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Kinetics and Mechanism of Oxidation of Promazine and Promethazine by Ferric Perchlorate

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Abstract □ The equilibrium constants, kinetics, and mechanism of promazine and promethazine oxidation by ferric perchlorate were investigated at different temperatures and acidities using a stopped-flow spectrophotometric technique. The overall reaction can be represented as follows:

$$\mathrm{Fe(III)} + \mathrm{P} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Fe(II)} + \mathrm{P}^{\cdot+}$$

where $\mathrm{P}^{\cdot+}$ represents the radical cation corresponding to the phenothiazine derivative. The equilibrium quotients were evaluated at 1.00 *M* $HClO_4$, 25.0°, and ionic strength 1.0 *M*. The kinetics of reaction follow the equation:

$$-\frac{d[\mathrm{P}]}{dt} = k_1[\mathrm{Fe}^{3+}][\mathrm{P}] - k_{-1}[\mathrm{Fe}^{2+}][\mathrm{P}^{\cdot+}]$$

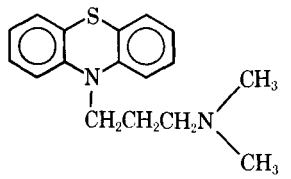
The rate constants k_1 and k_{-1} are independent of acidity and are related to the corresponding equilibrium quotients.

Keyphrases □ Promazine—kinetics and mechanism of oxidation by ferric perchlorate, various temperatures and pH values □ Promethazine—kinetics and mechanism of oxidation by ferric perchlorate, various temperatures and pH values □ Phenothiazines—promazine and promethazine, kinetics and mechanism of oxidation by ferric perchlorate, various temperatures and pH values □ Oxidation—kinetics and mechanism, promazine and promethazine by ferric perchlorate, various temperatures and pH values □ Ferric perchlorate—oxidation of promazine and promethazine, kinetics and mechanism, various temperatures and pH values

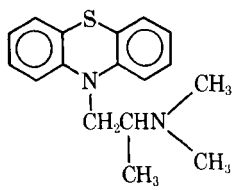
Free radicals of dialkylaminoalkylphenothiazine derivatives have been found in the urine of patients receiving phenothiazine drugs (1). Studies were carried out to elucidate both the role of such free radicals in biotransformation and structure–activity relationships.

Using electron spin resonance, Fenner (2, 3) noted the influence of the electron-donating and electron-withdrawing groups on the ring, as well as that of the side chain bonded to the nitrogen (in position 10), on radical formation. Investigation of the oxidation by inorganic agents also showed the large influence of the side chain (4, 5). In particular, the oxidation of the two isomers promazine[1] [10-(3-dimethylaminopropyl)phenothiazine] (I) and promethazine[2] [10-(2-dimethylaminopropyl)phenothiazine] (II), both with ammonium persulfate and ceric sulfate in aqueous solution at different pH values, gave different oxidation products (6, 7). Moreover, I and II show different pharmacodynamic properties; I is an antidepressant and II is an antihistaminic.

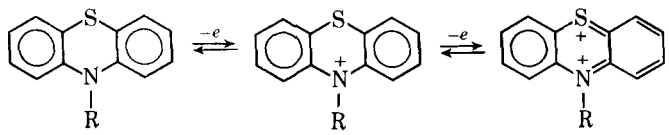
The differences in the behavior of these compounds toward oxidation suggested an investigation of the kinetics



I



II



III IV

Scheme I

and mechanism of the oxidation reaction; no data were available on the oxidation of these heteroaromatic nuclei in aqueous solution. The redox properties of the *N*-dialkylaminoalkylphenothiazine derivatives are characterized by two successive monoelectron steps (8); one step yields the free radical (III), and the other step yields the bivalent cation (IV) (Scheme I). This last species is unstable in water, giving rise to a sulfoxide (8).

The present work evaluates the equilibrium data and the kinetics and mechanism of oxidation of I and II to the first-step oxidation product, *i.e.*, the free radical (III). Ferric perchlorate was used as an oxidant; the formal reduction potential of the Fe(III)–Fe(II) couple does not allow I and II to be oxidized further to cation IV.

EXPERIMENTAL

Reagents—Compounds I[1] and II[2] were employed as chlorhydrates. Iron(III) perchlorate[3] was a reagent grade product. Iron(II) perchlorate was prepared by dissolution of pure iron[3] in perchloric acid. Perchloric acid[4] and lithium perchlorate[4] were used to bring the solutions to the proper acidity and ionic strength.

Procedure—Solutions of I and II were prepared daily and stored in the dark. Ferric perchlorate solutions were standardized by complexometric titration. The ferrous perchlorate content was determined with cerium(IV) sulfate titration. The spectra and equilibrium measurements were performed spectrophotometrically[5].

The kinetic runs were carried out with a stopped-flow spectrophotometer[6] at the wavelength of maximum absorption of free radicals (III) (path length of the cell was 2.00 cm).

The variations of transmittance as a function of time were stored on an oscilloscope screen[7] and photographed (Fig. 1).

RESULTS AND DISCUSSION

Spectrophotometric and Equilibrium Data—For I, the experiments

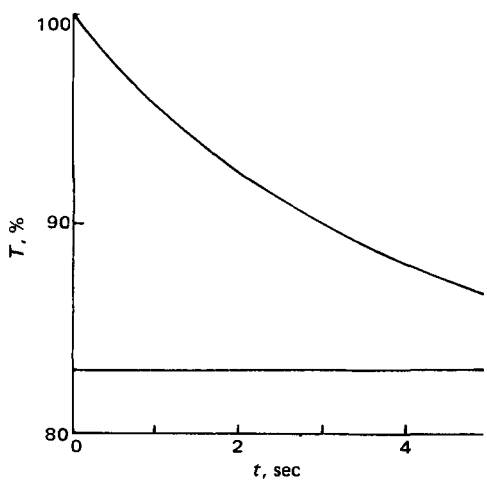


Figure 1—*Plot of transmittance as a function of time for a typical run [2 × 10⁻⁵ M I; 1 × 10⁻³ M Fe(ClO₄)₃; 2 × 10⁻⁴ M Fe(ClO₄)₂; 1.00 M HClO₄] at ionic strength 1.0 M and 25.0°.*

[1] Promazine, Rhône-Poulenc.
[2] Prometazine, Rhône-Poulenc.
[3] C. Erba reagent grade.
[4] Merck reagent grade.
[5] Perkin-Elmer EPS-3T spectrophotometer.
[6] Durrum-Gibson, Palo Alto, Calif.
[7] Tektronix 564.

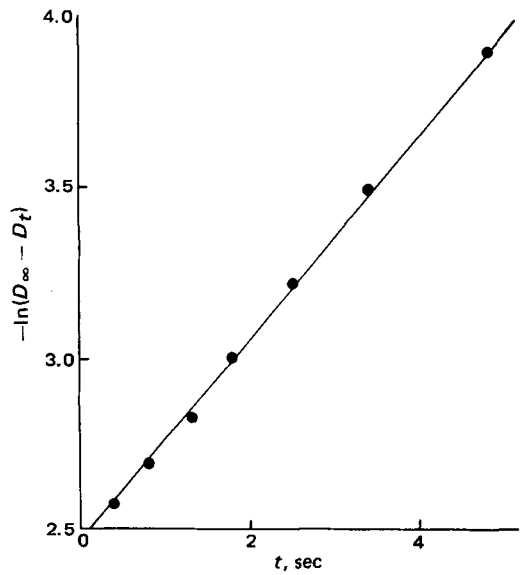


Figure 2—*Plot of ln* $(D_\infty - D_t)$ *versus time corresponding to the run of Fig. 1.*

were performed in solution with an excess of Fe(III) [4.0×10^{-5} *M* of I, $\geq 5.0 \times 10^{-5}$ *M* $Fe(ClO_4)_3$]. In the initial absence of Fe(II), the formation of a product with an absorbance maximum at λ 513 nm was observed; the absorbance did not increase further when $\geq 2 \times 10^{-4}$ *M* $Fe(ClO_4)_3$ was used. The molar absorptivity, ϵ_{513} $(1.00 \pm 0.05) \times 10^4$ M^{-1} cm^{-1}, was determined for this reaction product, which, according to literature data (8), is the radical cation (III).

The reaction can be depicted as follows:

$$Fe(III) + P \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} Fe(II) + P^{\cdot+}$$

Scheme II

where P represents the phenothiazine derivative and $P^{\cdot+}$ is the corresponding cation radical (III).

By running the experiments in different concentrations of ferric and ferrous perchlorate (at constant concentration of I), the equilibrium quotient corresponding to Scheme II was determined to be 1.4 ± 0.2 (1.00 *M* $HClO_4$ at 25.0° and ionic strength 1.0 *M*).

With II, the formation of a product with an absorbance maximum around 515 nm was observed. With a constant concentration of II, the absorbance increases by increasing the excess of ferric perchlorate (up to 1.0×10^{-2} *M*), thus suggesting that Scheme II has a low equilibrium quotient in this case. Then the molar absorptivity of the oxidation

Table I—Values of Pseudo-First-Order Rate Constants (k_{obs}, $seconds^{-1}$) for the Reaction of I (2.0×10^{-5} *M*) and Excess of Fe^{3+} at Different Experimental Conditions (at Ionic Strength 1.0 *M* and 1.00 *M* $HClO_4$, Except Where Stated)

$Fe(ClO_4)_3$, *mM*	$Fe(ClO_4)_2$, *mM*			
	0.50	1.00	1.50	2.00
		25.0°		
2.0	0.066	0.13_5[a] 0.14[b] 0.13[c] 0.13	0.19	0.24
4.0	0.084	0.16_5[a] 0.17[b] 0.16[c] 0.16	0.21	0.26_5
6.0	0.105	0.20[a] 0.19_5[b] 0.19[c] 0.18_5	0.23	0.27_5
8.0	0.125	0.22[a] 0.23[b] 0.22[c] 0.21_5	0.25_5	0.29_5
10.0	0.25	0.24_5[a] 0.24_5[b] 0.24[c] 0.25_5	0.27_5	0.31
		37.0°		
2.0	0.12	0.20	0.28	0.36_5
4.0	0.17	0.25_5	0.33	0.40
6.0	0.22_5	0.30_5	0.39_5	0.46
8.0	0.25	0.37_5	0.45_5	0.50
10.0	0.31	0.42_5	0.51	0.56
		10.0°		
2.0	0.042	0.073	0.093	0.12
4.0	0.048	0.081	0.10_5	0.13
6.0	0.055	0.091	0.11_5	0.13
8.0	0.063	0.103	0.13	0.15
10.0	0.068	0.11	0.14	0.16_5

[a] With 0.050 *M* $HClO_4$. [b] With 0.20 *M* $HClO_4$. [c] With 0.50 *M* $HClO_4$.

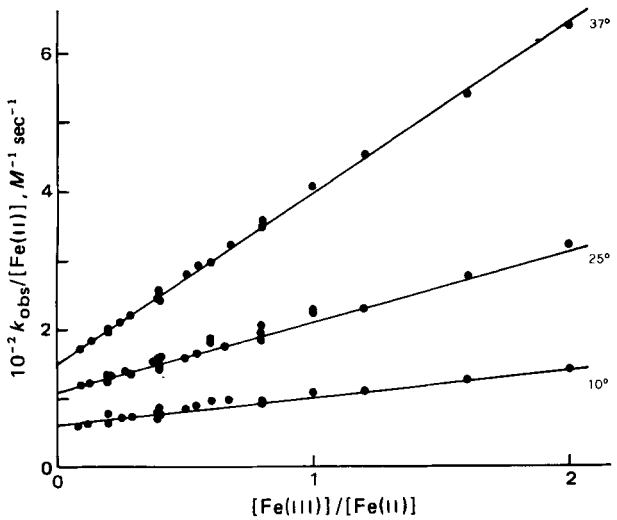


Figure 3—*Plots of* $k_{obs}/[Fe(II)]$ *as a function of* $[Fe(III)]/[Fe(II)]$ *for the reaction of I at different temperatures.*

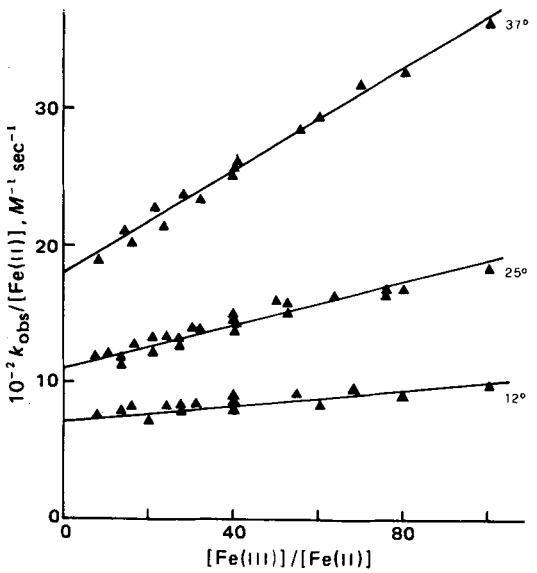


Figure 4—*Plots of* $k_{obs}/[Fe(II)]$ *as a function of* $[Fe(III)]/[Fe(II)]$ *for the reaction of II at different temperatures.*

product was evaluated by adopting an oxidizing agent with a higher formal redox potential, potassium hexachloroiridate(IV) (9) (E^0 0.96 v); ϵ_{515} (9.0 ± 0.7) × 10^3 M^{-1} cm^{-1} was obtained. By performing measurements at different concentrations of ferric and ferrous perchlorate, the equilibrium quotient of Scheme II for II was determined to be K_1 = (7.8 ± 1.3) × 10^{-3} (1.00 *M* $HClO_4$ at 25.0° and ionic strength 1.0 *M*).

Kinetics of Reaction—According to Scheme II, the kinetic law can be formulated as follows:

$$-\frac{d[P]}{dt} = \frac{d[P^{\cdot+}]}{dt} = k_1[P][Fe(III)] - k_{-1}[P^{\cdot+}][Fe(II)] \quad \text{(Eq. 1)}$$

In the presence of large excesses (>10-fold) of both ferric and ferrous perchlorate with respect to the organic substrate, it can be assumed that $k_1' = k_1[Fe(III)]$ and $k_{-1}' = k_{-1}[Fe(II)]$. Hence:

$$\frac{d[P^{\cdot+}]}{dt} = k_1'[P] - k_{-1}'[P^{\cdot+}] \quad \text{(Eq. 2)}$$

By substituting $[P]_0 = [P] + [P^{\cdot+}]$ and $[P^{\cdot+}]_0 = 0$ and integrating, it follows that:

$$\ln \frac{k_1'[P]_0}{k_1'([P]_0 - [P^{\cdot+}]) - k_{-1}'[P^{\cdot+}]} = (k_1' + k_{-1}')t \quad \text{(Eq. 3)}$$

Because $[P^{\cdot+}]_\infty/[P]_0 = k_1'/(k_1' + k_{-1}')$, where $[P^{\cdot+}]_\infty$ represents the radical concentration at equilibrium, it follows that:

$$\ln \frac{[P^{\cdot+}]_\infty}{[P^{\cdot+}]_\infty - [P^{\cdot+}]} = (k_1' + k_{-1}')t \quad \text{(Eq. 4)}$$

Table II—Values of Pseudo-First-Order Rate Constants (k_{obs}, seconds^{-1}) for Reaction of II (2.0 × 10^{-5} *M*) and Excess of Fe^{3+} at Different Experimental Conditions (Ionic Strength 1.0 *M* and 1.00 *M* $HClO_4$ Except Where Stated)

$Fe(ClO_4)_3$, *mM*	$Fe(ClO_4)_2$, m*M*			
	0.10	0.15	0.20	0.25
		25.0°		
2.0	0.118	0.18[a]	0.17_5	0.24	0.30
4.0	0.132	0.19_5[a]	0.18	0.26_5	0.32
6.0	0.15_5	0.20_5[a]	0.21	0.27_5	0.33
8.0	0.16_5	0.23_5[a]	0.23	0.31	0.34_5
10.0	0.18_5	0.24_5[a]	0.25	0.32_5	0.36
		37.0°		
2.0	0.23	0.32			0.47
4.0	0.26_5	0.36			0.49
6.0	0.29	0.38_5			0.53
8.0	0.31_5	0.42			0.57
10.0	0.35_5	0.47			0.63_5
		12.0°		
2.0	0.072	0.115			0.18_5
4.0	0.078	0.12			0.20
6.0	0.084	0.13			0.20_5
8.0	0.091	0.13_5			0.21
10.0	0.098	0.14			0.21_5

[a] With 0.50 *M* $HClO_4$.

Then the slopes of plots $\ln(D_\infty - D_t)$ (where D_∞ and D_t represent the absorbances for $P^{\cdot+}$ at equilibrium and at time t, respectively) as a function of time allow estimation of the observed rate constants (Fig. 2), given by the expression:

$$k_{obs} = k_1[Fe(III)] + k_{-1}[Fe(II)] \quad \text{(Eq. 5)}$$

The kinetic runs were carried out in the presence of excesses of both ferric perchlorate (2.0–10.0 × 10^{-4} *M* for I and 2.0–10.0 × 10^{-3} *M* for II) and ferrous perchlorate (0.50–2.0 × 10^{-3} *M* for I and 1.0–2.5 × 10^{-4} *M* for II) with respect to the phenothiazine derivatives (2.0 × 10^{-5} *M*). Measurements were performed at different acidities (0.050–1.00 *M* $HClO_4$) with a constant ionic strength (1.0 *M* $LiClO_4$) and at different temperatures (10.0, 25.0, and 37.0°). The rate constants were evaluated by means of the least-squares method, and the standard deviation of the single measurement ranged between 2 and 4% of the mean (Tables I and II).

According to Eq. 5, a plot of $k_{obs}/[Fe(II)]$ as a function of $[Fe(III)]/[Fe(II)]$ gives the value of k_{-1} from the intercept and of k_1 from the slope. Such plots are shown in Figs. 3 and 4 for I and II, respectively; the corresponding values of k_1, k_{-1}, and K_1 are listed in Table III along with the related thermodynamic activation parameters.

The equilibrium quotients from the kinetic data agree satisfactorily with the ones evaluated by spectrophotometric data. Such values allow one to estimate, from the E^0 value of the Fe(III)/Fe(II) couple in 1.0 *M* $HClO_4$ at 25.0° (0.738 v) (10), the formal reduction potentials of the couples $P^{\cdot+}/P$. The calculated values, 0.74 v for I and 0.865 v for II, correspond rather well with the half-wave potentials ($E_{1/2}$) determined by a polarographic technique (11).

Table III—Specific Rate Constants (M^{-1}/sec^{-1}) for the Reaction of I and II with Fe^{3+} (1.00 *M* $HClO_4$ and Ionic Strength 1.0 *M*) at Different Temperatures

	k_1	k_{-1}	K_1
		I	
10.0°	40 ± 2	61 ± 3	0.66
25.0°	(1.0 ± 0.05) × 10^2	(1.1 ± 0.05) × 10^2	0.91
37.0°	(2.5 ± 0.1) × 10^2	(1.5 ± 0.1) × 10^2	1.7
$\Delta H^{\neq}$, kcal mole^{-1}	11.2 ± 0.8	5.3 ± 0.9	
$\Delta S^{\neq}$, cal deg^{-1} mole^{-1}	−12 ± 3	−32 ± 3	
		II	
12.0°	3.2 ± 0.2	(7.1 ± 0.4) × 10^2	4.5 × 10^{-3}
25.0°	8.3 ± 0.4	(1.1 ± 0.1) × 10^3	7.5 × 10^{-3}
37.0°	19.0 ± 1.0	(1.8 ± 0.1) × 10^3	1.1 × 10^{-2}
$\Delta H^{\neq}$, kcal mole^{-1}	12.0 ± 1.0	6.0 ± 1.2	
$\Delta S^{\neq}$, cal deg^{-1} mole^{-1}	−14 ± 3	−25 ± 4	

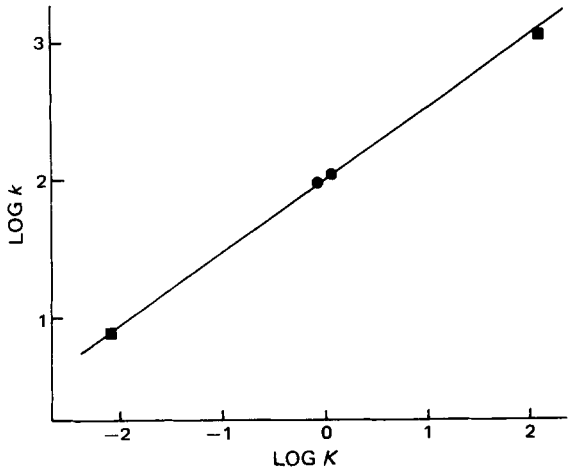


Figure 5—*Plot of log* k *against log* K *for the reactions corresponding to Scheme II for I (●) and II (■) at ionic strength 1.0* M *and 25.0°.*

Table III shows that the enthalpies of activation are higher for the forward reaction (involving Fe^{3+} and phenothiazines) than for the reverse reaction (involving Fe^{2+} and cation radicals); such low values for reactions involving radicals were found in other cases (12).

The reaction rates are independent of the acidity; it can be suggested that the reactive species, in the present conditions, is Fe^{3+}_{aq}. But in several other reactions involving Fe(III), *e.g.*, complexation (13) and redox (14), the reactive species is $FeOH^{2+}_{aq}$, which derives from the hydrolytic equilibrium:

$$Fe^{3+}_{aq} \rightleftarrows FeOH^{2+}_{aq} + H^+$$

Scheme III

with $K_7 = 1.63 \times 10^{-3}$ *M* (15). It follows that, in the present acidity range, the predominant species is Fe^{3+}_{aq}. This behavior can be ascribed to a mechanism involving a simple electron transfer rather than a hydrogen atom transfer, probably operating when $FeOH^{2+}_{aq}$ is the active species (16).

When the mechanism of the redox reaction is an electron transfer, a relationship between the free energy of activation and the overall free energy of reaction should hold. According to the Marcus (17) theory, a plot of log *k versus* log *K* is linear with a slope of about 0.50. Figure 5 shows that this expectation is satisfied in the present reactions. Such relationships have been found to be applicable in the redox reactions involving some relevant biological systems, such as cytochrome c, some catecholamines, and ascorbic acid (18).

The present findings suggest the possibility of correlating the oxidation rates of phenothiazines with thermodynamic and structural data of these systems.

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Alkaloids of *Strychnos dolichothyrsa* Gilg ex Onochie et Hepper

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Abstract □ Three alkaloids of the stem bark of *Strychnos dolichothyrsa* Gilg ex Onochie et Hepper (Loganiaceae) were isolated and identified as caracurine V and its mono- and di-*N*-oxide by comparison with synthesized compounds. ^{13}C-NMR was used to confirm the structure of the *N*-oxides. The muscle relaxant activity and the toxicity of the *N*-oxides were less than those of caracurine V.

Keyphrases □ *Strychnos dolichothyrsa*—stem bark alkaloids isolated and identified, muscle relaxant activity evaluated □ Alkaloids—from stem bark of *Strychnos dolichothyrsa* isolated and identified, muscle relaxant activity evaluated □ Caracurine V and *N*-oxides—isolated from stem bark of *Strychnos dolichothyrsa*, muscle relaxant activity evaluated □ Relaxant activity, muscle—alkaloids isolated from stem bark of *Strychnos dolichothyrsa* evaluated

Extracts of the stem bark of *Strychnos dolichothyrsa* Gilg ex Onochie et Hepper showed a strong muscle relaxant effect in pharmacological screenings (1, 2), especially in the tertiary alkaloid fractions. The isolation and identification of bisnordihydrotoxiferine, one main alkaloid of this species, and some minor alkaloids derived from