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Oxidation of psychotropic drugs by Chloramine-T in acid medium: a kinetic study using spectrophotometry

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Abstract

The kinetics of oxidation of psychotropic drugs, chlorpromazine hydrochloride (CPH) and fluphenazine dihydrochloride (FPH), by Chloramine-T (CAT) in pH 1.6 buffer medium has been studied spectrophotometrically at $\lambda_{max} = 570$ and 530 nm, respectively, at 30°C. The reaction rate shows a fractional-order dependence on [CAT] and first-order dependence on each [substrate]. The reaction rate also shows an inverse fractional-order in $[H^+]$. Additions of halide ions and the reduction product of CAT, *p*-toluenesulfonamide, and variation of ionic strength and dielectric constant of the medium do not have any significant effect on the reaction rate. The activation parameters for the reaction were evaluated. The proposed general mechanism and the derived rate law are consistent with the observed kinetics.

1. Introduction

The *N*-alkylphenothiazines (NAPs) play a prominent role in chemotherapy these days. Several reviews [1–5] have discussed the synthesis, structure, properties, and applications of NAPs. These drugs are versatile compounds possessing anticholinergic, antihistaminic, antiamoebic, and antiemetic activities. The NAPs, such as chlorpromazine hydrochloride (CPH) and fluphenazine dihydrochloride (FPH), have also been examined for antibacterial effect on some bacterial strains in vitro. Chlorpromazine hydrochloride is a white solid used for pre-anaesthetic medication, as a muscle relaxant and in the treatment of tetanus. It produces also a quieting effect on children with behavioral disorders, and it has been tested for antifungal activities and used in standard assays [2–5]. Fluphenazine dihydrochloride is also a white solid used as a tranquilizer and in chemotherapy [5]. Kinetic and spectroscopic studies [6] have shown that the one-equivalent oxidations of phenothiazine and phenoxazine (Ar_2NH) in neutral and acidic CH_3CN solution by Ce^{IV} and Fe^{III} occur via the following reaction sequence:

$$Ar_2NH \xrightarrow{-e^-} Ar_2NH^{+\cdot} \underset{-H^+}{\overset{-e^-}{\rightarrow}} Ar_2N^+ \rightarrow \text{product}$$

Reaction intermediates have been characterized by uv-visible spectroscopy [6].

A prominent member of the class of *N*-haloarylsulfonamides is sodium *N*-chloro-*p*-toluenesulfonamide or chloramine-T (p-$CH_3C_6H_4SO_2NClNa.3H_2O$ or CAT), which is a by-product in the manufacture of saccharin [7–10]. Generally, CAT undergoes a two-electron change in its reactions forming the reduction products, *p*-toluenesulfonaminde or PTS (p-$CH_3C_6H_4SO_2NH_2$) and sodium chloride. The

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oxidation potential of the CAT-PTS couple varies with the pH of the medium (1.139 v at pH 0.65, 0.778 v at pH 7.0 and 0.614 v at pH 9.7). The existing chemistry of CAT and other *N*-haloarylsulfonamides has been reviewed by Campbell and Johnson [10]. Since compounds such as hypochlorite and CAT can act as sources of chlorine, they are used in the disinfection of drinking water [11,12]. As a result, CAT can find its way into the animal stomach, including that of the human [12]. Ingested NAP drugs such as CPH and FPH can react with CAT under acidic conditions in the stomach. Therefore, there was a need for understanding the oxidation mechanism of the drug in acidic medium so that the study could throw some light on the fate of the drug in the biological systems in vivo.

After reviewing the literature, we found that there was no information available on the oxidation of the two substrates, CPH and FPH, by *N*-haloamines. In this paper, we report the spectrophotometrically-monitored kinetics of oxidation of CPH and FPH by CAT in pH 1.6 buffer medium in order to elucidate the reaction mechanism.

2. Experimental

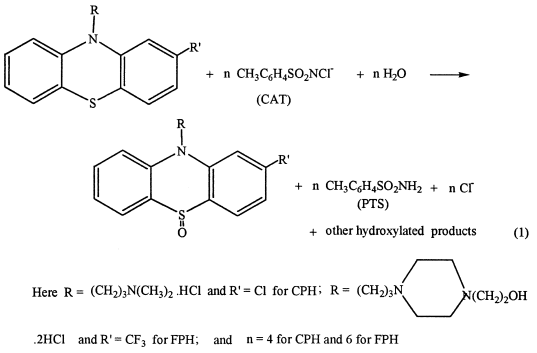
Chloramine-T (CAT) (E. Merck) was purified by the method of Morris et al. [13]. An aqueous solution of CAT was prepared, standardized periodically by the iodometric titration and stored in brown bottles to prevent its photochemical deterioration [13]. Aqueous solutions of CPH and FPH were prepared. Standard buffer systems [14,15] were prepared (e.g. for pH 1.6, a mixture of 0.20 M 50.0 ml KCl and 26.3 ml 0.20 M HCl was diluted to 200 ml) and used. All other chemicals were of analytical grade. Triply distilled water was used for preparing aqueous solutions.

2.1. Kinetic measurement

Kinetic runs were performed under pseudo-first order conditions with a large excess of the oxidant over the substrate (CPH or FPH) at 30°C. For each run, requisite amounts of solutions of CPH or FPH, $NaClO_4$ (to maintain a constant ionic strength) and a buffer of known pH and of given component concentrations [14,15] were mixed in a stoppered Pyrex glass tube whose outer surface was coated black. The tube was thermostatted in a water bath at a given temperature. To this solution was added a measured amount of pre-equilibrated CAT solution to give a desired overall concentration. The reaction mixture was periodically shaken for uniform concentration. The course of the reaction was monitored spectrophotometrically by measuring absorbance at the λ_{max} (570 nm for CPH and 530 nm for FPH) at regular time intervals for at least three half lives. The pseudo-first-order rate constants, k', calculated were reproducible within $\pm 3\%$.

2.2. Stoichiometry and product analysis

Reaction mixtures containing different compositions of CPH or FPH and Chloramine-T were equilibrated at 30°C in an acidic buffer of pH 1.6 for 24 h. The iodometric determination of unreacted CAT in the reaction mixture showed that 1 mole of NAP consumed 4 moles of CAT (CPH) or 6 moles of CAT (FPH).



(1)

Of the reaction products, PTS was isolated and recrystallized from dichloromethane and petroleum ether and identified by TLC ($R_f = 0.26$ with dichloromenthane solvent and iodine developing agent) [16,17]. Furthermore, the mass spectrum showed an M^+ peak at 171 amu confirming PTS. The conditions used in the GC-MS study for PTS were reported earlier [17]. The other products, sulfoxides of CPH and FPH, were identified through UV spectral studies.

3. Results and discussion

Under pseudo-first-order conditions of $[CAT]_o \gg [CPH]_o$ or $[FPH]_o$ at constant $[CAT]_o$, pH, and

Table 1
Effects of varying reactant concentrations on the reaction rate. Buffer pH = 1.6; $\mu = 0.10$ M; $T = 30$°C; $\lambda_{max} = 570$ nm (CPH) and 530 nm (FPH); NAP = CPH or FPH

$[CAT]_o \times 10^3$ (M)	$[NAP]_o \times 10^4$ (M)	$k' \times 10^3$ (s^{-1})	
		CPH	FPH
0.50	5.00	1.23	1.65
1.00	5.00	1.68	2.38
2.00	5.00	2.34	3.26
3.00	5.00	2.66	4.06
5.00	5.00	3.53	5.37
7.00	5.00	3.84	6.12
2.00	1.00	2.36	3.24
2.00	3.00	2.32	3.20
2.00	5.00	2.34	3.26
2.00	7.00	2.30	3.24
2.00	10.0	2.34	3.26

temperature, the substrate (NAP) concentration was varied. For each run, the plot of $\ln(A_0/A_t)$ vs time was linear indicating a first-order dependence of the reaction rate on [CPH] and [FPH]. A_o and A_t are absorbances of the reaction mixture at time intervals of zero and t, respectively. The pseudo-first-order rate constant obtained at 30°C is independent of $[CPH]_o$ and $[FPH]_o$ further confirming the first-order dependence on [NAP] (Table 1). At constant pH, $[CPH]_o$ or $[FPH]_o$, ionic strength, and temperature, the rate

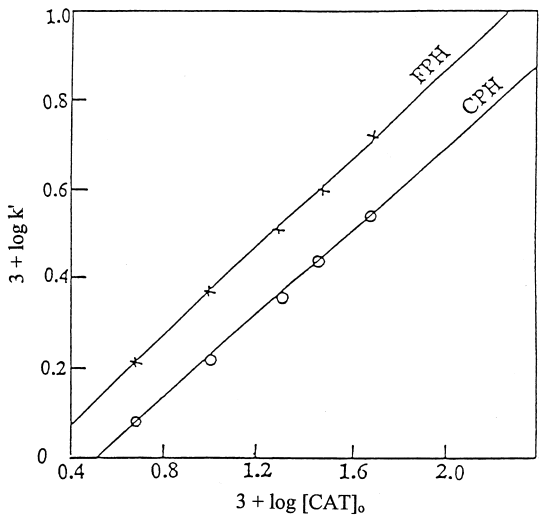


Fig. 1. Plots of $\log k'$ vs $\log[CAT]_o$. $[CPH]_o$ or $[FPH]_o = 5.00 \times 10^{-4}$ mol dm^{-3}; buffer pH = 1.6; $\mu = 0.10$ mol dm^{-3}; $T = 30$°C.

Table 2
Effects of pH on the reaction rate. $[CPH]_o$ or $[FPH]_o = 5.00 \times 10^{-4}$ M; $[CAT]_o = 2.00 \times 10^{-3}$ M; $\mu = 0.10$ M; $T = 30$°C

pH[a]	$k' \times 10^3$ (s^{-1})	
	CPH	FPH
1.0	0.960	1.52
1.2	1.32	1.95
1.4	1.68	2.52
1.6	2.34	3.26
1.8	3.22	4.28
2.0	4.05	5.32
2.2	5.65	6.98

[a] Procedure in Ref. [5] was used to prepare each buffer and its pH was verified using pH meter.

increased with increasing $[CAT]_o$ (Table 1). Furthermore, a plot of $\log k'$ vs $\log[CAT]_o$ was linear with a slope showing a fractional-order dependence on [CAT] (Fig. 1). The reaction rate increased with increasing pH of the medium (Table 2). A plot of $\log k'$ vs $\log[H^+]$ was linear with a negative slope showing an inverse fractional-order in $[H^+]$. An addition of Cl^- or Br^- ions in the form of NaCl or NaBr at constant $[H^+]$ and ionic strength did not affect the rate. An addition of *p*-toluenesulfonamide or the variation of the ionic strength of the medium by adding $NaClO_4$ had no effect on the reaction rate. Also, the variation of the solvent composition using MeOH did not affect the rate. The reaction was studied at varying temperatures, 25–40°C. The activation parameters, namely energy of activation (E_a), enthalpy of activation ($\Delta H^{\neq}$), and entropy of activation ($\Delta S^{\neq}$), were obtained from the Arrhenius and Eyring plots of $\ln k'$ vs $1/T$ and $\ln(k'/T)$ vs $1/T$. The kinetic and activation data obtained are presented in Table 3.

The existence of similar equilibria in acid and alkaline solutions of *N*-metallo-*N*-haloarylsulfonamides has been reported by Pryde and Soper [18], Morris et al. [13], and Bishop and Jennings [19]. Chloramine-T behaves as a strong electrolyte in aqueous solutions forming different species as shown in Eqs. (2)–(7).

$$ArSO_2NClNa \rightleftharpoons ArSO_2NCl^- + Na^+ \quad (2)$$

$$ArSO_2NCl^- + H^+ \rightleftharpoons ArSO_2NCl \quad (3)$$

Table 3
Temperature dependence and activation parameters for the oxidation of CPH and FPH by CAT in acidic buffer medium. $[CPH]_o$ or $[FPH]_o = 5.00 \times 10^{-4}$ M; $[CAT]_o = 2.00 \times 10^{-3}$ M; $\mu = 0.10$ M; buffer pH = 1.6

Substrate	$k' \times 10^3$ (s^{-1})				$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ ($Jk^{-1}mol^{-1}$)	E_a (kJ mol^{-1})
	298 K	303 K	308 K	313 K			
CPH	1.44	2.34	3.91	5.89	70.9	− 61.3	73.5
FPH	2.61	3.26	4.37	5.66	38.1	− 166.9	40.6

$$ArSO_2NHCl + H_2O \rightleftharpoons ArSO_2NH_2 + HOCl \quad (4)$$

$$2ArSO_2NHCl \rightleftharpoons ArSO_2NH_2 + ArSO_2NCl_2 \quad (5)$$

$$HOCl + H^+ \rightleftharpoons H_2OCl^+ \quad (6)$$

$$HOCl + HCl \rightleftharpoons Cl_2 + H_2O \quad (7)$$

In acid solutions, the probable oxidizing species are the conjugate free acid ($ArSO_2NHCl$), dichloramine-T ($ArSO_2NCl_2$), HOCl, H_2OCl^+, and molecular chlorine. As Eq. (4) indicates a slow hydrolysis, if HOCl were the primary oxidizing species, a first-order retardation of the rate by the added $ArSO_2NH_2$ would be expected, contrary to the experimental results. If $ArSO_2NC1_2$ were the reactive species, the rate law would predict a second-order dependence on [CAT] and a rate retardation by $ArSO_2NH_2$ [Eq. (5)], which are contrary to the experimental observations. Similarly, if H_2OCl^+ [Eq. (6)] or molecular chlorine [Eq. (7)] were the reactive species, there would be a positive effect of [HCl] on the rate, which did not occur. Narayanan and Rao [20] and Subhashini et al. [21] have reported that monohaloamines can be further protonated at pH ≤ 2 as shown in Eq. (8) for Chloramine-B (CAB, Ar = C_6H_5) and CAT (Ar = $CH_3C_6H_4$).

$$ArSO_2NHCl + H^+ KArSO_2N^+H_2Cl \quad (8)$$

The second protonation constants, K', for CAB and CAT are 61 ± 5 and $102\ M^{-1}$, respectively, at 25°C. Gupta [22] has suggested that the value could be lower than those reported by the above workers.

In the present case, an inverse fractional-order in $[H^+]$ suggests that the deprotonation of $ArSO_2N^+H_2Cl$ results in the regeneration of $ArSO_2NHCl$, which is the most likely active oxidant species involved in the mechanism of CPH and FPH oxidation. Thus the following reaction mechanism is proposed (Scheme 1):

The total effective concentration of the substrate, $[substrate]_t$, from Scheme 1 is given by

$$[S]_t = [S] + [X] \quad (9)$$

This equation leads to the rate law below,

$$\text{Rate} = \frac{K_1 K_2 k_3 [CAT][S]_t[H_2O]}{[H^+] + K_1 K_2 [CAT]} \quad (10)$$

which is in good agreement with the experimental data, including a first-order in substrate, a fractional-order in CAT and an inverse fractional-order in $[H^+]$.

Since the reaction was studied under pseudo-first-

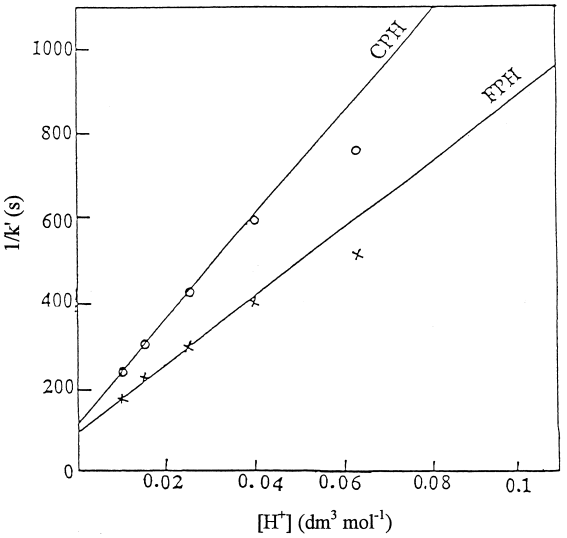
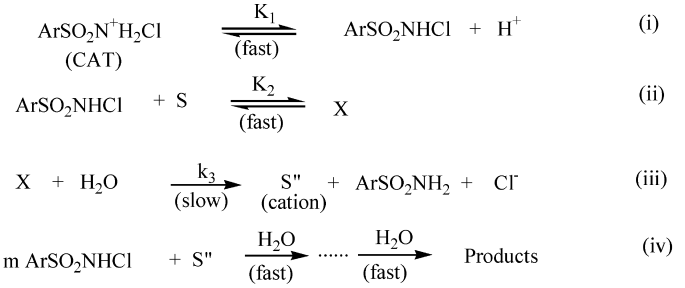
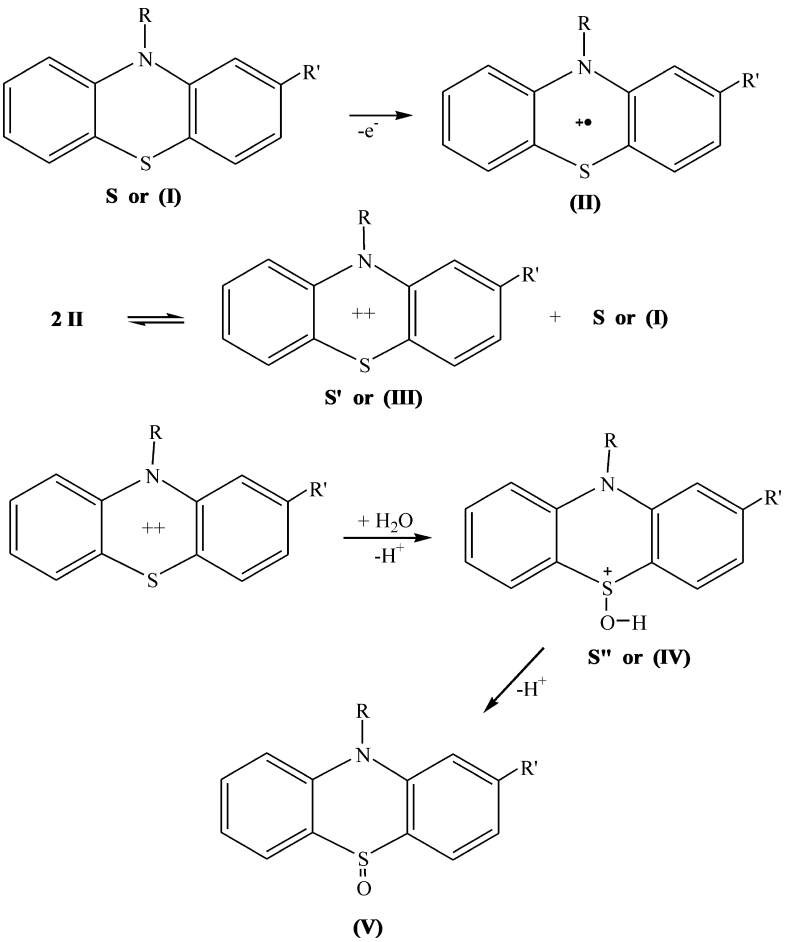


Fig. 2. Plots of $1/k'$ vs $[H^+]$. $[CPH]_o$ or $[FPH]_o = 5.00 \times 10^{-4}$ mol dm^{-3}; $[CAT]_o = 2.00 \times 10^{-3}$ mol dm^{-3}; $\mu = 0.10$ mol dm^{-3}; $T = 30$°C.



Where S and S" are as shown in scheme 2, X is a CAT-S Complex species, and m=n-1=3 for CPH or 5 for FPH oxidation (n values are as in eg.(1))

Scheme 1.



Scheme 2.

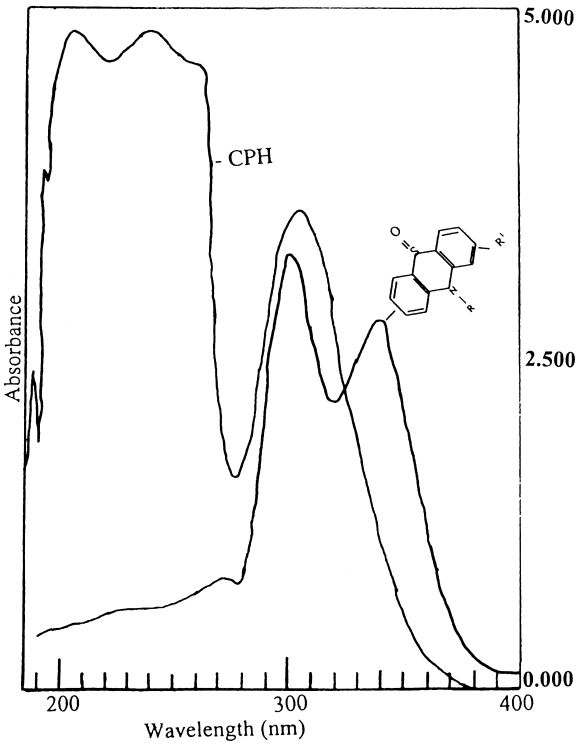


Fig. 3. UV spectra of Chlorpromazine Hydrochloride (CPH) and CPH + CAT. $[CPH]_o = 4.00 \times 10^{-4}$ mol dm^{-3}; $[CAT]_o = 2.00 \times 10^{-3}$ mol dm^{-3}; buffer pH = 1.6.

order conditions of $[S]_o < [CAT]_o$, rate $= k'[S]_t$. Therefore, Eq. (10) becomes,

$$k' = k_{obs} = \frac{K_1 K_2 k_3 [CAT][H_2O]}{[H^+] + K_1 K_2 [CAT]} \tag{11}$$

Eq. (11) can be transformed into the following forms:

$$\frac{1}{k'} = \frac{[H^+] + K_1 K_2 [CAT]}{K_1 K_2 k_3 [CAT][H_2O]} \quad \text{or}$$
$$\frac{1}{k'} = \frac{[H^+]}{K_1 K_2 k_3 [CAT][H_2O]} + \frac{1}{k_3 [H_2O]} \tag{12}$$

A plot of $1/k'$ vs $1/[CAT]$ at constant $[S]_o$, $[H^+]$, and temperature from Eq. (12) was found to be linear with

$$\text{slope} = \frac{[H^+]}{K_1 K_2 k_3 [H_2O]} \quad \text{and intercept} = \frac{1}{k_3 [H_2O]}$$

Also, from Eq. (12), a plot of $1/k'$ vs $[H^+]$ at constant $[CAT]_o$, $[S]_o$, and temperature is linear (Fig. 2) with

$$\text{slope} = \frac{1}{K_1 K_2 k_3 [CAT][H_2O]}$$

$$\text{and intercept} = \frac{1}{k_3 [H_2O]}$$

The values of k_3 (4.76×10^{-3} M^{-1} s^{-1} and 8.00×10^{-3} M^{-1} s^{-1} for CPH and 8.30×10^{-3} M^{-1} s^{-1} and 1.00×10^{-2} M^{-1} s^{-1} for FPH) have been calculated from the intercepts of the above plots. Narayanan and Rao [20], Subhashini et al. [21], and Gupta [22] have reported the value of K_1 (9.80×10^{-3} M) for other substrate oxidations by CAT. A value of K_1 (6.59×10^{-3} M for CPH and 9.80×10^{-3} M for FPH) obtained from Eq. (12) is similar to the one reported previously [20–22]. Hence this K_1 value indirectly supports the proposed Scheme 1.

The activation energies and rate constants (Table 3) show that the oxidation of FPH is faster than that of CPH. Several structure–activity relationship studies have shown that the pharmacological effects of NAP compounds in living systems depend on the nature of the N-alkyl side chain (R) and the aromatic ring substituent (R′) (structure I, Scheme 2) [2,3]. Quantitative changes depend on the electron-withdrawing or electron-donating power of R′ group, particularly at the 2-position, while the qualitative effects are directed by the steric and electronic nature of *R* group [2,3]. Therefore, in the present kinetic study, the difference in reactivities of FPH and CPH is mainly due to the inductive effects of the electron-withdrawing R′ group in the NAP molecule. As expected, the FPH molecule with a stronger electron-attracting CF_3 group has a greater reactivity than CPH, which has a weaker electron-attracting Cl group. The negative values of $\Delta S^{\neq}$ suggest the formation of a more ordered and rigid transition state for each NAP reaction (Table 3).

The absorption and ESR spectral studies have

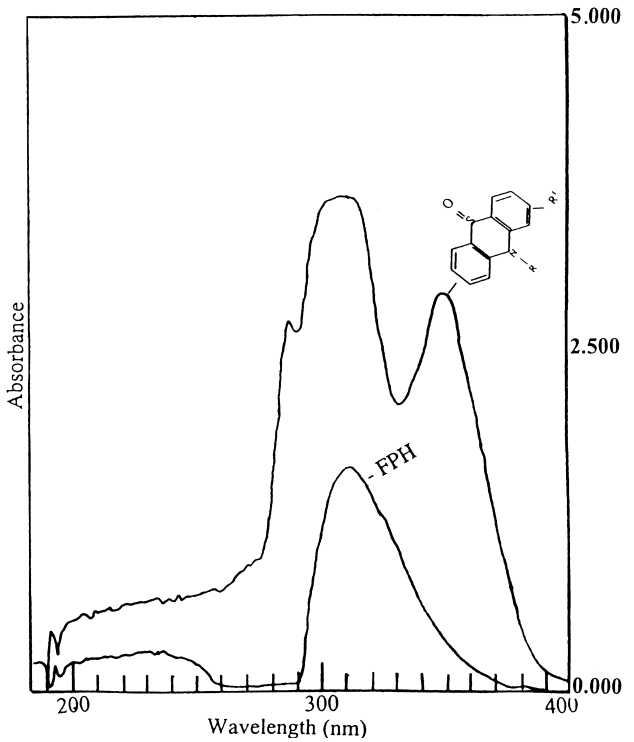


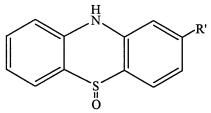
Fig. 4. UV spectra of Fluphenazine Dihydrochloride (FPH) and FPH + CAT. $[FPH]_o = 4.00 \times 10^{-4}$ mol dm^{-3}; $[CAT]_o = 2.00 \times 10^{-3}$ mol dm^{-3}; buffer pH = 1.6.

shown how the oxidation of NAP molecules occurs in acidic aqueous solutions [1–6,23]. Scheme 2 shows general structures of species involved in the NAP oxidation sequence.

The spectral data suggest that the oxidation proceeds through two single-electron steps from neutral molecule (I) to the free-radical cation (II) and then to the dication (III) [2,3]. The change in color from colorless to pink is due to the formation of a radical cation (II), which undergoes dismutation to form a mixture of I and III. A possible alternative route for the formation of III is an one-electron oxidation of II. The dication III exhibits absorption maxima (λ_{max}) at 570 nm for CPH and 530 nm for FPH. The hydrolysis of III followed by deprotonation of IV leads to the formation of sulfoxide product V [3].

The uv spectra of free CPH and FPH, and of their reaction mixtures in aqueous solutions were recorded (Figs. 3 and 4). Absorption maxima in aqueous medium appear at 254 and 306 nm for CPH and 256 and 308 nm for FPH [3,4]. Aqueous solutions of CAT exhibit a λ_{max} at 205 nm [24]. Examination of the uv spectral data obtained after completion of the NAP–CAT reaction showed additional peaks at 270, 302 and 336 nm, which correspond to the general sulfoxide product structure (V) shown in Scheme 2, consistent with the reported data [3–6,23,25].

The uv spectral data also suggest that the N–R bond (structure I in Scheme 2) remained intact when the radical cation (II) was oxidized to dication (III) since the loss of R group would have led to the formation of product VI [3,4,25,26].



(VI)

The expected λ_{max} values of 225, and 326 nm were not observed in the reaction mixture of NAP and

CAT, showing the absence of phenothiazine sulfoxide VI amongst the oxidation products [6,26].

The TLC analysis of the crude oxidation-reaction mixture indicated the presence of five to six products, but they were not separated. Therefore, as observed in the stoichiometry, more than two equivalents of the oxidant were consumed. Experiments are presently underway to separate the individual oxidation products.

4. Conclusion

The kinetic study involving the oxidation of CPH and FPH by CAT in acidic buffer medium has led to the following conclusions:

1. the oxidation stoichimetries of the two NAPs determined under similar experimental conditions differ: a mol-to-mol ratio of 1:4 for the CPH–CAT reaction and a mol-to-mol ratio of 1:6 for the FPH–CAT reaction;
2. the oxidation of FPH occurs at a faster rate than that of CPH, which is attributable to the electron-withdrawing ability of the aromatic ring substituent, R', in the NAP molecule;
3. the two NAPs follow the same general reaction mechanism as proposed in Scheme 1;
4. the values of deprotonation constant, K_1, of $ArSO_2N^+H_2Cl$ determined from the oxidation of CPH (6.59×10^{-3} M) and FPH (9.80×10^{-3} M) agree with the reported value of 9.80×10^{-3} M ($1/K_1 = K' = 102\ M^{-1}$) from other substrate oxidations [20–22] supporting the proposed mechanism.

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