

Free Radical Induced One-electron Oxidation of the Phenothiazines Chlorpromazine and Promethazine

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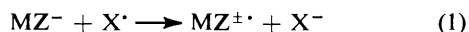
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Absolute rate constants have been measured for the reactions of the protonated forms of chlorpromazine and promethazine, CZH⁺ and PZH⁺, with the electrophilic radicals ·OH, Br₂^{·-}, (SCN)₂^{·-}, I₂^{·-}, N₃[·], TI²⁺, TI(OH)⁺, (t-C₄H₉S t-C₄H₉)^{·+}, (CH₃SSCH₃)^{·+}, and lipoate^{·+} in the pH range 2–8. Values for these one-electron oxidations vary from $k = 3.1 \times 10^8 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ for [(t-C₄H₉S t-C₄H₉)^{·+} + PZH⁺] to $5.5 \times 10^9 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ for (Br₂^{·-} + CZH⁺). The yields of the oxidation products, PTZH²⁺, vary from 28% for (·OH + CZH⁺) to 97% for [(SCN)₂^{·-} + CZH⁺]. The PTZH²⁺ radical cations exhibit characteristic absorption spectra with two maxima around 270 and 510 nm, and extinction coefficients of $\epsilon(\text{CZH}^{2+}) = 56\,000 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$ at 270 nm and $12\,000 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$ at 510 nm, and $\epsilon(\text{PZH}^{2+}) = 62\,500 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$ at 265 nm and $9\,500 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$ at 505 nm. A transient absorption around 350 nm observed in the reaction of the phenothiazines with hydroxyl radicals is most probably the ·OH-adduct, PTZH(OH)⁺. The mechanism of the ·OH-radical-induced oxidation of phenothiazines suggested in an earlier publication has been confirmed and enlarged.

Phenothiazine drugs have long been used for treatment of psychiatric diseases.^{1–4} 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 biochemical action.^{5–12}

Phenothiazine radical cations can readily be generated in aqueous as well as non-aqueous media by photo- and radiation-chemical methods.^{13–26} In a recent paper,¹³ for example, we reported how the anionic conjugate base of metiazinic acid, MZ⁻, can be oxidized in aqueous solution by a variety of electrophilic free radicals (X[·]) according to the general equation (1).

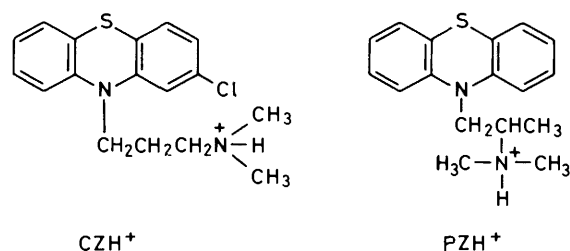


The zwitterionic radical formed by one-electron transfer exhibits a strong and characteristic optical absorption $\lambda_{\text{max.}} = 270$ and 530 nm that can easily be detected and studied by time-resolved pulse radiolysis experiments. We have now extended these studies to two other phenothiazines, namely chlorpromazine (CZH⁺) and promethazine (PZH⁺). All these studies have been undertaken in aqueous solution. For solubility reasons, studies with metiazinic acid were limited to solutions of $\text{pH} > 8$ where the carboxy group is ionized.¹³ For similar reasons the present studies have been limited to solutions of $\text{pH} < 8$ where the side-chain nitrogen atom of both compounds is protonated ($\text{p}K_a = 9.3$ ²⁷).

The present study is particularly concerned with the measurement of absolute rate constants for the oxidation of CZH⁺ and PZH⁺ by various oxidizing radicals. Some mechanistic aspects in connection with the ·OH-radical-induced processes are also considered.

Experimental

The pulse radiolysis experiments were performed using high-energy electrons from 1.6 and 3.8 MeV Van de Graaff accelerators at the Hahn-Meitner-Institute, Berlin. Pulse lengths were 0.5–5 μs and 5–50 ns for the two machines, respectively. The associated equipment and the analysis of data from time-resolved optical and conductivity measurements have been described.^{28–32} Dosimetry was based on the



reduction of tetranitromethane ($10^{-3} \text{ mol dm}^{-3}$) in deoxygenated aqueous solutions containing propan-2-ol ($2 \times 10^{-1} \text{ mol dm}^{-3}$).³³ Doses were generally in the range of 1–10 J kg^{-1} ($1 \text{ J kg}^{-1} = 1 \text{ Gy} = 100 \text{ rad}$).

Changes in absorption and conductance in the pulse-irradiated solutions were quantified in terms of $\Sigma \Gamma_i \epsilon_i$ and $\Sigma \Gamma_i l_i$, respectively, where Γ_i is the number of μmoles of a particular species i formed or destroyed per J of absorbed radiation energy in the solution, ϵ_i is the molar extinction coefficient in $\text{mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$, and l_i the equivalent conductance in $\Omega^{-1} \text{ cm}^2$ of species i .

All transient optical absorption spectra have been corrected for the loss of phenothiazine ground-state absorption as a result of the reaction of these compounds with the radiation chemically generated radicals. The ground-state absorptions have been measured with a Variscan spectrophotometer with $5 \times 10^{-5} \text{ mol dm}^{-3}$ phenothiazine solutions ($\text{pH} 3.5$) in a 10 mm quartz cell. For CZH⁺ and PZH⁺ absorption maxima at 305 and 310 nm, with $\epsilon = 4\,500$ and $3\,700 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$, respectively, were determined.

The compounds chlorpromazine hydrochloride (Largactil), and promethazine hydrochloride (Phenergan) were supplied by May and Baker Ltd. All other chemicals were of AnalaR grade and used without further purification. Solutions were prepared according to the general radiation chemical standards with Millipore-system purified water. The pH of the solution was generally adjusted by addition of NaOH or HClO₄. Deoxygenation of the solutions was achieved by bubbling the solutions with N₂.

Since both primary radicals of interest, namely the oxidizing ·OH radical and the reducing hydrated electron, e⁻_{aq}, are

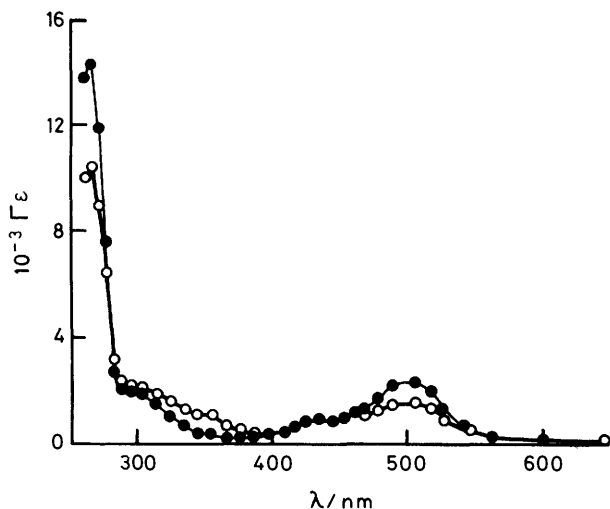


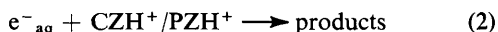
Figure 1. Optical absorption spectra taken 1 μs (○) and 100 μs (●) after a 2 μs pulse (5 J kg^{-1}) on an N_2O -saturated solution of promethazine ($1 \times 10^{-4} \text{ mol dm}^{-3}$, pH 4.5)

formed with about equal yield (Γ ca. $0.3 \mu\text{mol J}^{-1}$) in the irradiation of the aqueous system either *t*-butyl alcohol or N_2O were added to the solution to facilitate the study of the respective radical reactions. Solute concentrations were chosen so that in the presence of *t*-butyl alcohol $\cdot\text{OH}$ radicals reacted according to $\cdot\text{OH} + (\text{CH}_3)_3\text{COH} \rightarrow \text{H}_2\text{O} + \dot{\text{C}}\text{H}_2(\text{CH}_3)_2\text{COH}$,^{34,35} while in N_2O -saturated solutions the hydrated electrons reacted according to $\text{N}_2\text{O} + \text{e}^-_{\text{aq}} \rightarrow \text{N}_2 + \text{OH}^- + \cdot\text{OH}$ to yield additional $\cdot\text{OH}$ radicals.³⁶

For convenience and higher accuracy the evaluation of the pulse data was undertaken using a computer-assisted sampling and analysis program (PDP 11/40³²). All experiments have been carried out at room temperature.

Results and Discussion

Reduction by e^-_{aq} .—As a necessary preliminary to the study of the one-electron oxidation reactions, the reduction of the two phenothiazines chlorpromazine and promethazine, by hydrated electrons [reaction (2)] was studied. Neutral,



N_2 -saturated aqueous solutions containing $10^{-1} \text{ mol dm}^{-3}$ *t*-butyl alcohol and various concentrations [$(0.5\text{--}5) \times 10^{-4} \text{ mol dm}^{-3}$] of the respective drugs were pulse irradiated. With both compounds the characteristic optical absorption of the hydrated electron ($\lambda_{\text{max}} = 720 \text{ nm}$) was seen to decay exponentially with the half-lives inversely proportional to the phenothiazine concentrations. Bimolecular rate constants $k_2 = 1.2 \times 10^{10}$ and $5.6 \times 10^9 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ for CZH^+ and PZH^+ , respectively, were obtained indicating that these processes are essentially diffusion controlled. In an additional experiment with neutral, N_2O -saturated aqueous solutions of the phenothiazines ($10^{-4} \text{ mol dm}^{-3}$) containing $10^{-1} \text{ mol dm}^{-3}$ *t*-butyl alcohol it was shown that *t*-butyl alcohol radicals do not interfere in these experiments, *i.e.* $k < 10^6 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ (no bleaching of the parent compound is observed on the milli-second time-scale).

A mechanistic study on the formation of the reaction products from the reaction of e^-_{aq} with chlorpromazine has already been published²² and no further studies into the one-electron reduction of these drugs were undertaken.

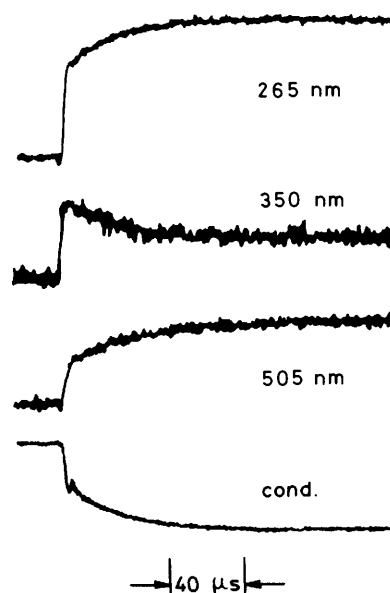


Figure 2. Optical and conductivity *versus* time signals observed after a 2 μs pulse (5 J kg^{-1}) on an N_2O -saturated solution of promethazine ($1 \times 10^{-4} \text{ mol dm}^{-3}$, pH 4)

Reaction with $\cdot\text{OH}$ Radicals.—The reaction of CZH^+ and PZH^+ with the strongly oxidizing hydroxyl radical $\cdot\text{OH}$ was studied by pulse irradiating N_2O -saturated solutions of the two drugs. The results obtained are qualitatively similar to those already reported for metiazinic acid with the similar formation of a strongly optically absorbing species.¹³ The example shown (Figure 1) is for an N_2O -saturated solution of $10^{-4} \text{ mol dm}^{-3}$ promethazine at pH 4.5. The optical absorption spectrum recorded immediately after the 2 μs pulse (open circles) exhibits a strong u.v. band (λ_{max} , 265 nm) and a comparatively weaker visible band (λ_{max} , 505 nm). Small shoulders are also apparent at around 350 and 450 nm. This spectrum like all others in these studies has been corrected for the loss of ground-state absorption of the phenothiazine, assuming a quantitative phenothiazine + radical reaction. The spectrum recorded 100 μs after the pulse looks qualitatively similar (full circles) but with the absorption at 265 and 505 nm increased and in the 300–350 nm range decreased. The corresponding kinetics are illustrated in Figure 2. Both at 265 and at 505 nm an initial fast step is followed by a relatively slow and exponential second increase, which is completed after ca. 100 μs . At 350 nm a fast initial increase in absorption is also observed. However, this is now followed by an exponential decrease the kinetics of which correspond to the slow increase at the other two wavelengths. The associated time-resolved conductivity picture (bottom curve of Figure 2) is almost a mirror image of the optical curves at 265 and 505 nm, *i.e.* the change in conductivity occurs also in two steps. The fact that it decreases in these acid solutions is indicative of the consumption of highly conducting free protons and their substitution by less conducting cationic species. The results shown in Figures 1 and 2 clearly imply that (a) the 265 and 505 nm bands are due to a species of higher positive charge than the parent promethazine, (b) the decay of the 350 nm species leads to an additional yield of the 265/505 nm species, and (c) the formation of the 350 nm species is not associated with a change in charge.

Essentially similar results were obtained for the $\cdot\text{OH}$ -radical-induced oxidation of chlorpromazine and for the corresponding previous study with metiazinic acid.¹³ In accordance

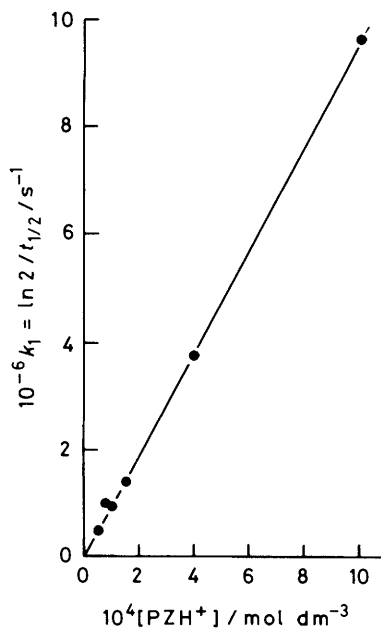


Figure 3. Plot of first-order rate constant k_1 obtained from the initial increase in absorption at 505 nm against promethazine concentration in N_2O -saturated solutions at pH 3.5

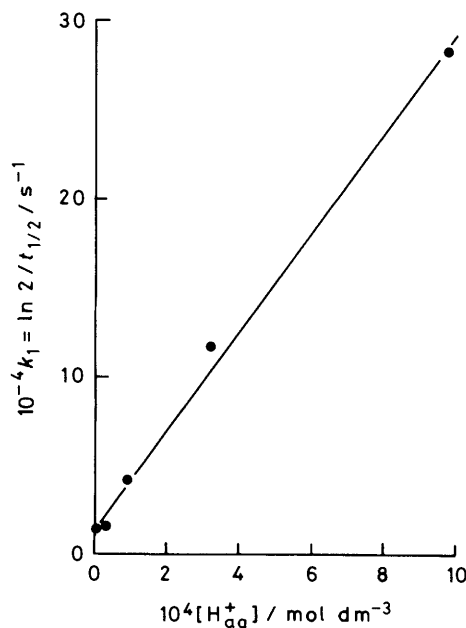
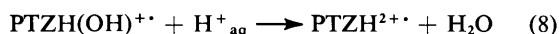


Figure 4. Plot of the first-order rate constant k_1 against proton concentration for the decay in absorption at 350 nm observed in N_2O -saturated solutions of $5 \times 10^{-5} \text{ mol dm}^{-3}$ promethazine

tions also being present and the limited concentration range. The data derived from the visible band and the corresponding data for chlorpromazine are listed in Table 1.

The second slow processes shown in Figure 2, *i.e.* the build-up of absorption at 265 and 505 nm, the decay of absorption at 350 nm, and the decay of the conductivity also occur exponentially. However, the rates of change are not dependent on the promethazine concentration. They do become increasingly fast, however, with decreasing pH. For example, a plot of the measured first-order rate constant $k = \ln 2 / t_{\frac{1}{2}}$ versus $[\text{H}^+_{\text{aq}}]$ for the 350 nm data is shown in Figure 4. Similar plots were also derived using data obtained at the other wavelengths and from the conductivity changes. The intercepts on the ordinate axis of the linear plots observed in all instances imply that the secondary radical cation formation from the $\cdot\text{OH}$ adduct (or possibly but less likely a hydrogen atom abstraction product) proceeds not only by a proton-assisted second-order process (8) but also a first-order,

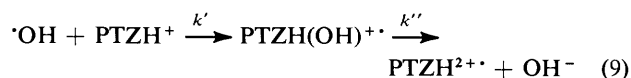


probably H_2O -assisted, process as formulated in equation (6). The respective rate constants, derived for the promethazine system from the slope and the intercept of such straight lines, are $k_8 = 2.8 \times 10^8 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ and $k_6 = 1.7 \times 10^4 \text{ s}^{-1}$, respectively.

Similar values for chlorpromazine are also listed in Table 1. It is interesting to note that both values of k_6 are about one order of magnitude lower than for the corresponding ionization of the $\cdot\text{OH}$ adduct of metiazinic acid ($k_6 = 1.3 \times 10^5 \text{ s}^{-1}$).¹³ This is possibly explained by the fact that both the $\text{CZH}^{2+\cdot}$ and $\text{PZH}^{2+\cdot}$ radical cations have to accommodate two positive charges in the same species while the one-electron oxidation product of metiazinic acid is a zwitterion, $\text{MZ}^{z\cdot}$, in the pH range of investigation. A corresponding comparison of the k_8 values is not possible, since metiazinic acid could only be studied in basic solutions.

On the basis of all the above information a quantitative understanding of the yield and formation kinetics of the

absorption at 350 nm is now possible. Taking the consecutive reaction scheme (9) the maximum concentration of the intermediate $\cdot\text{OH}$ adduct is given by equation (10)⁴¹ and this



$$[\text{PTZH}(\text{OH})^{+\cdot}]_{\text{max.}} = [\cdot\text{OH}]_0 \left(\frac{k'}{k''} \right)^{k''/k' - k'} \quad (10)$$

$$t_{\text{max.}} = \left(\frac{1}{k'' - k'} \right) \ln \frac{k''}{k'} \quad (11)$$

occurs at a time given by (11) where $[\cdot\text{OH}]_0$ is the total concentration of $\cdot\text{OH}$ radicals that add to the phenothiazine to yield $\text{PTZH}(\text{OH})^{+\cdot}$, and k' and k'' are the first-order rate constants, with $k' = k(\cdot\text{OH} + \text{PTZH}^+)[\text{PTZH}^+]$ and $k'' = k_6 + k_8[\text{H}^+_{\text{aq}}]$.

The calculated curves for $[\text{PTZH}(\text{OH})^{+\cdot}]$ (given in terms of $t_{\text{max.}}$ and $\Gamma\epsilon$ and normalized to the yield at high PTZH^+ concentration, *i.e.* where $k' \gg k''$) both as a function of PTZH^+ concentration are given as the solid lines in Figure 5a and b, respectively. The excellent fit of the experimental points to these curves is taken as further strong support for our assumed reaction mechanism. This complex kinetic behaviour is also reflected in the dependence of the absorption yield at 350 nm (again in terms of $\Gamma\epsilon$) on the phenothiazine concentration. This is seen to increase over the concentration range of 10^{-5} – $10^{-3} \text{ mol dm}^{-3}$ whereas the yield at 510 nm is practically independent of the phenothiazine concentration (Figure 5a).

Reaction with Other Oxidizing Radicals and Radical Ions.— Both phenothiazines are also oxidized by a large number of other oxidizing radicals and radical ions by the general reaction (12). The oxidizing species X^{\cdot} itself usually results



Table 2. Rate constants and yields of PTZH²⁺ radical cations (expressed as percentage relative to the yield of the oxidant)

PTZH ⁺	Oxidizing agent X [*]	Salt concentration (mol dm ⁻³)	pH	$k(X^+ + PTZH^+)$ (k_{15})/ mol ⁻¹ dm ³ s ⁻¹	PTZH ²⁺ formation (%)	$k_{\text{electron transfer}}$ (k_{12})/ mol ⁻¹ cm ³ s ⁻¹
Chlorpromazine	Br ₂ ^{-•}	0.1 (KBr)	3.5	5.3×10^9	83	4.4×10^9
		0.02 (KBr)	3.5	6.5×10^9	85	5.5×10^9
		0	3.5	7.7×10^9 ^a		
	(SCN) ₂ ^{-•}	0.1 (KSCN)	3.5	3.6×10^9	97	3.5×10^9
	N ₃ [•]	0.01 (NaN ₃)	7.5	4.6×10^9	47	2.2×10^9
	Tl ²⁺	0.003 (Tl ₂ SO ₄)	2.0	1.5×10^9	86 ^b	1.3×10^9
	Tl(OH) ⁺	0.003 (Tl ₂ SO ₄)	6.5	1.6×10^9	59 ^b	0.9×10^9
	I ₂ ^{-•}	0.1 (KI)	3.5	2.0×10^9	58	1.2×10^9
	(t-C ₄ H ₉) ₂ S ^{•+}	0.1 (KBr)	3.5	1.2×10^9	57	0.7×10^9
	(CH ₃ SSCH ₃) ^{•+}	0.1 (KBr)	3.5	3.5×10^9	56	2.0×10^9
Lipoate ^{•+}	0.02 (KBr)	3.5	2.7×10^9	66	1.8×10^9	
Promethazine	Br ₂ ^{-•}	0.1 (KBr)	3.5	4.0×10^9	78	3.1×10^9
		0.02 (KBr)	3.5	5.1×10^9	80	4.1×10^9
		0	3.5	6.2×10^9 ^a		
	(SCN) ₂ ^{-•}	0.1 (KSCN)	3.5	1.9×10^9	64	1.2×10^9
	N ₃ [•]	0.01 (NaN ₃)	7.5	4.6×10^9	66	2.9×10^9
	Tl ²⁺	0.003 (Tl ₂ SO ₄)	2.5	1.2×10^9	93 ^b	1.1×10^9
	I ₂ ^{-•} ^c		3.5	6.6×10^8		
	(t-C ₄ H ₉) ₂ S ^{•+}	0.1 (KBr)	3.5	5.4×10^8	57	3.1×10^8
	(CH ₃ SSCH ₃) ^{•+}	0.1 (KBr)	3.5	3.2×10^9	71	2.3×10^9
	Lipoate ^{•+}	0.02 (KBr)	3.5	1.8×10^9	70	1.3×10^9

^a Extrapolated value, see text. ^b Corrected for the reduction of the yield of Tl²⁺ or Tl(OH)⁺ owing to (Tl⁺ + e⁻_{aq} and H⁺_{aq} + e⁻_{aq}).⁴³ ^c See ref. 44 (consecutive paper). I₂^{-•} establishes equilibrium with PZH²⁺.

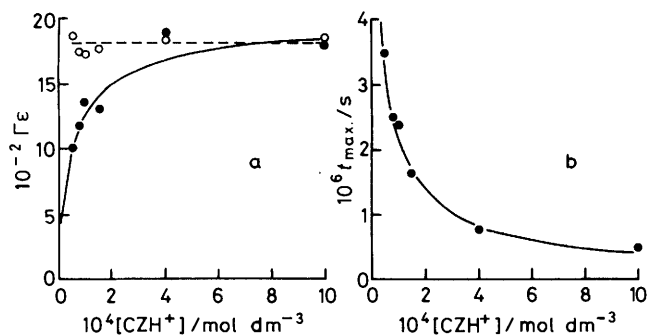


Figure 5. Primary processes observed in N₂O-saturated solutions of chlorpromazine (pH 3) after a 5 ns pulse (7 J kg⁻¹). a, Maximum yield $\Gamma\epsilon$ at 510 nm (○) and 350 nm (●) taken after completion of the primary build-up as a function of CZH⁺ concentration; b, time t_{max} at which the absorption maximum at 350 nm was reached as a function of CZH⁺ concentration. The solid lines represent the calculated curves (see text)

from an [•]OH or Br₂^{-•} reaction with X⁻. In order to study reaction (12), the concentration of X⁻ is therefore kept high compared with the phenothiazine concentration. An example is illustrated in Figure 6, which shows two absorption-time traces at 360 and 505 nm and the absorption spectra taken immediately and 200 μs after a 2 μs pulse given to an N₂O-saturated, pH 3.5 solution of 10⁻¹ mol dm⁻³ Br⁻ and 10⁻⁴ mol dm⁻³ promethazine. The initial spectrum (open circles) refers to the Br₂^{-•} radical anion, which is formed in the reaction sequence (13).⁴²

The electron transfer process (14) then leads to the form-

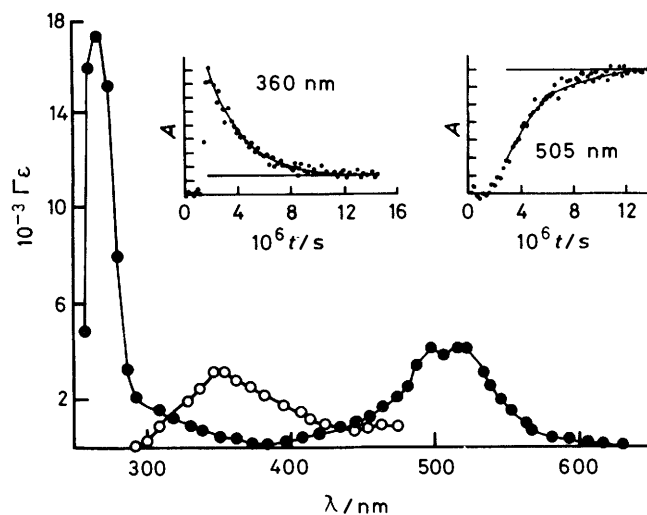
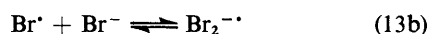
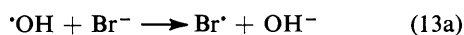
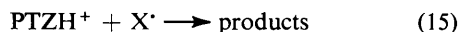


Figure 6. Optical absorption spectra taken 1 μs (○) and 100 μs (●) after a 2 μs pulse (5 J kg⁻¹) on an N₂O-saturated solution containing 1 × 10⁻⁴ mol dm⁻³ PZH⁺ and 0.1 mol dm⁻³ KBr at pH 3.5. Inserts: Optical traces at 360 and 505 nm with the first-order kinetic fits

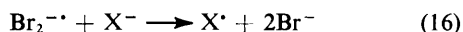
ation of the PZH²⁺ spectrum (full circles). Interestingly, in comparison with the initial spectrum of the [•]OH-radical-induced reaction shown in Figure 1 no intermediate addition product is apparent.

The yield of PZH²⁺ formed by reaction (14), derived using the extinction coefficient of PZH²⁺ (see Table 1), amounts to 78% of the initial [•]OH radical yield. The bimolecular rate constant of 4.0×10^9 mol⁻¹ dm³ s⁻¹ can be derived for the overall reaction of Br₂^{-•} with PZH⁺ from both the decay of the Br₂^{-•} absorption at 360 nm or the PZH²⁺ formation at 505 or 265 nm. All three curves are exponential with half-lives inversely proportional to the PZH⁺ concentration. Table 2

summarizes all rate constants for the overall reaction (15)



obtained for the reaction of promethazine and chlorpromazine with the various oxidizing radicals. In the reaction of $\text{I}_2^{\cdot-}$ with promethazine, equilibrium conditions have been observed, and this reaction will be dealt with in detail in the following paper.⁴⁴ The percentages of electron transfer from the PTZH^{2+} absorptions after completion of reaction (14) are also listed in Table 2. For solutions containing $(t\text{-C}_4\text{H}_9)_2\text{S}$, CH_3SSCH_3 , and lipoate (X^-) the oxidizing sulphur-centred radical cations (X^{\cdot}) have not been produced through reaction of these compounds with $\cdot\text{OH}$ radicals but *via* reaction (13) followed by (16).



These reactions (16) occur with near 100% efficiency^{13,45} while the corresponding reactions (17) do not.⁴⁶



The bimolecular rate constants k_{14} for the actual electron transfer processes are also included in Table 2. They have been calculated by multiplying the overall rate constants k_{15} with the fraction of X^{\cdot} that undergoes electron transfer to form the radical cation.

It should be finally mentioned that all rate constants listed in this paper refer to the actual ionic strength conditions of the individual experiments. For the particular oxidation of promethazine and chlorpromazine by $\text{Br}_2^{\cdot-}$, measurements have

also been made with solutions of different ionic strength, which allowed the extrapolation of the rate constants at zero ionic strength. The latter are also listed in Table 2.

In summary the various electron transfer reactions are seen to proceed with rate constants that are within or close to the limits set by the diffusion of the reactants. Oxidation of promethazine occurs on average slightly slower than oxidation of chlorpromazine, which would be in agreement with the higher oxidation potential of the $\text{PZH}^{2+}/\text{PZH}^+$ compared with the $\text{CZH}^{2+}/\text{CZH}^+$ system.⁴⁴ The high rate constants for all processes also indicate that the varying electron transfer yields find their explanation in competing reactions that occur with similar rate constants. Our experiments, however, do not allow us to evaluate the specific nature of these reaction pathways.

Multi-step Electron Transfer.—The results so far have demonstrated that phenothiazines are very easily oxidized and that their one-electron oxidation products are rather stable, *i.e.* long-lived species. Phenothiazine radical cations have, in fact, been identified in the urine of patients who have been treated with these drugs.¹² Since it is usually highly improbable in a living cell, for example, that an oxidizing short-lived radical is generated right at the site of a phenothiazine molecule⁴⁷ one has to consider a step-wise transfer of the oxidizing potential *via* various intermediate species until it eventually reaches the phenothiazine. The possibility that such multi-step electron transfer reactions may indeed occur has been demonstrated by the following chemical model system, namely an N_2O -saturated pH 3.5 solution containing 10^{-3} mol dm^{-3} $(t\text{-C}_4\text{H}_9)_2\text{S}$, 10^{-4} mol dm^{-3} CH_3SSCH_3 , and 10^{-5} mol dm^{-3} promethazine. In such solutions the primary

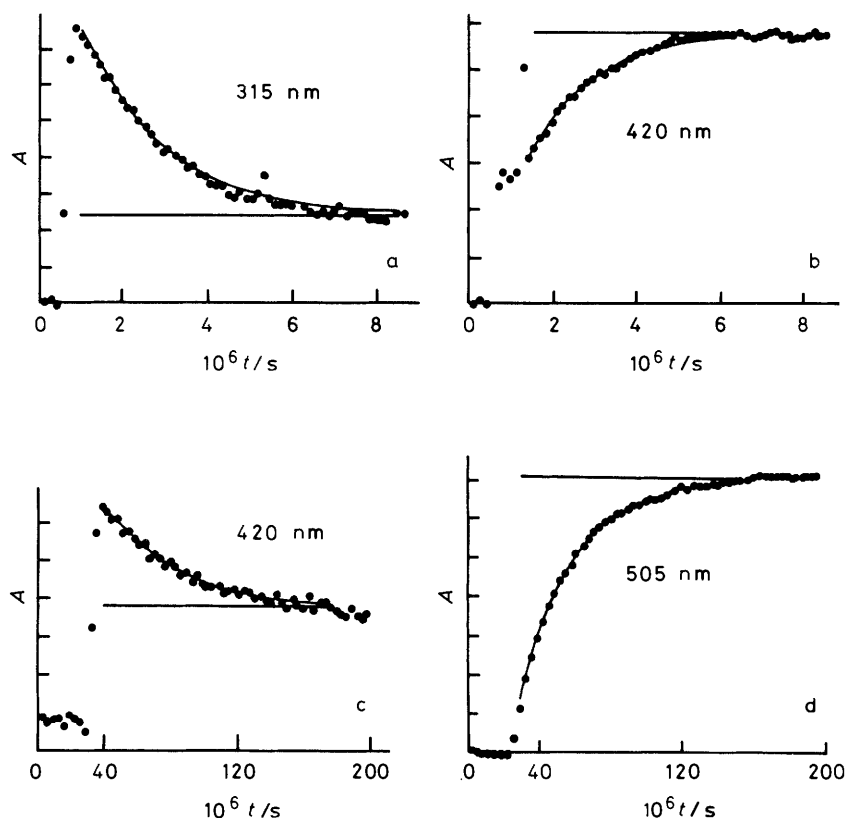
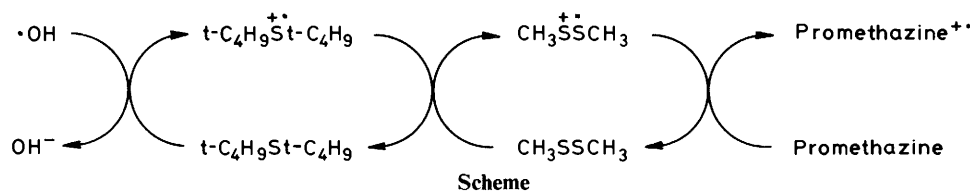
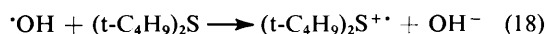


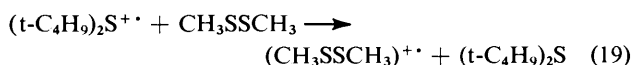
Figure 7. Multi-step electron transfer. Changes in optical absorption with time observed after a 5 ns pulse (5 J kg^{-1}) on an N_2O -saturated solution containing 1×10^{-3} mol dm^{-3} $(t\text{-C}_4\text{H}_9)_2\text{S}$, 1×10^{-4} mol dm^{-3} CH_3SSCH_3 , and 1×10^{-5} mol dm^{-3} PZH^+ at pH 3.5; solid lines, first-order kinetic fits, horizontal lines refer t_∞ .



$\cdot\text{OH}$ radicals react with the sulphide [reaction (18)] to produce

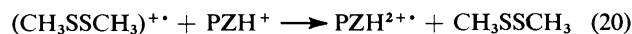


the molecular sulphur-centred sulphide radical cation within a period of 200 ns after a 5 ns pulse [mechanistically reaction (18) actually proceeds *via* a very-short-lived $\cdot\text{OH}$ adduct^{46a}]. The $(\text{t-C}_4\text{H}_9)_2\text{S}^{\cdot+}$ formation is indicated through its optical absorption at 315 nm, which can be seen in Figure 7a. The exponential decay of this absorption then coincides with an increase in absorption at 420 nm (Figure 7b), which is due to the formation of the $(\text{CH}_3\text{SSCH}_3)^{\cdot+}$ radical cation *via* reaction (19).



Kinetic analysis yields a bimolecular rate constant of $k_{19} = 5.2 \times 10^9 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$, which is practically identical with the known literature value of $5.0 \times 10^9 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ for the reaction of $(\text{t-C}_4\text{H}_9)_2\text{S}^{\cdot+}$ with $\text{C}_2\text{H}_5\text{SSC}_2\text{H}_5$.^{45b}

At longer times the $(\text{CH}_3\text{SSCH}_3)^{\cdot+}$ absorption then also decays exponentially (Figure 7c) and simultaneously the PZH^{2+} absorption appears at 505 nm indicating the consecutive reaction (20). The bimolecular rate constant derived



from these experiments amounts to $3.0 \times 10^9 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$, *i.e.* is also in excellent agreement with the individually measured value listed in Table 2.

The overall electron transfer scheme of this system can be written as given in the Scheme.

Clearly such systems can be extended by including other radical-molecule couples. Indeed, subsequent studies have shown that thiyl radicals, RS^{\cdot} , can also react with phenothiazines, and the radical cations, PTZH^{2+} , can themselves react with reducing compounds including cysteine, ascorbate, and iodide.^{44,48} Some of these reactions are described in the following paper.⁴⁴

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