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Stopped-Flow Kinetic Investigations of One-Electron Transfer Reactions of Phenothiazines and Their Radical Cations in Aqueous Solution

Lakshmanan VENKATASUBRAMANIAN and Pichai MARUTHAMUTHU*
Department of Energy, University of Madras, A. C. College Campus, Madras 600025, India
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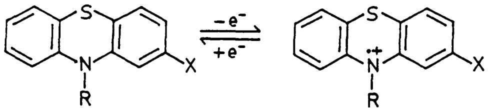
The kinetics of one-electron oxidation of the protonated forms of phenothiazines namely, chlorpromazine (CPZH$^+$) and promethazine (PMZH$^+$) with the inorganic peroxides, peroxomonosulfate and peroxodisulfate in aqueous medium, were investigated by stopped flow spectrophotometric technique. The reactions of both the phenothiazines obeyed a total second-order kinetics, first-order each with respect to [phenothiazine] and [peroxide]. Both peroxides generated radical cations from the respective phenothiazines by one-electron transfer. The radical cations, CPZH$^{\cdot 2+}$ and PMZH$^{\cdot 2+}$ were found to oxidize ascorbic acid generating the parent compounds, whereas CPZH$^{\cdot 2+}$ alone was able to react with sulfite, thiosulfate and dithionite to regenerate CPZH$^+$. The kinetics of all these reactions were investigated and discussed.

There is currently a considerable interest focussed on the thermal and photoinduced electron-transfer reactions of phenothiazines and their radical cations. The primary interest in this group of compounds stems from two aspects: (i) they undergo reversible one-electron redox reaction and (ii) the possible use of phenothiazines as photoredox sensitizers in solar energy conversion systems.[1–3] Furthermore, the diamine derivative of phenothiazine in conjunction with Fe(II) constitutes one of the most studied systems for photogalvanic effects.[4] Phenothiazine drugs have long been used for treatment of psychiatric diseases.[5–8] The effective use of *N*-alkylphenothiazines in psychiatric therapy is attributed to their redox reactivity. The sensitivity of these compounds towards chemical oxidation is well-known and it has been suggested that free-radical cations derived from them may be important intermediates in their potential biochemical action.[9–11]



	R	X
Phenothiazine	H	H
Chlorpromazine	$(CH_2)_3$-$N(CH_3)_2$	Cl
Promethazine	$CH_2CH(CH_3)N(CH_3)_2$	H

In the present study, the kinetics of electron-transfer reactions of the protonated forms of phenothiazines (chlorpromazine, CPZH$^+$ and promethazine PMZH$^+$) with peroxosulfur salts, peroxomonosulfate (PMS) and peroxodisulfate (PDS) and the reactions of phenothiazine radical cations (CPZH$^{\cdot 2+}$ and PMZH$^{\cdot 2+}$) with various reducing agents, sulfite, thiosulfate dithionite, and ascorbic acid have been investigated.

Experimental

Chlorpromazine and promethazine were from Fluka (Switzerland). Peroxomonosulfate (Du Pont de Nemours & Co., USA) in the form of a triple salt $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$ was used as such. All the other chemicals used were of the research grade available from E. Merck (India). The reaction solutions were prepared with doubly distilled water and were thoroughly deaerated by purified N_2 or Ar. The kinetic experiments were carried out in aqueous medium using stopped-flow technique. The details of the stopped-flow spectrophotometer and the kinetic analysis are given elsewhere.[12] The kinetics of the formation and decay of the radical cations were measured at their respective absorption maxima[13] (CPZH$^{\cdot 2+}$: $\lambda_{max}=510$ nm; $\varepsilon=1.2\times10^4$ dm^3 mol^{-1} cm^{-1} and PMZH$^{\cdot 2+}$: $\lambda_{max}=505$ nm; $\varepsilon=9.5\times10^3$ dm^3 mol^{-1}cm^{-1}).

Results and Discussion

Because of low solubility of the titled compounds in aqueous medium in neutral and alkaline conditions, the experiments have been limited to solution of pH<7, where the side-chain nitrogen atoms of both the phenothiazines are protonated (pK_a=9.3).[14] Hence the phenothiazines are represented as protonated forms, CPZH$^+$ and PMZH$^+$. The oxidants, peroxomonosulfate and peroxodisulfate were found to oxidize the protonated phenothiazines to their respective radical cations. The radical cations were found to be quite stable for several hours even in the presence of excess concentrations of these oxidants or in the absence of any other reducing agents. The radical cations generated with the stoichiometric amounts of the reactants (phenothiazine : peroxide=1 : 2) were stable for about a week.

All the experiments were carried out under pseudo-first-order conditions, [peroxide]$\gg$[phenothiazine]. The kinetic runs were performed with [PMS] or [PDS]=1.0—5.0×10^{-3} mol dm^{-3} and [CPZH$^+$]=1.0—5.0×10^{-4} mol dm^{-3}; and [PMS]=1.0—5.0×10^{-3} mol dm^{-3}; [PDS]=1.0—5.0×10^{-2} mol dm^{-3}; and [PMZH$^+$]=1.0—5.0×10^{-4} mol dm^{-3}. The plots of log $(A_\infty-A_t)$ (where A_∞ is the absorbance at the end of the reaction and A_t is the absorbance at time 't') vs. time for different initial [phenothiazine] were linear with almost the same slope indicating the first-order dependence of the rate on [phenothiazine]. The pseudo-first-order rate constants for the formation of the radical cation, k_f'/s^{-1} were calculated from the slopes of the above mentioned plots. Variation of the initial [peroxide] at a fixed [phenothiazine] increased the rate and the corresponding plots of k_f' vs. [peroxide] were linear passing through the origin (Figs. 1 and 2) confirming the first-order dependence of the rate on [peroxide]. The overall second-order rate constants for the formation of the radical cation, $k_{2d}/dm^3\,mol^{-1}s^{-1}$ were evaluated from the slopes of the above plots (Table 1). From the observed kinetics the general rate law for the one-electron oxidation of phenothiazines by peroxides may be given as

$$\text{Rate}=\frac{d[\text{CPZH}^{\cdot 2+}\text{ or PMZH}^{\cdot 2+}]}{dt}=k_{2f}[\text{peroxide}][\text{CPZH}^{+}\text{ or PMZH}^{+}]$$

where $k_{2f}/dm^3\,mol^{-1}s^{-1}$ is the overall second-order rate constant for the formation of the radical cation.

Table 1. Rate Constants for the One-Electron Transfer Reactions of the Phenothiazines at pH 4.0 and Temp=25 °C

	Oxidizing agent	$k_{2f}/dm^3\,mol^{-1}\,s^{-1}$
$CPZH^+$	PMS	6.4×10^2
	PDS	2.1×10^2
$PMZH^+$	PMS	10.0
	PDS	3.1

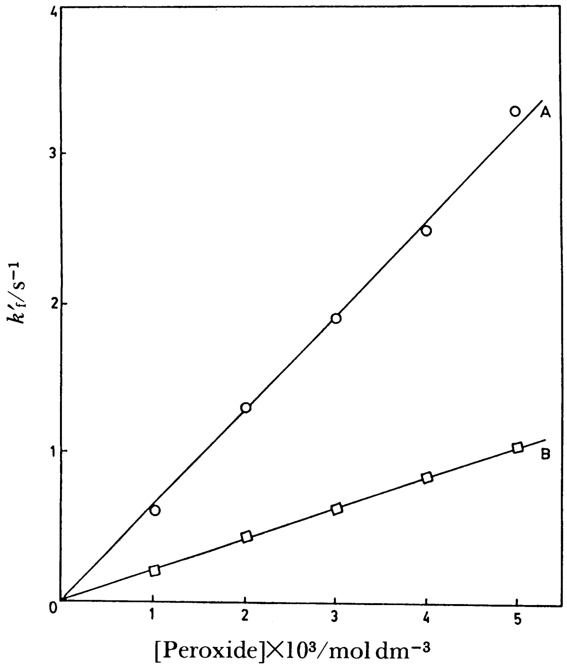


Fig. 1. Formation of $CPZH^{\cdot 2+}$: k_f' vs. [peroxide] A : PMS; B : PDS.

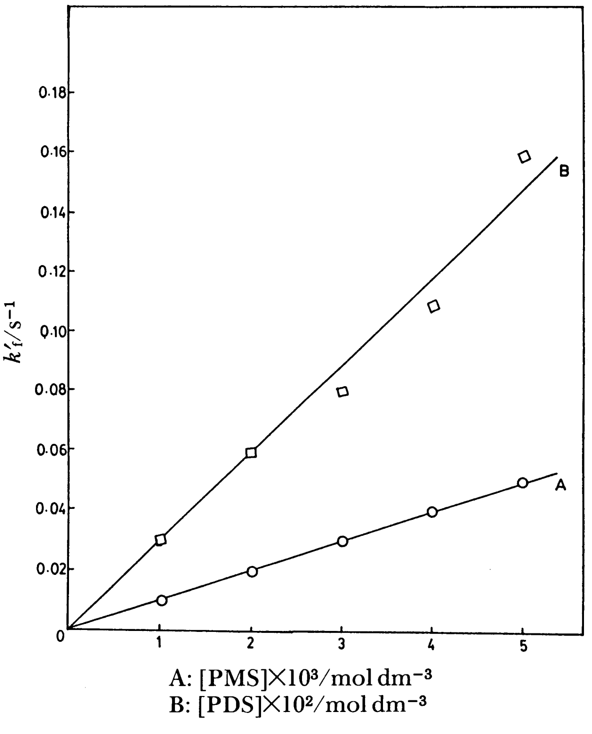


Fig. 2. Formation of $PMZH^{\cdot 2+}$: k_f' vs. [peroxide] A : PMS; B : PDS.

It is known that both peroxomonosulfate and peroxodisulfate are potential electron acceptors and are two-electron oxidants. Even though the reactions are carried out at excess concentrations of these oxidants, the formation of only the radical cations and the absence of further reaction of these radical cations indicate that these peroxo salts undergo stepwise two one-electron reduction process, probably with the formation of $SO_4^{\cdot-}$ and $SO_4^{\cdot-}/\dot{O}H$ as the radical intermediates respectively with $S_2O_8^{2-}$ and HSO_5^-. These radical intermediates react fast with the substrates, again generating the respective radical cation.

The following mechanisms may be proposed for the reactions of the peroxides with phenothiazines.

Peroxomonosulfate:

$$\text{CPZH}^+/\text{PMZH}^+ + \text{HSO}_5^- \xrightarrow{\text{slow}} \text{CPZH}^{\cdot 2+}/\text{PMZH}^{\cdot 2+} + (\dot{O}\text{H} + \text{SO}_4^{2-})/(\text{OH}^- + \text{SO}_4^{\cdot-}) \quad (1)$$

$$\text{CPZH}^+/\text{PMZH}^+ + \dot{O}\text{H}/\text{SO}_4^{\cdot-} \xrightarrow{\text{fast}} \text{CPZH}^{\cdot 2+}/\text{PMZH}^{\cdot 2+} + \text{OH}^-/\text{SO}_4^{2-} \quad (2)$$

Peroxodisulfate:

$$\text{CPZH}^+/\text{PMZH}^+ + \text{S}_2\text{O}_8^{2-} \xrightarrow{\text{slow}} \text{CPZH}^{\cdot 2+}/\text{PMZH}^{\cdot 2+} + \text{SO}_4^{\cdot-} + \text{SO}_4^{2-} \quad (3)$$

$$\text{CPZH}^+/\text{PMZH}^+ + \text{SO}_4^{\cdot-} \xrightarrow{\text{fast}} \text{CPZH}^{\cdot 2+}/\text{PMZH}^{\cdot 2+} + \text{SO}_4^{2-} \quad (4)$$

From the magnitude of the second-order rate constants (Table 1) it is observed that peroxomonosulfate is ca. 3 times more reactive than peroxodisulfate, albeit, on thermodynamic grounds, peroxomonosulfate is more powerful than peroxodisulfate ($E^\circ_{PMS}=1.84$ V[15] and $E^\circ_{PDS}=2.01$ V[16]). The higher reactivity of

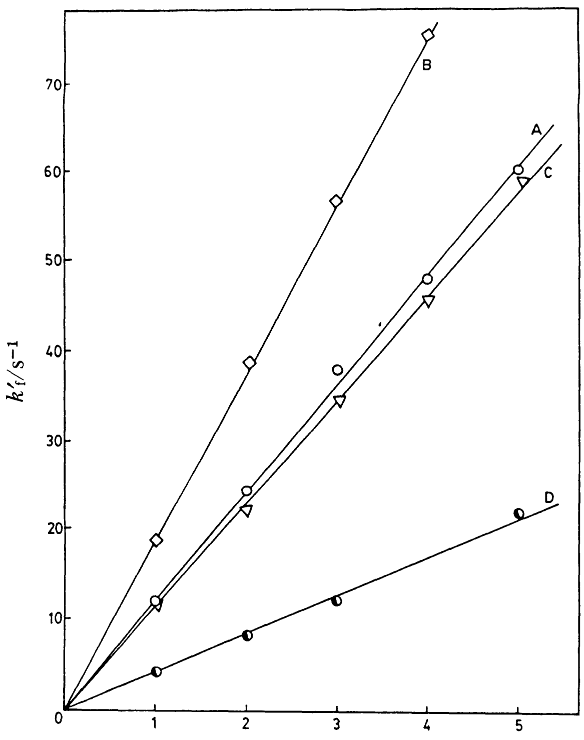
PMS over that of PDS has already been observed for the reactions of halide ions[17] and 2,2′-azinobis-(3-ethylbenzothiazole-6-sulfonate)[18] with these peroxides.

Among the phenothiazines investigated, chlorpromazine is found to be more reactive than promethazine. The rate constants measured for the formation of $CPZH^{\cdot 2+}$ and $PMZH^{\cdot 2+}$ by both the peroxides indicate that chlorpromazine reacts ca. 60—70 times faster than promethazine. This difference in reactivities is probably due to the difference in the redox potentials of the phenothiazines (E_{CPZ}=0.78 V and E_{PMZ}=0,86 V).[19]

Reactions of the Radical Cations. The reactions of the radical cations, $CPZH^{\cdot 2+}$ and $PMZH^{\cdot 2+}$ with reducing agents were performed using freshly prepared radical cations by the oxidation of $CPZH^+$ and $PMZH^+$ with stoichiometric amount of peroxomonosulfate. The radical cations were found to undergo one-electron reduction with ascorbic acid. The reaction of $CPZH^{\cdot 2+}$ with ascorbic acid was very fast and found to occur within the mixing time of the instrument (2 ms) even at a very low concentrations of the reactants ([ascorbic acid]=1×10^{-5} mol dm^{-3} and [$CPZH^{\cdot 2+}$]=1×10^{-6} mol dm^{-3}) and at low pH≤1. However the reactions of $PMZH^{\cdot 2+}$ with ascorbic acid ([ascorbic acid]=1.0—5.0×10^{-5} mol dm^{-3} and [$PMZH^{\cdot 2+}$]=1.0—5.0×10^{-6} mol dm^{-3}) was found to occur at convenient rates measurable by the stopped-flow technique. By pulse-radiolysis technique, Pelizzetti and coworkers[19] have reported the rate constant, k_2($CPZ^{\cdot 2+}$+ascorbic acid)=1.4×10^9 dm^3 mol^{-1}s^{-1} at pH 5.9. Even though it is expected that decrease of pH will decrease the reactivity of ascorbic acid (AH_2) due to the acid-base equilibrium,[20]

$$AH_2 \underset{pKa}{\overset{4.25}{\rightleftarrows}} AH^- + H^+ \tag{5}$$

it is found that even at pH 1, the reaction between ascorbic acid and $CPZH^{\cdot 2+}$ is immeasurably fast to be monitored by the stopped-flow technique. The kinetic investigation of the reaction of $PMZH^{\cdot 2+}$ with ascorbic acid exhibited an overall second-order reaction, first-order each with respect to [ascorbic acid] and [$PMZH^{\cdot 2+}$]. The linear plots of log (absorbance) vs. time and the almost constant slope for different initial [$PMZH^{\cdot 2+}$] indicate the first-order dependence of the rate on [$PMZH^{\cdot 2+}$]. The pseudo-first-order rate constants for the decay of the radical cation, k_d'/s^{-1} were calculated from the slopes of the above plots. Increase in the [ascorbic acid] increased the rate and the plot of k_d' vs. [ascorbic acid] is a straight line passing through the origin confirming the first-order dependence of the rate on [ascorbic acid]. The slope of the above plot gives the second-order decay rate constant, k_{2d}/dm^{3}mol^{-1}s^{-1}. The rate constants for the reaction of $CPZH^{\cdot 2+}$ with the other reducing agents, SO_3^{2-}, $S_2O_3^{2-}$, and $S_2O_4^{2-}$ were also determined (Fig. 3 and Table 2; [$CPZH^{\cdot 2+}$]=1.0—5.0×10^{-4} mol dm^{-3}; [SO_3^{2-}] or [$S_2O_3^{2-}$]=1.0—5.0×10^{-3} mol dm^{-3} and [$S_2O_4^{2-}$]=1.0—5.0×10^{-4} mol dm^{-3}). There was no detectable reaction between these reducing agents with $PMZH^{\cdot 2+}$.



[Reducing agent]
A and B, [RA]$\times10^3$/mol dm^{-3}; C, [RA]$\times10^4$/mol dm^{-3}; D, [RA]$\times10^5$/mol dm^{-3};

Fig. 3. Decay of $CPZH^{\cdot 2+}$ or $PMZH^{\cdot 2+}$: k_d' vs. [reducing agent] A : SO_3^{2-}; B : $S_2O_3^{2-}$; C : $S_2O_4^{2-}$; and D : AH_2.

Table 2. Rate Constants for the One-Electron Transfer Reactions of the Phenothiazine Radical Cations at Temp=25 °C

	Reducing agent	pH	k_{2d}/dm^3 mol^{-1} s^{-1}
$PMZH^{\cdot 2+}$	Ascorbic acid	2.2	4.1×10^5
		5.9	1.3×10^9 a)
$CPZH^{\cdot 2+}$	Ascorbic acid	1.0	$>10^6$
		5.9	1.4×10^9 a)
	SO_3^{2-}/HSO_3^-	6.0	1.2×10^4
	$S_2O_3^{2-}$	6.0	1.9×10^4
	$S_2O_4^{2-}$	6.0	1.2×10^5

a) Data from Ref. 19.

The mechanism of oxidation of ascorbic acid may be given as

$$PMZH^{\cdot 2+} + AH_2/AH^- \xrightarrow{\text{slow}} PMZH^+ + (AH^{\cdot} + H^+)/(A^{\cdot -} + H^+) \tag{6}$$

$$AH^{\cdot}/A^{\cdot -} \xrightarrow{\text{fast}} \text{product} \tag{7}$$

conforming to the rate law,

$$\text{Rate} = \frac{-d[PMZH^{\cdot 2+}]}{dt} = k_{2d}[PMZH^{\cdot 2+}][\text{reducing agent}].$$

From the magnitudes of the second-order rate constants for the above reaction at two different pH, 2.2 and 5.9, the reactivity of AH^- is found to be ca. 10^3 times higher than that of AH_2.

The proposed rate law and the mechanisms for the reactions of $CPZH^{\cdot 2+}$ with sulfite, thiosulfate and dithionite may be given as,

$$\text{Rate} = \frac{-d[CPZH^{\cdot 2+}]}{dt} = k_{2d}[CPZH^{\cdot 2+}][\text{reducing agent}].$$

$$CPZH^{\cdot 2+} + SO_3^{2-}/HSO_3^- \xrightarrow{\text{slow}} CPZH^+ + SO_3^{\cdot -}/SO_3^{\cdot -} + H^+ \quad (8)$$

$$2SO_3^{\cdot -} \xrightarrow{\text{fast}} S_2O_6^{2-} \quad (9)$$

$$CPZH^{\cdot 2+} + S_2O_n^{2-} \xrightarrow{\text{slow}} CPZH^+ + S_2O_n^{\cdot -} \quad (10)$$

$(n=3 \text{ and } 4)$

$$2S_2O_n^{\cdot -} \xrightarrow{\text{fast}} S_4O_6^{2-} + (n-3)O_2. \quad (11)$$

From the magnitudes of the second-order rate constants, the reactivity trend of the reducing agents is in the order, ascorbic acid>dithionite>thiosulfate>sulfite.

In conclusion, chlorpromazine and promethazine are oxidized to the stable radical cations, $CPZH^{\cdot 2+}$ and $PMZH^{\cdot 2+}$ by the inorganic peroxides, peroxomonosulfate and peroxodisulfate. Although these two radical cations individually oxidize ascorbic acid to revert back to the parent compounds, only $CPZH^{\cdot 2+}$ was found to react with the other reducing sulfur compounds, sulfite, thiosulfate, and dithionite.

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