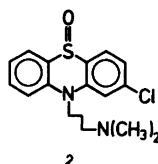
(3) was proposed to be a primary intermediate in citrate and phosphate buffers and the mechanism for the reaction was formulated as (1)−(3). We
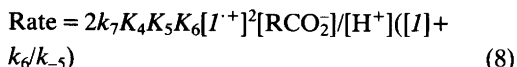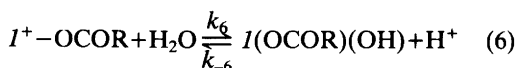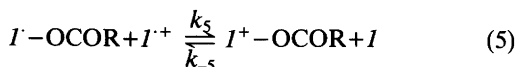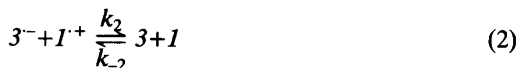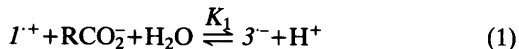

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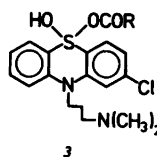
were not able to visualize a reasonable structure for 3^{-} and concluded that the proposed mechanism was not meaningful. Another feature of the mechanism which is unacceptable is the assumption that the homogeneous electron transfer reaction (2) can be treated as an equilibrium with a backward rate constant k_{-2} of a magnitude comparable to k_3, the rate constant for the rate determining step (3). Under the experimental conditions E_o for the redox couple $1/1^{\cdot+}$ was observed to be close to $+0.6$ V vs. SCE. Values of E_o for reduction of sulfuranes like 3 are not available, but may be estimated to be close to the peak potential, -1.9 vs. SCE, reported [20] for the related structure 4. From these values an


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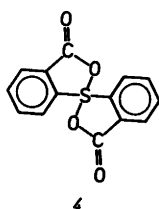
approximate value for K_2 of 10^{42} can be calculated. The analysis presented earlier in connection with the possible disproportionation mechanism for the pyridination of 9,10-diphenyl-lanthracene cation radical [21] then predicts the maximum value of k_{-2} to be of the order of 10^{-32} $M^{-1}s^{-1}$ assuming the forward rate of (2) being diffusion controlled, i.e. $k_2 \approx 10^{10}$ $M^{-1}s^{-1}$. This value of k_{-2} is surely so small that the electron transfer reaction (2) has to be treated kinetically as an irreversible process and not as an equilibrium. Doing this results in a rate law inconsistent with the observed kinetics.

A reexamination of the kinetic data showed that mechanism (4)–(7) gives rise to rate law (8) which is consistent with that observed experimentally. This mechanism, which is similar to that proposed [5] for the reaction in acetate buffer, shows that the kinetics in citrate and phosphate buffers do not require the postulation of any unlikely anion radical intermediate like 3^{-}.

$$1^{\cdot+}+RCO_2^-+H_2O \overset{K_1}{\rightleftharpoons} 3^-+H^+ \qquad (1)$$

$$3^-+1^{\cdot+} \overset{k_2}{\underset{k_{-2}}{\rightleftharpoons}} 3+1 \qquad (2)$$

$$3 \overset{k_3}{\rightarrow} 2+RCO_2H \qquad (3)$$

$$1^{\cdot+}+RCO_2^- \overset{K_4}{\rightleftharpoons} 1^{\cdot}-OCOR \qquad (4)$$

$$1^{\cdot}-OCOR+1^{\cdot+} \overset{k_5}{\underset{k_{-5}}{\rightleftharpoons}} 1^+-OCOR+1 \qquad (5)$$

$$1^+-OCOR+H_2O \overset{k_6}{\underset{k_{-6}}{\rightleftharpoons}} 1(OCOR)(OH)+H^+ \qquad (6)$$

$$1(OCOR)(OH) \overset{k_7}{\rightarrow} 2+RCO_2H \qquad (7)$$

$$Rate = 2k_7K_4K_5K_6[1^{\cdot+}]^2[RCO_2^-]/[H^+]([1]+ k_6/k_{-5}) \qquad (8)$$

Mechanism (4)–(7) suggested another possibility. If the reactions were conducted in solvents

$1^{\cdot}-OCOR$
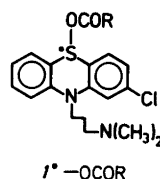
where the nucleophilic activity of RCO_2^- is greater or with more nucleophilic carboxylate ions reactions between 1^+-OCOR and RCO_2^- as

1^+-OCOR
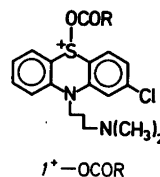
illustrated by (9) and (10) might become significant.

$$1^+-OCOR+RCO_2^- \overset{k_9}{\underset{k_{-9}}{\rightleftharpoons}} 1(OCOR)_2 \qquad (9)$$

$$1^+-OCOR+RCO_2^- \overset{k_{10}}{\rightarrow} 2+(RCO)_2O \qquad (10)$$
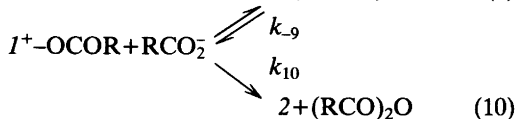
This would cause the reaction order in RCO_2^- to approach 2, which would provide convincing evidence for the mechanism.

A mechanism similar to (4)–(7) has recently been ruled out for the hydroxylation of thianthrene cation radical in the presence of trifluoroacetate ion.[22] Significant deuterium kinetic

isotope effects were observed when the kinetics were studied in acetonitrile containing H_2O or D_2O and the reaction was observed to be first order in both water and trifluoroacetate ion. Thus, the mechanism of the hydroxylation of thianthrene cation radical involves water as the nucleophile under the conditions studied, i.e. when no other good nucleophiles are present.

The kinetics of the decay of a number of phenothiazine derivative cation radicals were studied in aqueous acetic acid using ESR and visible absorption spectrophotometry.[6] The rate of cation radical decay was observed to be second order in ion radical and disproportionation mechanisms were proposed. A similar study was later carried out in H_2SO_4 on a large number of 10-alkylphenothiazine cation radicals and a disproportionation mechanism was also assumed.[7] In general, the products of the reaction of water with 10-alkylphenothiazine cation radicals are the S-oxides analogous to 2.[17-19]

No fewer than five disproportionation mechanisms were considered by Evans, Lenhard and Blount[9] in their discussion of the kinetics of the decomposition of 10-phenylphenothiazine cation radical in pyridine. They concluded, on the basis of an analysis used earlier to rule out disproportionation during the reaction of thianthrene cation radical with anisole,[23] that disproportiona-

tion is not involved. However, the analysis and the entire discussion by Evans, Lenhard and Blount[9] concerning the possibility of disproportionation during the decomposition of 10-phenylphenothiazine (5) cation radical is trivial. The equilibrium constant for reaction (11),

$$2\,5^{\cdot+} \xrightleftharpoons{K_{11}} 5^{2+} + 5 \tag{11}$$

was determined using cyclic voltammetry to be equal to 2.2×10^{-12} and apparent second order rate constants as great as 10^3 $M^{-1}s^{-1}$ were determined for the decomposition. The analysis already referred to[21] gives an immediate answer on the feasibility of disproportionation in this case. The assumption that back reaction (11) is diffusion controlled gives the maximum possible value of the rate constant for the forward reaction, k_{11}, to be of the order of 10^{-2} $M^{-1}s^{-1}$. This value is about 10^5 times lower than the observed apparent second order rate constants, a fact which eliminates the necessity to consider disproportionation mechanisms for the decomposition of $5^{\cdot+}$.

RESULTS

The most simple of the 10-alkylphenothiazines, 6, was chosen as a model substrate for the

Table 1. Reaction order analysis of the kinetics of the reactions of N-methylphenothiazine cation radical in acetonitrile.[a]

C_A^b/mM	C_{AcO^-}/mM	$_{1/2}$/V s^{-1}	$\nu_{1/2}/C_{AcO^-}^{1.5}$	$((\nu_{1/2}/C_{AcO^-}^{1.5})/C_A^{0.5}) \times 10^{-4}$
0.5	17.4	0.655	285	
0.5	38.1	2.56	344	
0.5	68.8	6.56	364	
			331±41	1.48
1.0	17.4	0.950	414	
1.0	38.1	3.46	465	
1.0	68.8	7.71	427	
			435±27	1.38
2.0	17.4	1.38	601	
2.0	38.1	4.91	660	
2.0	68.8	11.2	621	
			627±30	1.40
				1.42±0.05

[a] Measurements at 19.5 °C. C_{H_2O}=2.78 M. [b] Substrate concentration.

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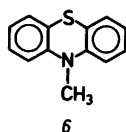
hydroxylation of phenothiazine derivative cation radicals. The much lower reactivity of $6^{.+}$ as compared to thianthrene cation radical forced us to a much more nucleophilic buffer system than $CF_3CO_2^-LH^+$ (L=2,6-lutidine) which was used in the latter study.[22] Acetate buffers prepared from Bu_4NOAc and AcOH in aqueous acetonitrile provided a sufficiently reactive medium to study the hydroxylation reaction.

Since the derivative cyclic voltammetry kinetic method [24,25] was described in a recent paper [22] discussion of the kinetic procedures is not necessary here.

The data in Table 1 were measured in order to obtain reaction orders in cation radical, substrate and acetate ion. At each substrate concentration, $v_{1/2}$ was obtained over a fourfold range of [AcO⁻]. Data were obtained at substrate concentrations of 0.50, 1.00 and 2.00 mM. The next to last column in Table 1 gives the values of $v_{1/2}/C_{AcO^-}^{1.5}$. The fact that these values are very nearly constant at all substrate concentrations indicates that the reaction order in acetate ion is very close to 1.5 under the conditions of the measurements. The average values of $v_{1/2}/C_{AcO^-}^{1.5}$ were then used to determine the reaction orders in substrate and cation radical, $R_{A/B}$. The last column in Table 1 shows that $(v_{1/2}/C_{AcO^-}^{1.5})/C_A^z$ is

very nearly constant when z is equal to 0.5. It follows that $R_{A/B}$ is very close to 1.5.

The data in Table 2 show that the decomposition of $6^{.+}$ in aqueous acetonitrile acetate buffer is inhibited by acetic acid. However, in both series of experiments, $v_{1/2}$ decreased by only about 25 % as the concentration of added AcOH was changed from 0 to 21.9 mM. The concentration of AcOH in the aqueous acetonitrile solution of AcO⁻ before addition of the acid was estimated to be less than 10^{-2} mM assuming that the pK_a was the same as in water. This estimation is a maximum value and indicates that [AcOH] is negligibly small before the addition of AcOH.

The data in Tables 3 and 4 indicate an absence of a deuterium kinetic isotope effect in the presence of D_2O when the water concentration was varied in the range of 0.69 to 2.78 M with [AcO⁻] ranging from 15.8 to 63.2 mM.

Table 3. Search for a deuterium kinetic isotope effect during decomposition of N-methylphenothiazine cation radical in acetonitrile.[a]

C_{AcO^-}/mM	Y[b]	$v_{1/2}$/V s⁻¹	k_H/k_D
15.8	H_2O	2.02	1.06
15.8	D_2O	1.91	
31.6	H_2O	4.76	1.03
31.6	D_2O	4.61	
63.2	H_2O	11.7	1.03
63.2	D_2O	11.4	

[a] Measurements at 19.5 °C. C_A=2.0 mM. [b] Y=H_2O or D_2O, C_Y=2.78 M.

Table 2. The effect of acetic acid on the rate of decomposition of N-methylphenothiazine cation radical in acetonitrile.[a]

C_{AcOH}/mM	C_{AcO^-}/mM	$v_{1/2}$/V s⁻¹
0	38.1	4.91
21.9	38.1	3.39
43.8	38.1	2.98
87.6	38.1	1.45
0	63.2	11.0
21.9	63.2	8.22
43.8	63.2	6.54
87.6	63.2	4.08
175.2	63.2	1.82

[a] Measurements at 19.5 °C. C_A=2.0 mM, C_{H_2O}=2.78 M.

Table 4. The effect of H_2O and D_2O concentration on the apparent rate of decomposition of N-methylphenothiazine cation radical in acetonitrile.[a]

Y[b]	C_y/M	$v_{1/2}$/V s⁻¹	k_H/k_D
H_2O	0.69	66.4	0.97
D_2O	0.69	68.5	
H_2O	1.39	24.6	1.13
D_2O	1.39	21.8	
H_2O	2.78	3.60	0.99
D_2O	2.78	3.62	

[a] Measurements at 19.5 °C. C_A=2.0 mM, C_{AcO^-}=33.2 mM. [b] Y=H_2O or D_2O.

Table 5. Kinetic data for the reactions of chlorpromazine cation radical in acetonitrile.[a]

C_A^b/mM	C_{H_2O}/M	C_{AcOH}/mM	$v_{1/2}$/V s^{-1}
0.5	1.39	0	225
0.5	2.78	0	62.9
1.0	2.78	0	77.0
2.0	2.78	0	74.0
2.0	2.78	4.38	67.4
2.0	2.78	8.75	60.0
2.0	2.78	17.5	47.1
2.0	2.78	35.0	35.0
2.0	2.78	52.5	20.6
2.0	2.78	70.0	15.0
2.0	2.78	105	9.38

[a] Measurements at 19.5 °C. C_{AcO^-}=8.29 mM.
[b] Substrate concentration.

Table 6. The effect of water concentration on the nucleophilic activity of acetate ion in acetonitrile.[a]

C_{H_2O}/mM	$v_{1/2}$/V s^{-1}
0	171.7
69.4	128.0
139	95.9
278	64.4
556	24.9
1112	4.48
2224	0.820

[a] Data for the decomposition of *N*-methylphenothiazine cation radical in solution containing Bu$_4$NOAc (8.8 mM) and substrate (1.90 mM) at 19.5 °C.

A less extensive set of experiments was also carried out with *1* as substrate under the same conditions. The decomposition of *1*$^{\cdot +}$ was observed to be significantly more rapid which required that [AcO$^-$] be limited to lower values. The data in Table 5 were obtained in solutions 8.3 mM in AcO$^-$. At a water concentration of 2.78 M in the absence of added AcOH, $v_{1/2}$ was observed to be very nearly independent of C_A which indicates that $R_{A/B}$ is very close to 1 under the reaction conditions. The reaction was observed to be inhibited by AcOH in a similar manner to that of *6*$^{\cdot +}$.

The rate of the decomposition of *6*$^{\cdot +}$ in acetonitrile in the presence of AcO$^-$ was observed to be strongly dependent on the concentration of water. The data in Table 6 show the effect of increasing [H$_2$O] successively by factors of 2.
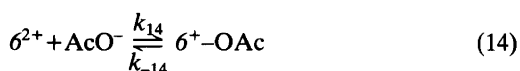
DISCUSSION

The observation of $R_{A/B}$ equal to 1.5 (Table 1) suggests that the reaction order in cation radical is 2 and that in substrate is –0.5 during the decomposition of *6*$^{\cdot +}$ in aqueous acetonitrile solutions of acetate ion. The observation of a reaction order of 2 in cation radical makes it necessary to consider the possibility of a disproportionation mechanism.[6–9,23,26–32] When possible, the measurement of the reversible electrode potential for the oxidation of the cation radical to the dication [33] provides a reliable estimate of K_{disp}, the equilibrium constant for the disproportionation. It was not possible to measure the reversible oxidation potential of *6*$^{\cdot +}$ (or for *1*$^{\cdot +}$) under the conditions used in this study due to the rapid reaction of the cation radicals with acetate ion. When K_{disp} is available, the analysis [21] mentioned in the introduction can be used in the evaluation of the feasibility of disproportionation. However, when K_{disp} is not available as in the present study, it is necessary to rely on the form of the rate law. An effective kinetic analysis to distinguish disproportionation from other mechanisms was presented for the anisylation of thianthrene cation radical.[23] The analysis involves measuring second order rate constants (k_{obs}) for the decomposition of the cation radical in the presence of excess substrate (S). After obtaining several k_{obs} values over a range of [S], a plot of $1/k_{obs}$ will often give a staight line obeying eqn. (12).[23]

$$1/k_{obs} = A[S] + B \qquad (12)$$

This analysis is commonly used for complex reaction schemes where steady state kinetics are assumed.[34] The intercept B can either be a constant independent of the concentration of other reactants, relatable to rate constants, or variable depending on another reactant. In the case of the anisylation of thianthrene cation radical B was observed to be dependent on the anisole concentration and provided a means of eliminating the disproportionation mechanism. This same analysis was later used by McCreery

and coworkers [2] in the analysis of the kinetics of the decomposition of $1^{\cdot+}$ and extensively by Evans, Lenhard and Blount [9] in related reactions.

The observation of a reaction order close to 1.5 for acetate ion provides us with still another tool to analyze for a possible disproportionation mechanism for the decomposition of $6^{\cdot+}$ under the conditions of this study. Disproportionation (13) could be followed by reaction of 6^{2+} with acetate ion to give 6^+-OAc which could then react with a second acetate ion to give products.

$$2\ 6^{\cdot+} \underset{k_{-13}}{\overset{k_{13}}{\rightleftharpoons}} 6^{2+}+6 \qquad (13)$$

$$6^{2+}+AcO^- \underset{k_{-14}}{\overset{k_{14}}{\rightleftharpoons}} 6^+\text{-OAc} \qquad (14)$$

$$6^+\text{-OAc}+AcO^- \overset{k_{15}}{\longrightarrow} \text{Products} \qquad (15)$$

In general, dications are at the minimum 10^6 times as reactive towards nucleophiles as cation radicals are.[35] This implies that k_{14} is very large and subsequently (13) cannot be considered as a fast equilibrium prior to (14), but has to be represented by the individual rate constants in the kinetic analysis. Application of the steady state approximation for both 6^{2+} and 6^+-OAc leads to rate law (16)
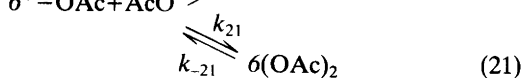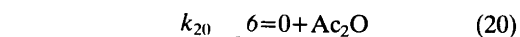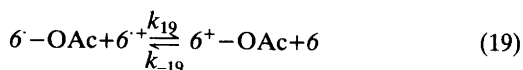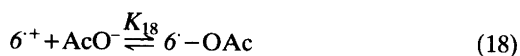
$$\text{Rate}=\frac{2\ k_{15}K_{13}K_{14}[6^{\cdot+}]^2[AcO^-]^2}{[6]+\dfrac{k_{15}}{k_{-14}}[6][AcO^-]+\dfrac{k_{15}K_{14}}{k_{-13}}[AcO^-]^2} \qquad (16)$$

for the disproportionation mechanism. Since the dissociation of 6^+-OAc is expected to be very slow compared to further reaction with acetate ion *i.e.* $k_{-14} \ll k_{15}[AcO^-]$, rate law (16) reduces to (17),

$$\text{Rate}=\frac{2\ k_{15}K_{13}K_{14}[6^{\cdot+}]^2[AcO^-]}{\dfrac{k_{15}}{k_{-14}}\left([6]+\dfrac{k_{14}}{k_{-13}}[AcO^-]\right)} \qquad (17)$$

which predicts a reaction order less than or equal to 1 in acetate ion which is inconsistent with the data. If the assumption is made that K_{13} is the same in the presence of acetate as in acetonitrile with nucleophiles excluded, the disproportionation mechanism is ruled out without resort to eqn. (17).
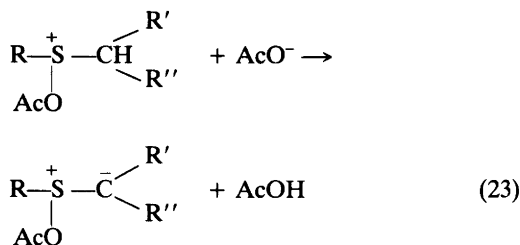
The most likely mechanism, one which takes into account all of the experimental data, involves reactions (18)−(20) and gives rise to rate law (22).

$$6^{\cdot+}+AcO^- \overset{K_{18}}{\rightleftharpoons} 6^\cdot\text{-OAc} \qquad (18)$$

$$6^\cdot\text{-OAc}+6^{\cdot+} \underset{k_{-19}}{\overset{k_{19}}{\rightleftharpoons}} 6^+\text{-OAc}+6 \qquad (19)$$

$$6^+\text{-OAc}+AcO^- \overset{k_{20}}{\underset{\substack{k_{21}\\k_{-21}}}{\nearrow\searrow}} \begin{array}{l} 6{=}0+Ac_2O \qquad (20) \\[6pt] 6(OAc)_2 \qquad (21) \end{array}$$

$$\text{Rate}=\frac{2\ k_{20}K_{18}K_{19}[6^{\cdot+}]^2[AcO^-]^2}{[6]+\dfrac{k_{20}}{k_{-19}}[AcO^-]} \qquad (22)$$

The acetic anhydride formed in eqn. (20) suffers hydrolysis in a subsequent slow step which does not influence the kinetics.

A key intermediate in the mechanism is the acetoxysulfonium ion, 6^+-OAc. Acetoxysulfonium ions are also believed to play an important role in the Pummerer reaction [36-38] in which a sulfoxide containing an α-hydrogen atom is converted to the corresponding α-acetoxysulfide by treatment with acetic anhydride. The first step of the Pummerer reaction is usually formulated as the reverse of reaction (20), but the step is very slow at room temperature compared to forward (20) which under the conditions of the present study can be treated kinetically as an irreversible step. The second step of the Pummerer reaction involves base attack by acetate ion at the α-position of the acetoxysulfonium ion resulting in the formation of an acetoxysulfonium ylide [eqn. (23)].

$$\underset{AcO}{\overset{+}{R{-}S}}{-}\overset{R'}{\underset{R''}{CH}} + AcO^- \rightarrow$$

$$\underset{AcO}{\overset{+}{R{-}S}}{-}\overset{R'}{\underset{R''}{C}} + AcOH \qquad (23)$$

However, this pathway is not possible for 6^+-OAc due to the lack of α-hydrogen atoms.

Thus, except for dissociation (back reaction (19)), 6^+–OAc is restricted to suffer nucleophilic attack by acetate (reactions (20) and (21)) or eventually water.

In discussions of the mechanism of the Pummerer reaction [36,37] the possible involvement of sulfuranes as intermediates has been considered. Sulfuranes, which contain a tetracovalent sulfur atom, have been isolated in special cases [39–42] and sulfurane-type intermediates have been proposed in racemization and oxygen exchange reactions of optically active sulfonium ions.[36,43] In the preliminary report on this work [1] a sulfurane, $6(OAc)_2$, was proposed as the primary product which could then undergo transformation to $6=0$ (reaction (24)).

$$6(OAc)_2 \xrightarrow{k_{24}} 6=0+Ac_2O \qquad (24)$$
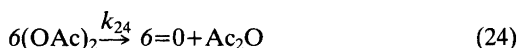
The inclusion of $6(OAc)_2$ in the reaction scheme gives rise to rate law (25) (reaction (21) slow and irreversible) or rate law (26) (reaction (21) reversible, reaction (24) slow and irreversible), which both are of the same form as eqn. (22) and therefore kinetically indistinguishable.

$$\text{Rate}=\frac{2\,k_{21}K_{18}K_{19}[6^{\cdot+}]^2[AcO^-]^2}{[6]+\dfrac{k_{21}}{k_{-19}}\,[AcO^-]} \qquad (25)$$

$$\text{Rate}=\frac{2\,k_{21}K_{18}K_{19}[6^{\cdot+}]^2[AcO^-]^2}{\left(1+\dfrac{k_{-21}}{k_{24}}\right)[6]+\dfrac{k_{21}}{k_{-19}}\,[AcO^-]} \qquad (26)$$

It should be pointed out that rate law (25) does not require that $6(OAc)_2$ is long lived, but in lack of further evidence in support of the participation of $6(OAc)_2$ we prefer the simpler scheme which only includes reaction (20).

Nucleophilic attack by acetate ion on an acetoxysulfonium ion intermediate (eqn. (20)) is in agreement with the observation that anodic oxidation of thianthrene in non-aqueous Ac_2O–AcOH–NaOAc gives the S-oxide exclusively.[44] Similarly, when p-bromothioanisole was subjected to anodic oxidation under the same conditions, a 2:3 mixture of the S-oxide and α-acetoxy-p-bromothioanisole was obtained.[44]

The cation radical, $1^{\cdot+}$, of chlorpromazine was found to react at a significantly higher rate than did $6^{\cdot+}$. Extrapolation of $v_{1/2}$ for $6^{\cdot+}$ to $[AcO^-]$ $=8.3\times10^{-3}$ (Table 1) gives an approximate value

of 0.2 V s^{-1} which by comparison with the value observed for $1^{\cdot+}$, 62.9 V s^{-1} (Table 5), demonstrates that the latter cation radical is 300 times more reactive under the same conditions. This rate enhancement is most likely due to the presence of the 2-chloro substituent in $1^{\cdot+}$ rather than the difference in the N-alkyl groups since both compounds show only small sensitivity to the presence of acetic acid in the solvent. If the increased reactivity of $1^{\cdot+}$ compared to $6^{\cdot+}$ was due to the difference in structure of the N-alkyl groups, $1^{\cdot+}$ would be expected to be much more sensitive to the acidity of the solvent because of the terminal N,N-dimethylamino group.

Most of the kinetic runs were conducted at a rather high concentration of water, a typical value being 2.78 M. In Table 4 are reported the results of experiments carried out to test for a possible deuterium kinetic isotope effect.[45] Although no such effect could be detected, pointing to the absence of proton transfer reactions before or during the rate determining step, the over-all reaction rate was in fact found to depend significantly on the concentration of water. The value of $v_{1/2}$ increased by a factor of almost 20 when the water concentration was diminished from 2.78 M to 0.69 M. The effect is demonstrated even more dramatically by the data in Table 6 where the concentration of added water was varied between 0 and 2.22 M resulting in a decrease in $v_{1/2}$ from 171.1 to 0.820 V s^{-1} which corresponds to a reduction of the rate by a factor of 200. A similar effect was observed when acetic acid was added to the solvent system. Although this effect cannot be rationalized quantitatively, a qualitative explanation can be found in the influence of water and/or acetic acid on the reactivity of acetate ion in acetonitrile. Numerous studies have been devoted to the question of the interactions between ions and protic or aprotic dipolar solvents.[46–51] The general conclusion drawn from the studies relevant to the present work is that acetate ion in acetonitrile–water mixtures is strongly associated to water, most likely through hydrogen bonding (eqn. (27)),

$$(CH_3CO_2^-\cdot H_2O)_{solv} \overset{K_{27}}{\rightleftharpoons} (CH_3CO_2^-)_{solv}+(H_2O)_{solv} \qquad (27)$$
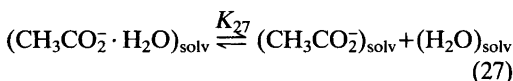
because of which the observed nucleophilicity is significantly diminished compared to that of

acetate ion in "water-free" acetonitrile. Acetate has been found to be one of the most powerful nucleophiles in acetonitrile being 30 times as reactive as thiocyanate,[48] whereas acetate is generally considered to be a poor nucleophile in protic solvents. The effect of increasing water concentration on equilibria like (27) is not straight-forward to predict,[49] but the data in Tables 4 and 6 are in agreement with the effect intuitively expected at low water concentrations that increasing values of C_{H_2O} will cause the equilibrium to be displaced more and more effectively to the left. It should be mentioned at this point that the inclusion of water in acetonitrile to the extent of 2.78 M does not change the macroscopic properties of the solvent significantly as reflected in the dielectric constant and the viscosity.[52] Thus, the rate reduction observed in aqueous acetonitrile can be satisfactorily explained by deactivation of acetate by water.

At increasing water concentrations the direct reaction of 6^+–OAc with water [eqn. (28)] might be expected to be of importance.

$$6^+\text{–OAc}+H_2O \xrightarrow{k_{28}} 6=0+\text{AcOH}+H^+ \qquad (28)$$
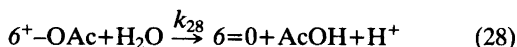
However, the fact that the reaction order in acetate ion even at $C_{H_2O}=2.78$ M is close to 1.5 demonstrates that reaction (28) is not the major pathway under our experimental conditions. A small contribution from (28) cannot be excluded, but the over-all retardation caused by the presence of water precludes the possibility to detect it kinetically.

EXPERIMENTAL

The instrumentation, electrodes, cells, data handling procedure and solvent and supporting electrolyte purification have recently been described.[53] N-methylphenothiazine was prepared by a standard procedure.[54] Chlorpromazine was kindly provided by Dr. J. Jaroszewski. Tetrabutylammonium acetate was FLUKA (*pract.*) and used as received.

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