Kinetics and mechanism of oxidation of N-substituted phenothiazines by chromium(VI)

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Abstract. The kinetics of oxidation of N-acetylphenothiazine (NAPT) by Cr(VI) in 80% acetic acid–20% water (v/v) mixture is first-order each in [NAPT] and [Cr(VI)]. The reaction is catalysed by added acid with a third-order dependence in [$HClO_4$]. Increase in polarity of the solvent medium decreases the rate. The oxidation is insensitive to variations in ionic strength as well as added acrylamide. Oxidations of phenothiazine (PT) and N-methylphenothiazine (NMPT) under similar conditions are found to be very fast. However kinetic investigations with NMPT in an acetic acid–sodium acetate buffer show first-order dependence each in [NMPT] and [Cr(VI)] and a fractional-order dependence in [H^+] in the pH range 1·80–3·09. Increase in polarity of the medium increases the rate. In both the cases, the corresponding sulphoxides are identified as oxidation products. Based on the kinetic results, mechanisms for oxidations are proposed.

Keywords. Chromium(VI); N-acetylphenothiazine; N-methylphenothiazine; oxidation; kinetics and mechanism.

1. Introduction

Phenothiazine derivatives have wide industrial applications as dyes (Bodea and Silberg 1968), antioxidants, pharmaceutical preparations (chloropromazine is a well-known phenothiazine-derived tranquilizer) and also in agriculture. Their potential value in solar energy convertors have also been demonstrated (Albery 1979). Many phenothiazine-containing drugs have side effects such as allergic skin reactions and occular opacity (Blois 1965) and it is presumed that the possible cause may be photooxidation. However, studies on the oxidations of phenothiazines are limited. A group of 9-substituted phenothiazine derivatives are oxidised by $Ce(SO_4)_2$ and $Pb(OAc)_4$ and all are found to undergo two-electron oxidation on the sulphur atom (Dymes and Zyka 1988). Sensitized photooxidation of NMPT in homogeneous and microheterogeneous media has also been reported (Oliveros et al 1987). Because of the possible role of oxidation of phenothiazines in biological systems and of the lack of detailed mechanistic studies on oxidation, the kinetics and mechanism of oxidation of NAPT and NMPT by Cr(VI) have been studied and the results are discussed in this paper.

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2. Experimental

2.1 *Materials and methods*

NAPT and NMPT were prepared according to reported procedures (Gilman and Nelson 1953) and purified by recrystallisation. Acetic acid (Orton and Bradfield 1927) and acetonitrile were purified by standard procedures. All other reagents used were of AnalaR grade. Rate studies for the oxidation of NAPT were carried out in 80% acetic acid–20% water (v/v) mixture under pseudo-first-order conditions with at least ten-fold excess of the substrate over oxidant concentration. The reaction was followed by monitoring the decrease in Cr(VI) concentration by a titrimetric procedure (Wiberg and Mill 1958). In acid and solvent variations, acetonitrile–water mixture was employed as the solvent. Kinetic studies with NMPT were carried out at constant pH maintained by acetic acid–sodium acetate buffer in a solvent mixture of 67% acetonitrile–33% water (v/v) mixture. The reactions were generally followed upto 60–70% completion. The pseudo-first-order constants were evaluated from the slopes of the linear plots of log $(a-x)$ versus time, by the method of least squares.

2.2 *Stoichiometry and product analysis*

Various mixtures containing known concentrations of NAPT or NMPT and Cr(VI) (the concentration of Cr(VI) being greater than that of substrate) were kept for 12 hours for completion of reaction. From the estimation of the unconsumed oxidant, the stoichiometric ratio of substrate to oxidant was found to be 3:2 in both NAPT and NMPT.

The solvent from the reaction mixture was removed under reduced pressure and extracted with ether. After the removal of ether, the residue was analysed by thin layer chromatography in a solvent mixture of 75% hexane and 25% chloroform and it gave spots corresponding to authentic samples of the sulphoxide of NAPT or NMPT and the substrate.

3. Results and discussion

3.1a *Rate studies with NAPT*

Rate measurements in 80% acetic acid – 20% water (v/v) mixture were carried out at various initial concentrations of NAPT and Cr (VI) at constant ionic strength and hydrogen ion concentration under pseudo-first-order conditions (table 1). Plots of log [Cr(VI)] versus time are linear showing first-order dependence in [Cr(VI)]. The double logarithmic plot of k_1 versus [NAPT] (slope $= 0.997 \pm 0.11, r = 0.998$) reveals that the oxidation is first-order in NAPT which is again confirmed by the constancy of second-order rate constants, k_2. A plot of k_1 versus [NAPT] ($r = 0.998$) passes through the origin indicating the absence of any substrate-independent path under the conditions employed. The slight decrease in rate at higher [Cr(VI)] may be due to the shifting of the equilibrium to the $Cr_2O_7{}^{2-}$ side (see equilibrium (7) below).

The rate of oxidation increases with increase in $HClO_4$ concentration (table 2). A plot of log k_2 against log $[HClO_4]$ (slope $= 3.11 \pm 0.51, r = 0.999$) reveals a third-order dependence in $[HClO_4]$ which is further confirmed by the linear plot of k_2 versus $[HClO_4]^3$ ($r = 0.998$) passing through the origin.

Table 1. Pseudo-first-order (k_1) and second-order (k_2) rate constants for the Cr(VI) oxidation of NAPT[a] and NMPT[b] at 303 K.

10^2[NAPT] (mol dm⁻³)	10^3[Cr(VI)] (mol dm⁻³)	$10^4 k_1$[c] (s⁻¹)	10^2[NMPT] (mol dm⁻³)	10^3[Cr(VI)] (mol dm⁻³)	$10^4 k_1$ (s⁻¹)
1·00	1·00	6·72 ± 0·29(6·72 ± 0·29)[d]	1·00	1·00	3·28 ± 0·15(3·28 ± 0·15)
1·50	1·00	9·66 ± 0·57(6·44 ± 0·38)	1·50	1·00	4·90 ± 0·26(3·26 ± 0·17)
2·00	1·00	13·3 ± 1·71(6·65 ± 0·86)	2·00	1·00	6·79 ± 0·49(3·39 ± 0·25)
2·50	1·00	17·2 ± 1·61(6·88 ± 0·64)	2·50	1·00	8·02 ± 0·23(3·21 ± 0·09)
3·00	1·00	19·8 ± 0·86(6·28 ± 0·29)	3·00	1·00	8·88 ± 0·37(3·10 ± 0·12)
4·00	1·00	25·7 ± 0·48(6·42 ± 0·12)	1·00	0·50	3·70 ± 0·41(3·70 ± 0·41)
1·50	0·50	10·3 ± 0·43(6·86 ± 0·29)	1·00	0·75	3·48 ± 0·17(3·48 ± 0·17)
1·50	0·75	10·1 ± 0·30(6·73 ± 0·20)	1·00	1·15	3·62 ± 0·19(3·62 ± 0·19)
1·50	1·50	9·35 ± 0·47(6·23 ± 0·31)			

[a][H^+] = 0·1 mol dm⁻³ in a solvent of 80% acetic acid–20% water (v/v) mixture at $I = 0·128$ mol dm⁻³. [b]pH 3·09 in a solvent system of 67% acetonitrile–33% water (v/v) mixture. [c]The error quoted in k values is the 95% confidence limit of Student's t-test. [d]Values in parentheses correspond to second-order rate constants.

The influence of solvent polarity on the rate of oxidation is studied in acetonitrile-water mixture. Perusal of table 2 indicates that the rate decreases as the polarity of the medium is increased. This may be attributed to the formation on an activated complex in which there is dispersal of charges over a larger area compared to the reactants. It is pertinent to mention here that this behaviour is in striking contrast to that observed in the oxidation of alkyl aryl sulphides and diaryl sulphides (Srinivasan *et al* 1985) in which the rate of oxidation is accelerated by an increase in water content of the medium. This has been explained by the formation of a charge-separated complex in the rate-determining step.

Variation in ionic strength of the medium has no effect on the rate of oxidation indicating that the reaction occurs between an ion and a neutral molecule in the rate-limiting step. Addition of acrylamide has no effect on rate ruling out a radical route. The activation parameters (table 2) computed from Eyring's plot ($r = 0·998$) indicate that the reaction is characterised by a low enthalpy but considerable negative entropy of activation. The magnitude of ΔH^{*} and ΔS^{*} correspond to those expected for a bimolecular nucleophilic reaction (Edwards 1962).

3.1b Mechanism and rate law

Cr(VI) can exist in different ionic forms (equations 1 to 5) depending on the hydrogen ion concentration of the medium in which the oxidation is carried out. The various ionic species and their equilibrium constants have been already reported (Wiberg 1965):

$$H_2CrO_4 \rightleftharpoons H^+ + HCrO_4^-, \tag{1}$$

$$HCrO_4^- \rightleftharpoons H^+ + CrO_4^{2-}, \tag{2}$$

$$2HCrO_4^- \rightleftharpoons Cr_2O_7^{2-} + H_2O, \tag{3}$$

$$HCr_2O_7^- \rightleftharpoons H^+ + Cr_2O_7^{2-}, \tag{4}$$

$$H_2Cr_2O_7 \rightleftharpoons H^+ + HCr_2O_7^-. \tag{5}$$

Table 2. Effects of varying $[H^+]$, solvent composition and temperature on oxidation of NAPT under pseudo-first-order conditions.

$10^1[H^+]$ (mol dm^{-3})	$10^2 k_2^a$ (dm^3 mol^{-1} s^{-1})	CH$_3$CN–H$_2$O %(v/v)	$10^2 k_2^b$ (dm^3 mol^{-1} s^{-1})	T (K)	$10^2 k_2^c$ (dm^3 mol^{-1} s^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$-\Delta S^{\neq}$ (J K^{-1} mol^{-1})
5·00	2·02 ± 0·16	40–60	0·84 ± 0·01	303	6·72 ± 0·29		
6·00	4·25 ± 0·27	50–50	1·30 ± 0·06	313	9·39 ± 0·47		
7·00	6·84 ± 0·32	65–35	2·64 ± 0·35	318	10·5 ± 0·10	20·9	134
8·00	8·99 ± 0·09	76–24	6·84 ± 0·82	323	13·7 ± 0·65		
9·00	14·0 ± 0·83						

[a] In 60% acetonitrile–40% water mixture (v/v) at 303 K; [b] $[H^+] = 0.5$ mol dm^{-3} at 303 K; [c] In 80% acetic acid–20% water (v/v) mixture with a $[H^+]$ of 0·1 mol dm^{-3}.

In aqueous solutions, at concentrations greater than $0.05 \, mol \, dm^{-3}$, the $Cr_2O_7^{2-}$ and its protonated form are the predominant species. But at lower concentrations and at $[H^+]$ between 0.001 to $0.003 \, mol \, dm^{-3}$, the monomer $HCrO_4^-$ predominates. This gets protonated at higher concentrations ($0.1 \, mol \, dm^{-3}$ and above) wherein the species $HCrO_3^+$ becomes dominant (Levitt 1955; Graham and Westheimer 1958; Venkateswara Rao and Jagannadham 1988):

$$HCrO_4^- + 2H^+ \rightleftharpoons HCrO_3^+ + H_2O. \tag{6}$$

Equilibrium (6) has been employed (Levitt 1955) to explain the oxidation of secondary alcohols by Cr(VI). The mechanism of oxidation of dimethyl sulphoxide (Venkateswara Rao and Jagannadham 1988) by Cr(VI) has been supported *inter alia* by the overall hydrolytic and protolytic equilibrium

$$Cr_2O_7^- + 4H^+ \rightleftharpoons 2HCrO_3^+ + H_2O. \tag{7}$$

Based on the above considerations, in the present investigation, the active oxidising species may be $HCrO_3^+$ as the concentration of H^+ falls in the range of 0.1 to $0.9 \, mol \, dm^{-3}$.

As a third-order dependence in $[H^+]$ is observed, an equilibrium, (8) below, involving the protonation of the substrate is suggested. The formation of a positively
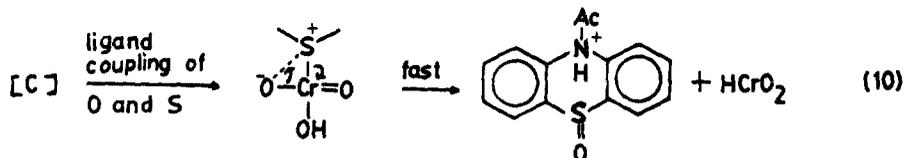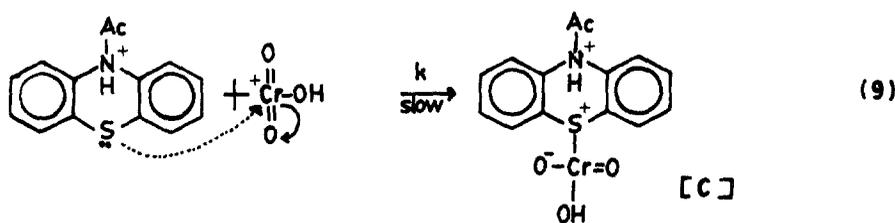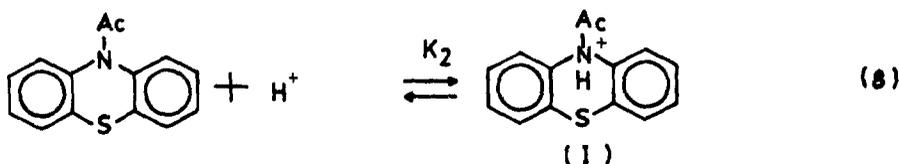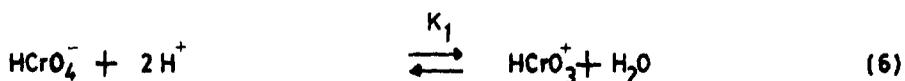
Scheme 1.

charged nitrogen through electron-donation in N-alkylphenothiazines has already been reported (Biehl *et al* 1975). The slow step involves the nucleophilic attack of the sulphide function of NAPT on $HCrO_3^+$ (scheme 1) with the electron-deficient nitrogen being away from the reaction centre. This leads to the formation of a complex 'C' which on subsequent ligand coupling of O and S, followed by decomposition, leads to the formation of sulphoxide and Cr(VI). Although such ligand coupling is not a familiar reaction, its occurrence was recently advocated (Oae *et al* 1984, 1987; Oae 1986) in the reaction of benzyl 2-pyridyl and related sulphoxides with Grignard reagents. In the pyridinium chlorochromate oxidation of aliphatic and diphenyl sulphides (Panigrahi and Mahapatro 1981) the formation of S–O species and also a S–Cr linkage formed by attack of the sulphur on chromium have been postulated.

Alternatively it is also probable (Srinivasan *et al* 1985, 1990) that attack of NAPT on Cr(VI) gives a sulphide cation radical in a slow-step followed by a subsequent faster one in which the radical cation readily attacks the Cr–O bond to yield the products. This is analogous to the mechanism proposed (Wiberg and Lepse 1964) in the diacetyl chromate oxidation of diphenyl sulphide where electron transfer from sulphur to chromium(VI) has been suggested from ^{18}O-labelling studies. The initial nucleophilic attack of sulphur on the oxygen of Cr(VI) may also the visualised (Srinivasan *et al* 1985, 1990). However, the observation that no visible polymerisation occurs with the added acrylamide does not favour stepwise one-electron transfers which may eventually lead to polymerisation through cation-radical formation. However, this observation cannot be taken as evidence for the absence of free radicals. At higher acidities, it is not possible to detect these radicals owing to the fact that their own oxidation is catalysed by acid (Hasan and Rocek 1972). A similar rationale has been suggested for a mechanism (Venkateswara Rao and Jagannadham 1988) involving $HCrO_3^+$ in the oxidation of dimethyl sulphoxide by Cr(VI).

The rate-law below is in conformity with the proposed mechanism and kinetic results.

$$\frac{d[Cr(VI)]}{dt} = k_2[NAPT][Cr(VI)][H^+]^3, \qquad (13)$$

where $k_2 = kK_1K_2$.

3.2a   *Rate studies with N-methylphenothiazine*

When rate measurements for NMPT oxidations are carried out in acetonitrile solvent under conditions similar to those employed for NAPT, it is observed that the rates of oxidation are very fast. Attempts to study the reaction using very low $[HClO_4]$ and increasing the water content of the medium result in poor solubility of the reaction mixture. This prompted us to study the rate of oxidation of NMPT at constant pH.

The dependence of rate on [NMPT] and [Cr(VI)] are found to be similar to that of NAPT oxidations when rate measurements are carried out at a pH of 3·09 in 67% acetonitrile–33% water (v/v) mixture (table 1). This is evidenced by the straight lines in the $\log[Cr(VI)]$ against time plots and also the unit slope in the plot of $\log k_1$ versus $\log$ [NMPT] (slope $= 1·00 \pm 0·09, r = 0·998$). The observation of a straight line passing through the origin for the plot of k_1 versus [NMPT] ($r = 0·997$) rules out a substrate-independent decomposition.

Table 3. Effect of varying $[H^+]$, solvent composition and temperature on oxidation of NMPT under pseudo-first-order conditions.

$10^3[H^+]$ (mol dm^{-3})	$10^2 k_2{}^a$ (dm^3 mol^{-1} s^{-1})	CH$_3$CN–H$_2$O %(v/v)	$10^2 k_2{}^b$ (dm^3 mol^{-1} s^{-1})	T (K)	$10^2 k_2{}^c$ (dm^3 mol^{-1} s^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$-\Delta S^{\neq}$ (J K^{-1} mol^{-1})
0·80	3·28 ± 0·15	39–61	11·8 ± 1·5	303	3·28 ± 0·15	34·1	132
1·20	4·12 ± 0·27	49–51	10·2 ± 0·78	313	5·45 ± 0·26		
3·60	8·38 ± 0·44	59–41	6·90 ± 0·61	318	6·49 ± 0·28		
7·70	12·6 ± 0·14			323	9·50 ± 0·92		
15·7	13·7 ± 0·27						

^{a}In a solvent system of 67% acetonitrile–33% water (v/v); ^{b}pH 2·54; ^{c}In 67% acetonitrile–33% water (v/v) mixture at a pH of 3·09.

The order in $[H^+]$ has been established by varying the pH (table 3) and it is found to be fractional as revealed by the linear plot of log k_2 versus log $[H^+]$ ($r = 0.998$, slope $= 0.63 \pm 0.12$). A plot of k_2 versus $[H^+]$ gives a curve which is convex to the rate axis and tending to a limiting value at high acidity (figure 1). Such a situation would generally conform (Gupta and Gupta 1984) to the rate law given below

$$k_{obs} = \frac{(k' K [H^+])}{(1 + K[H^+])}.$$ (14)

It can be inferred from this type of acid-dependence that there is a pre-equilibrium between the protonated and the deprotonated forms of the oxidant, (see (15)). Also the value of the protonation equilibrium constant is large enough such that at higher acidities, protonation is almost complete and only the protonated form of the oxidant species is reactive here (Gupta and Gupta 1984). A plot of $1/k_2$ versus $1/[H^+]$ is linear ($r = 0.998$). From the slope and intercept the k' and K values are found to be $17.9 \times 10^{-4} s^{-1}$ and $2.73 \times 10^2 dm^3 mol^{-1}$ respectively.

The variation in second-order rate constants, k_2, with various percentages of the solvent mixture of acetonitrile and water studied at a pH of 2.54 (table 3) reveal that the rate increases with the polarity of the medium. This behaviour is in contrast to NAPT oxidation and this may be attributed to the formation of a dipolar activated complex formed from neutral reactants in the rate-determining step (scheme 2). Similar solvent effects were also observed in the oxidation of alkyl aryl sulphides and diaryl sulphides (Srinivasan *et al* 1985).

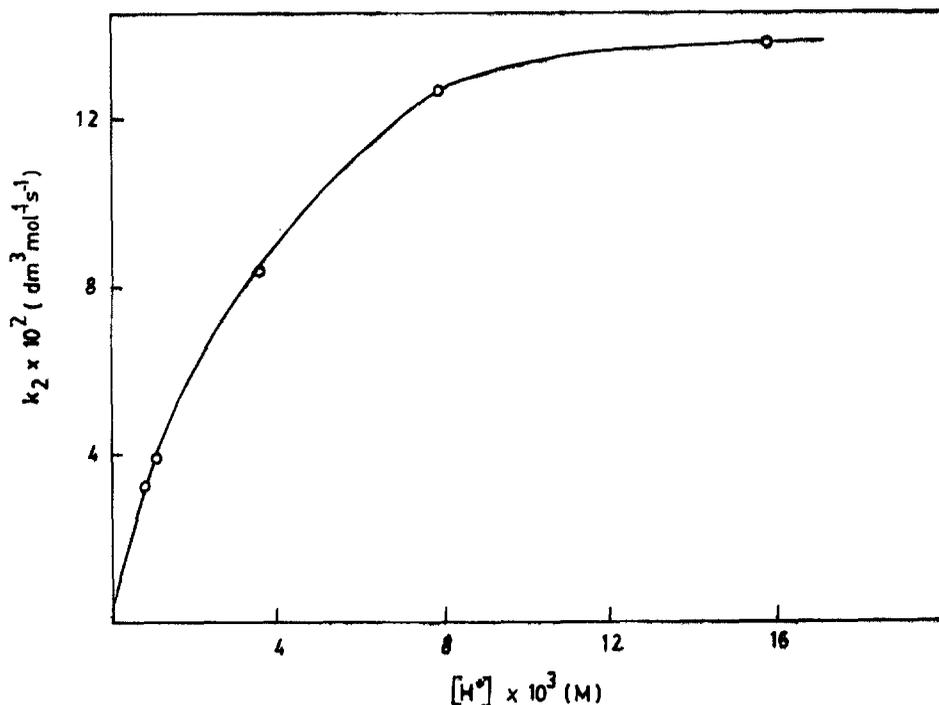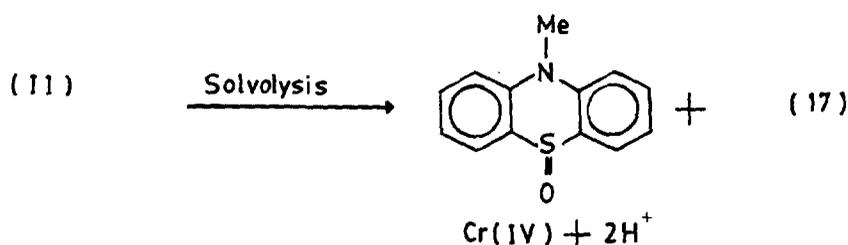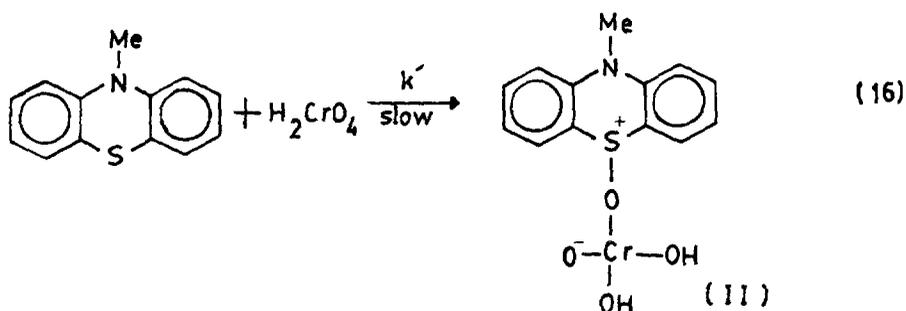In solutions of dichromate concentration less than $0.05 \ mol \ dm^{-3}$, Cr(VI) is present

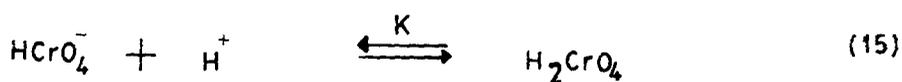Figure 1.   Variation of k_2 with $[H^+]$ at 303 K.

$$HCrO_4^- + H^+ \overset{K}{\rightleftharpoons} H_2CrO_4 \qquad (15)$$

$$\text{(phenothiazine, Me-N)} + H_2CrO_4 \xrightarrow[\text{slow}]{k'} \text{(dipolar complex)} \quad (II) \qquad (16)$$

where (II) bears the group $O^--Cr-OH$ with OH substituents.

$$(II) \xrightarrow{\text{Solvolysis}} \text{(sulphoxide)} + Cr(IV) + 2H^+ \qquad (17)$$

Scheme 2.

(Wiberg 1965) in the form of $HCrO_4^-$. Since the rate dependence on $[H^+]$ obeys the rate law discussed earlier, (14), the protonated form of $HCrO_4^-$, namely H_2CrO_4, is considered to be the active species. The activation parameters (table 3) calculated from Eyring's plot ($r = 0.998$) reveal that the reaction is characterised by a low enthalpy but considerable negative entropy of activation as in the case of NAPT. The magnitudes of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values correspond to those expected for a bimolecular reaction (Edwards 1962).

3.2b *Mechanism and rate law*

The first-order dependence each in [NMPT] and [Cr(VI)], and the fractional-order dependence of rate on $[H^+]$ suggest the mechanism shown in scheme 2 for the oxidation of NMPT by Cr(VI). The observed solvent effect is due to the formation of a dipolar activated complex from neutral molecules, (16), followed by its solvolysis to yield the sulphoxide and Cr(VI). The corresponding rate-law is

$$\frac{-d[Cr(VI)]}{dt} = k_2[NMPT][Cr(VI)], \qquad (18)$$

where $k_2 = (k' K[H^+])/(1 + K[H^+])$.

3.3 *Comparison with diphenyl sulphide oxidations*

The close structural similarity between diphenyl sulphide and phenothiazines prompted us to compare the rates of oxidation of these substrates with Cr(VI). Under analogous

conditions, the rate of oxidation of NAPT is faster than that of diphenyl sulphide. Second-order rate constants, $10^2 k_2\, dm^2\, mol^{-3}\, s^{-1}$ for DPS (Srinivasan *et al* 1985) and NAPT (table 1) oxidations are 2·08 and 6·72 respectively. The faster rate for NAPT may be ascribed to the fact that the sulphide group is more exposed in phenothiazines than in diphenyl sulphide thereby enhancing its nucleophilicity. With an electron-releasing methyl group as in NMPT, the rate is still faster by several orders, thus substantiating our conclusion.

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