$\Delta\delta = -4.5$ Hz; also the broad band, $\Delta\delta \simeq -30$ Hz (relative to the CH_2 signal of **9d**), resulting from subsequent reactions of the *p*-methoxybenzyl carbonium ion in acidic medium.

9e, $(CH_3)_2$ (d, $J = 7$ Hz); product, P–N cleavage, $(CH_3)_2$ (d, $J = 7$ Hz), $\Delta\delta = 13$ Hz.

10a, CH_3(d, $J = 7$ Hz); products, N–C cleavage, CH_3 (d, $J = 7$ Hz), $\Delta\delta = 6$ Hz; P–N cleavage, CH_3 (d, $J = 7$ Hz), $\Delta\delta = 13$ Hz.

10b, CH_2 (d, $J_{H,P} = 7$ Hz); product, P–N cleavage, CH_2 (q, $J = 6$ Hz), $\Delta\delta = 11$ Hz.

10c, CH_2 (d of d), $\delta = 2.8$ (relative to Me_4Si) changed to the multiplet, $\delta = 2.8$ (relative to Me_4Si), identical with that from the authentic sample of the cyclopropylmethylamine.

Kinetics. The substrate (25 mg) was placed in an NMR tube which was equilibrated in a bath at the temperature of the kinetic run. The acid (0.5 mL) was pipetted from a container also kept in the bath and added to the substrate. Immediately after mixing, the tube was placed in the spectrometer probe and measurements were started. The integration curve was plotted repeatedly in the range of the *tert*-butyl groups signals (between 1 and 2 ppm) or in the appropriate range for substrates **9** and **10**, at the sweep width 100 or 50 Hz. Even for fast runs ($t_{1/2} < 5$ min) it was possible to collect not less than five points, first of which corresponded to not more than 30% of conversion. For these runs the reported rate constants are the average of at least three measurements and are reproducible to ca. ±20%. For slower runs ($t_{1/2} > 5$ min), reaction was followed for about 3 half-lives. The pseudo-first-order rate constants k_ψ were determined from changes in the intensity of the signals from the selected protons in the substrate molecule. Good straight-line plots ($r > 0.998$) were obtained in all cases. Identical results were obtained by following the decrease in the intensity of the signal from the substrate or by following the increase in the intensity of the signals derived from the reaction products. Rates obtained for slower runs are reproducible to within ±5%.

Acknowledgments. The financial assistance of the National Research Council of Canada is gratefully acknowledged.

Registry No.—*tert*-Butylamine, 75-64-9; dimethylphosphinic chloride, 111-92-8; diphenylphosphinic chloride, 1499-21-4; dimethyl phosphorochloridate, 813-77-4; 2-chloro-1,3,2-dioxaphospholane 2-oxide, 6609-64-9; 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide, 4090-55-5; diphenyl phosphorochloridate, 2524-64-3; α-methylbenzylamine, 98-84-0; benzylamine, 100-46-9; *p*-methylbenzylamine, 104-84-7; *p*-methoxybenzylamine, 2393-23-9; isopropylamine, 75-31-0; cyclopropylmethylamine, 2516-47-4.

References and Notes

(1) T. Koizumi and P. Haake, *J. Am. Chem. Soc.*, **95**, 8073 (1973), and references cited therein.
(2) M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 2057 (1977), and references cited therein.
(3) A. Zwierzak and I. Podstawczynska, *Angew. Chem., Int. Ed. Engl.*, **16**, 702 (1977).
(4) This term was proposed by Haake[5] to include phosphoryl, phosphonyl, and phosphinyl groupings.
(5) P. Haake and P. S. Ossip, *J. Am. Chem. Soc.*, **93**, 6924 (1971).
(6) See, for example, K. E. De Bruin, A. G. Padilla, and D. M. Johnson, *Tetrahedron Lett.*, 4279 (1971).
(7) D. A. Tyssee, L. P. Bausher, and P. Haake, *J. Am. Chem. Soc.*, **95**, 8066 (1973).
(8) See, for example, C. R. Smith and K. Yates, *J. Am. Chem. Soc.*, **93**, 6578 (1971).
(9) A. G. Cook and G. W. Mason, *J. Inorg. Nucl. Chem.*, **35**, 2090 (1973).
(10) J. F. Coetzee and C. D. Ritchie, "Solute–Solvent Interactions", Marcel Dekker, New York, N.Y., 1969, Chapter 3.V.
(11) For the full discussion of the A2 vs. A1 mechanism of solvolysis at phosphorus more complete rate profiles are needed. If the A2 mechanism operates over the whole range of acidity, rate decrease should be observed at high acidities, where substrates are fully protonated. Any change in a rate profile at high acidity should also indicate the change in reaction mechanism. However, more complete rate profiles are not available in the medium such as aqueous $HClO_4$, since above 0.2 mol fraction of $HClO_4$ solvolysis is extremely fast and involves almost exclusively the N–C bond cleavage.
(12) M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 514 (1975); 605 (1977).
(13) For **7**, the approach of the nucleophile is particularly hindered because of the interactions with two 4,6-axial hydrogens and the *cis*-5-methyl group.
(14) The acidity function of aqueous TFA increases in the 0.4–1.0 mol fraction range by ca. 1.4 H_0 units.[15]
(15) U. A. Spitzer, T. W. Toone, and R. Stewart, *Can. J. Chem.*, **54**, 440 (1976).
(16) For the acid-catalyzed hydrolysis of some *N*-alkyl-substituted phosphoramidates similar values of $k_H/k_D = 0.5$–0.6 have been found.[17]
(17) A. W. Garrison and C. E. Boozer, *J. Am. Chem. Soc.*, **90**, 3486 (1968).
(18) U. Svanholm and V. D. Parker, *J. Chem. Soc., Perkin Trans. 2*, 169 (1974).
(19) Reference 10, Chapter 3.III.
(20) A. Streitwieser, *Chem. Rev.*, **56**, 571 (1956).
(21) D. Bethel and V. Gold, "Carbonium Ions", Academic Press, London, 1967, p 96–98.
(22) H. Reinhardt, D. Bianchi, and D. Mölle, *Ber.*, **90**, 1656 (1957).
(23) G. M. Kosolapoff and R. M. Watson, *J. Am. Chem. Soc.*, **73**, 5466 (1951).
(24) N. Kreutzkamp and H. Schindler, *Arch. Pharm. (Weinheim, Ger.)*, **293**, 296 (1960).
(25) B. Fiszer and J. Michalski, *Rocz. Chem.*, **26**, 688 (1952).
(26) H. J. Lucas, F. W. Mitchell, and L. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).
(27) R. S. Edmundson, *Chem. Ind. (London)*, 1828 (1962).
(28) R. S. Edmundson, *Tetrahedron*, **21**, 2379 (1965).
(29) N. L. Smith and H. H. Sisler, *J. Org. Chem.*, **26**, 5145 (1961).
(30) J. A. Stock, W. J. Hopwood, and P. D. Regan, *J. Chem. Soc. C*, 637 (1966).
(31) V. F. Kucherov, *Zh. Obshch. Khim.*, **19**, 126 (1949).
(32) V. Gutmann, G. Mörtl, and K. Utvary, *Monatsh. Chem.*, **93**, 1114 (1962).

Characteristics and Reactions of Cation Radicals and Quinone Imines Derived from Hydroxylated Chlorpromazine Derivatives

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Received July 27, 1978

The mechanisms of the chemical and electrochemical oxidations of two monohydroxylated and one dihydroxylated derivative of chlorpromazine, an N-substituted phenothiazine, are presented. In aqueous solutions at low pH, all three compounds form protonated cation radical oxidation products, and one derivative forms an uncharged radical center at neutral pH. The radicals are much more stable in aqueous solutions than radical ions derived from similar heterocyclic systems. Comparatively unstable quinone imines may be formed from the radicals, either by electrochemical oxidation or disproportionation of the radical ions. These quinone imines undergo a variety of reactions, including hydrolysis to quinones, hydroxylation, and nucleophilic substitution of chloride by hydroxide. The products and relative rates of these reactions are presented, and the overall pathways of the oxidations of the chlorpromazine derivatives are discussed.

Of the many radical ions which have been examined in recent years, the aromatic heterocyclic cation radicals have been of particular interest. The large majority of efforts in this area have been carried out in nonaqueous solvents due to the very short aqueous lifetimes of the radicals derived from such precursors as anthracene,[1-3] thianthrene,[4,5] and phenothiazine.[6,7] Recently, it was reported[8] that the radical of an N-substituted phenothiazine, chlorpromazine (CPZ, 1), has a

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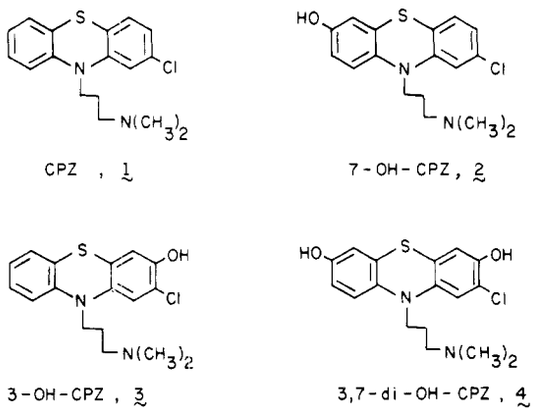


lifetime in neutral aqueous solutions ranging from a few milliseconds to several tens of minutes, depending on buffer and pH. Although the stability of CPZ cation radical in strong aqueous acids is well established,[9,10] its stability in neutral media is in contrast to similar heterocyclic radicals. In addition to this distinctive feature of N-substituted phenothiazines, drugs derived from them, particularly chlorpromazine, are the most widely used agents for the treatment of mental disorders such as schizophrenia. The radical cation of CPZ has been implicated as an intermediate in the metabolism and activity of the parent drug,[11,12] and the radical has greater pharmacological activity in several biochemical tests.[13-15]

The hydroxylated derivatives of CPZ, which are among its primary metabolites in humans,[16] are themselves pharmacologically active,[17,18] unlike several other CPZ metabolites. 7-Hydroxychlorpromazine (7-OH-CPZ, **2**) is the most important of this class of metabolites, and it has been shown that blood levels of 7-OH-CPZ correlate well with clinical improvement, whereas levels of CPZ itself do not.[19,20] Furthermore, numerous reports have indicated that the oxidation of the hydroxylated metabolites is responsible for some of the side effects of CPZ treatment.[21-23] In addition to this likely involvement of the hydroxylated CPZ metabolites in pharmacology, their chemistry is very different from that of CPZ itself. This difference arises mainly from the ability to form quinone imines as well as cation radicals when a hydroxy group is para to the thiazine nitrogen.

In two previous reports[24,25] from this laboratory, it was shown that 7-OH-CPZ can be chemically or electrochemically oxidized to a quinone imine, which rapidly hydrolyzes to form a substituted benzoquinone and other products. The pH range of the aqueous solutions used in previous work did not allow the observation of radical cations derived from the 7 substituted compound.

Questions about the formation of radical ions from hydroxylated CPZ derivatives remain unanswered, despite an ESR study carried out in concentrated HCl.[26] The characteristics and reactions of the radicals, should they form, are unknown. Due to the importance of these radicals and other oxidized forms to the pharmacology of chlorpromazine, the present study was undertaken. The approach involves electrochemical and spectroscopic characterization of three hydroxylated chlorpromazine metabolites,[16] 7-OH-CPZ, 3-hydroxychlorpromazine (3-OH-CPZ, **3**), and 3,7-dihydroxychlorpromazine (3,7-diOH-CPZ, **4**). Due to the very limited quantities of these compounds which are available (<100 mg each), microscale methods such as electrochemistry are necessary to study the oxidation mechanisms. While the limited supplies of starting materials precluded isolation of products, electrochemistry and spectroscopy permit identification of intermediates and products and construction of oxidative mechanisms. The results of this approach show that both radical ions and quinone imines may be formed from these hydroxylated chlorpromazine derivatives, and information about the characteristics, reactions, and lifetimes of the products is presented.

Experimental Section

All electrochemical techniques used here are well established and are discussed in detail elsewhere.[27,28] Voltammetric experiments with scan rates of 0.5 V/s or less were done with a potentiostat of conventional design based on operational amplifiers. Experiments requiring fast voltammetric scan rates (greater than 0.5 V/s) or short electrolysis times (less than 2 s) were performed with the aid of a minicomputer interfaced to a conventional potentiostat. Large-scale electrolysis was carried out with a potentiostat based on a 54 W power amplifier. In all cases, small volume (~2 mL) electrochemical cells were used to minimize consumption of chlorpromazine derivatives. A graphite paste working electrode was used for voltammetry and chronoamperometry, while a carbon cloth electrode was necessary for coulometric electrolysis. In all results, potentials are referred to a saturated calomel electrode (SCE).

UV–vis absorption spectra were recorded using a Cary 15 spectrophotometer. In some cases, absorption spectra were obtained using a custom built rapid scanning spectrophotometer interfaced to the minicomputer. The device allowed acquisition of spectra at the rate of 150 nm/s, and up to 30 spectra could be obtained and stored in a period of 2 min. The utility of this system in the present work arose from the ability to obtain a 200-nm wide spectrum within several seconds after a reaction was initiated.

McIlvaine buffers made from 0.2 M Na_2HPO_4 and 0.1 M citric acid were used in the pH 3–8 range. A 0.2 M phosphate buffer at pH 2 was prepared from reagent grade NaH_2PO_4 and HCl. Stock solutions of Ce^{4+} were prepared from $Ce(NH_4)_4(SO_4)_4$ dissolved in 0.5 M H_2SO_4. Stock solutions of H_2O_2 were standardized by Ce^{4+} titration using ferroin indicator. Homogeneous oxidations were carried out by the rapid addition of a measured amount of oxidant (Ce^{4+} or H_2O_2) from a microburet to a well-stirred solution. For H_2O_2 oxidations, horseradish peroxidase (Sigma Chemical Co.) was used as a catalyst. All hydroxylated chlorpromazine and promazine derivatives were obtained from Dr. A. A. Manian of the Psychopharmacology branch of NIMH and were used without further purification.

Results

Electrochemistry. The electrochemical oxidations of 3-OH-CPZ, 7-OH-CPZ, and 3,7-diOH-CPZ were examined using chronoamperometry, cyclic voltammetry, and controlled potential electrolysis.

Cyclic voltammograms of 7-OH-CPZ are shown in Figure 1. Curve A, obtained at pH 3 at a scan rate of 0.1 V/s, is representative of the pH 3–7 range and shows a single chemically irreversible oxidation wave at 0.5 V vs. SCE on the first anodic scan. In subsequent scans there appeared two new redox couples due to electroactive products of reactions of the initial unstable oxidized species. The improved resolution of the cathodic waves of these couples over that observed previously[24] is presumably due to differences in graphite paste characteristics and to variations in charge-transfer reversibility with pH. At fast scan rates (20 V/s or more), a reverse wave for the initial oxidation was observed. The half-life of

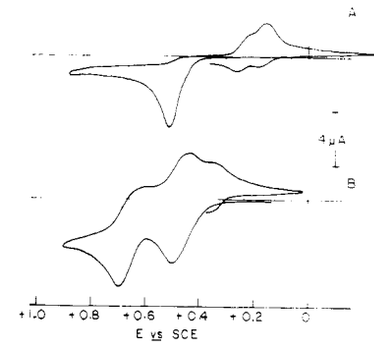


Figure 1. Voltammograms of 7-OH-CPZ at a graphite paste electrode: A, pH 3 McIlvaine buffer, 2.10×10^{-4} M **2**, scan rate = 0.10 V/s; B, 1.0 M HCl ($H_0 = -0.20$), 7.49×10^{-4} M **2**, scan rate = 0.20 V/s.

Table I. Half-Lives of Quinone Imines Derived from Hydroxylated Chlorpromazine Derivatives (in seconds)

precursor	7-OH-CPZ	3-OH-CPZ	3,7-diOH-CPZ
pH 2.0	0.14[a]	1.1[a]	~15[b]
pH 5.0	0.005[b]	0.13[a]	2.1[a]

[a] Determined by double-step chronoamperometry. [b] Determined by cyclic voltammetry.

the oxidized material was estimated from these data (Table I) and will be discussed later. Throughout the pH range 2–7, potential step chronoamperometry gave an n value of 2 or more electrons per molecule of 7-OH-CPZ. In order to calculate n from the Cottrell equation, the diffusion coefficient for 7,8-diOH-CPZ, a known 2 electron reversible system,[24] was used ($D = 3 \times 10^{-6}$ cm^2/s). Coulometric oxidation of 7-OH-CPZ in the same pH range required 4 faradays/mol of starting material. The reactions of oxidized 7-OH-CPZ in this pH range have been studied in detail previously[25] and will be compared later with the reactions of both 3-OH-CPZ and 3,7-diOH-CPZ.

A voltammogram of 7-OH-CPZ in 1 M HCl ($H_0 = -0.20$) at a scan rate of 0.2 V/s shows two oxidation waves at +0.5 and +0.7 V vs. SCE on the first scan and a new couple at +0.35 V, appearing after the first scan (Figure 1B). A plot of anodic peak potentials (E_p) vs. pH is given in Figure 2A. At pH (H_0) values less than 2, the initial 2-electron oxidation wave of 7-OH-CPZ splits into two waves, one with a positive pH dependence (region I) and the other with a −0.059 V/pH unit pH dependence (region II). Electrolysis of 7-OH-CPZ in 5 M HCl ($H_0 = -1.76$) at an applied potential of +0.5 V (between the first and second voltammetric waves) required 1.01 faradays/mol. A voltammogram of the resulting purple solution was identical to that of reduced 7-OH-CPZ, except the voltammogram was initiated as a reduction rather than an oxidation. One-second potential step experiments in 3 M HCl ($H_0 = -1.05$) revealed that the first wave corresponds to a 0.80 electron per molecule oxidation, again using the diffusion coefficient of 7,8-diOH-CPZ.

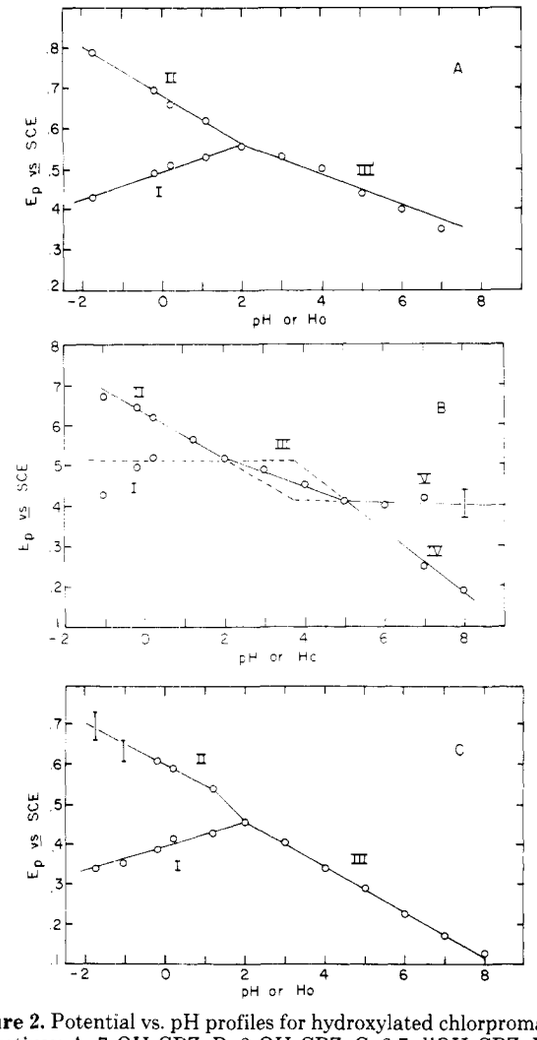


Figure 2. Potential vs. pH profiles for hydroxylated chlorpromazine derivatives: A, 7-OH-CPZ; B, 3-OH-CPZ; C, 3,7-diOH-CPZ. In all cases potentials are anodic peak potentials (E_p) from voltammograms obtained using a graphite paste electrode.

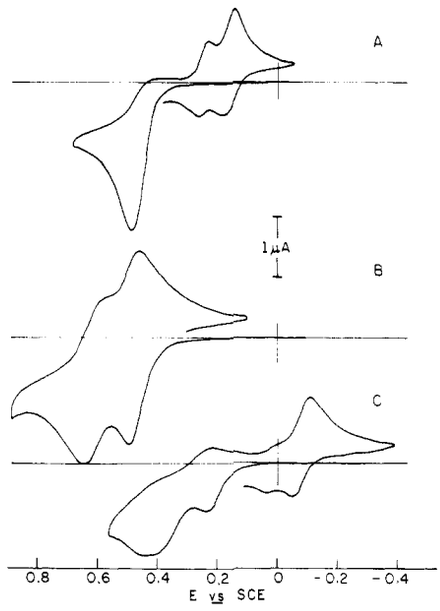


Figure 3. Voltammograms of 3-OH-CPZ at a graphite paste electrode: A, pH 3 McIlvaine buffer, 2.34×10^{-4} M **3**, scan rate = 0.10 V/s; B, 1.0 M HCl ($H_0 = -0.20$), 1.61×10^{-4} M **3**, scan rate = 0.10 V/s; C, pH 7 McIlvaine buffer, 2.45×10^{-4} M **3**, scan rate = 0.20 V/s.

Three voltammograms of 3-OH-CPZ are shown in Figure 3. Voltammogram A, qualitatively similar to others in the pH region 3–6, reveals that 3-OH-CPZ oxidation at pH 3 is chemically irreversible and has a peak potential of 0.49 V. Reversible voltammetric waves due to two products are at +0.19 and +0.27 V. Voltammetry at scan rates of at least 0.2 V/s yielded a sufficiently short time frame to observe a reduction wave corresponding to the initial oxidation. Double potential step chronoamperometry was used to estimate the half-life of oxidized 3-OH-CPZ (Table I).

Coulometric oxidation in the pH 3–7 region required 2.01 ± 0.17 faraday/mol of original 3-OH-CPZ. A single reversible redox system, identical to the reversible voltammetric wave of 2,3-dihydroxypromazine, was observed in the voltammograms of the electrolysis products of 3-OH-CPZ from pH 2–7. Plots of E_p vs. pH for 2,3-dihydroxypromazine and the electrolysis product are identical, with slopes of −0.060 V/pH unit.

Although they were obtained in solutions of very different pH, both voltammograms B ($H_0 = -0.2$) and C (pH 7.0) in Figure 3 show two waves on the first anodic scan. The pH profile for oxidation potentials (E_p) of 3-OH-CPZ over the entire pH range studied is presented in Figure 2B. The 2-electron wave observed at intermediate pH (region III) splits below pH 1 into two waves, both pH dependent. One has a positive E_p vs. pH slope (region I) and the second an E_p vs. pH slope of −0.062 V/pH unit (region II). Coulometric oxidation of 3-OH-CPZ at a potential between the two anodic waves required 0.97 faraday/mol in 5 M HCl. The splitting of the

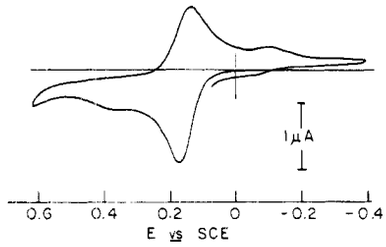


Figure 4. Cyclic voltammogram of 3,7-diOH-CPZ in pH 7 McIlvaine buffer. Graphite paste electrode, 3.35×10^{-4} M 7, scan rate = 0.089 V/s.

anodic wave is similar to that observed for 7-OH-CPZ at low pH. Unlike 7-OH-CPZ, anodic wave splitting for 3-OH-CPZ occurs above pH 6, where the potential of the first wave has a pH dependence of −0.070 V/pH unit (region IV) and the potential of the second wave is pH independent (region V). Chronoamperometric oxidation of 3-OH-CPZ at a potential between regions IV and V required 0.70 electron/molecule at pH 7, again using the diffusion coefficient for 7,8-diOH-CPZ.

Figure 4 shows a cyclic voltammogram of 3,7-diOH-CPZ at pH 7, taken at a scan rate of 0.09 V/s. The large reverse wave for the initial oxidation at +0.17 V reveals that oxidized 3,7-diOH-CPZ has a longer lifetime than the oxidized forms of 3-OH-CPZ and 7-OH-CPZ. The half-life of oxidized 3,7-diOH-CPZ was calculated from voltammetric and double potential step chronoamperometric data (Table I). However, the 3,7-diOH-CPZ redox system is not completely chemically reversible on the time scale of the cyclic voltammogram; a small redox couple due to electroactive products appears at −0.1 V after the first anodic scan. The voltammograms for pH 2–8 were qualitatively similar, with the shifts in anodic peak potential due to pH shown in Figure 2C. The slope in region III is −0.059 V/pH unit. Chronoamperometry for 1 s at pH 5 indicated that the initial oxidation required 2.09 electrons per molecule of 3,7-diOH-CPZ. Electrolysis in the pH range 2–7 required 2.08 ± 0.25 faradays/mol for the overall oxidation process. For the first 1–2 min the electrolysis solution was blue, with a gradual transition to purple as the electrolysis proceeded. Voltammograms of the electrolysis products at pH 5 and 7 revealed reversible waves at +0.06 and −0.05 V, respectively. They were identical to voltammograms of 3,7,8-trihydroxychlorpromazine at those pH values. If the pH was less than 2, the two-electron voltammetric wave split into two 1-electron waves, with peak potentials plotted in Figure 2C. E_p variations with pH for 3,7-diOH-CPZ in regions I and II are qualitatively similar to those of 7-OH-CPZ and 3-OH-CPZ below pH 2. The first wave has a positive pH dependence (region I) and the second an E_p vs. pH slope of −0.054 V/pH unit (region II). At an applied potential between the waves (+0.48 V) in 5 M HCl ($H_0 = -1.76$), coulometric oxidation required 0.91 faraday/mol of 3,7-diOH-CPZ. A voltammogram of the resulting blue solution was identical to one taken before electrolysis, with the exception of initial potential.

Spectroscopy. UV–vis spectroscopy was used to characterize products of both electrochemical and chemical oxidation of all three compounds. One-electron chemical oxidations in acidic solutions were done by the addition of a stoichiometric amount of Ce^{4+} to solutions of each compound. In all cases where the pH was low enough to observe wave splitting in the voltammograms, a color characteristic of the 1-electron oxidized species appeared instantly. The persistence of the color was pH dependent, being greater at lower pH. A UV–vis spectrum was obtained for each species at an acidity sufficiently high that the decay of chromophore was very slow. The 1-electron oxidized species were also generated electrochemically in acidic solutions using controlled potential

Table II. UV–Vis Absorption Bands for Reduced CPZ Derivatives and Their Cation Radicals

reduced forms

CPZ[35]		7-OH-CPZ[a] (3 M H_2SO_4)		3-OH-CPZ[b] (3 M H_2SO_4)		3,7-diOH-CPZ[c] (5 M HCl)	
λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε
255	4.51	253	4.39	252	4.34	225	4.44
305	3.58	283	3.60	280	3.68	274	4.17
		308	3.66	307	3.58	281	4.23

cation radicals

$CPZ^{+\cdot}$[d] (3 M H_2SO_4)		7-OH-$CPZ^{+\cdot}$[e] (5 M HCl)		3-OH-$CPZ^{+\cdot}$[f] (3 M HCl)		3,7-diOH-$CPZ^{+\cdot}$[g] (5 M HCl)	
λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε
217	4.44	226	4.42	228	4.39	242	4.46
268	4.66	254	4.20	256	4.21	282	4.67
277	4.70	283	4.70	280	4.62	357	3.68
325	3.44	349	3.46	348	3.43	398	3.50
374	2.86	568	4.00	389	3.43	623	4.10
525	4.10			581	3.97		

[a] Registry no. 2095-62-7. [b] Registry no. 3930-47-0. [c] Registry no. 14339-66-3. [d] Registry no. 34468-21-8. [e] Registry no. 68050-95-3. [f] Registry no. 68090-96-4. [g] Registry no. 68050-97-5.

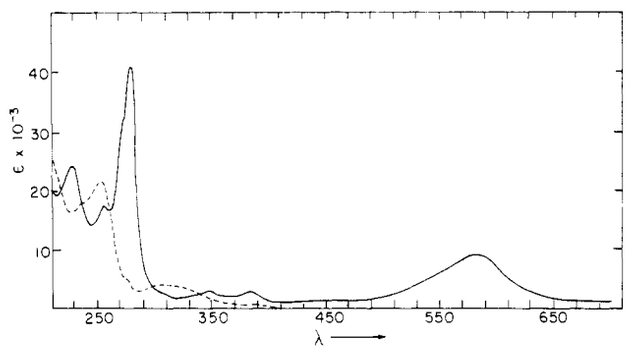


Figure 5. UV–vis spectra of 3-OH-CPZ in its fully reduced and cation radical forms: dashed line, reduced form in 3 M H_2SO_4; solid line, cation radical in 3 M HCl.

electrolysis at a potential between the first and second voltammetric waves. The absorption maxima agreed with those obtained from chemical oxidation, but molar absorptivities calculated from electrolyzed solutions were higher because of the selectivity in oxidizing potential afforded by the electrochemical method. Absorption maxima (λ_{max}) and molar absorptivities (ε) are presented in Table II, and typical spectra are shown in Figure 5. In acid solutions the 2 electron/molecule oxidized form of 3-OH-CPZ was stable enough to be observed spectroscopically. When 3-OH-CPZ in 3 M HCl ($H_0 = -1.05$) was oxidized with 2 mol of Ce^{4+} per mol of starting material, the solution immediately turned yellow. Spectra recorded as a function of time showed that the yellow (440 nm) absorbance decreased with time, and completely disappeared after 20 min. Since the absorbance decrease had already begun by the time the first spectrum was recorded (20 s after oxidation), the molar absorptivity can only be estimated.

A blue color appeared instantly when 3,7-diOH-CPZ at pH 7 was oxidized with 2 equiv/mol of H_2O_2. Spectra as a function of time revealed a gradual transition from this blue chromophore (λ_{max} 601 nm) to the same spectrum observed at pH 7 for the electrolysis products of 3,7-diOH-CPZ.

Spectroscopic studies of the oxidation products of 7-OH-

CPZ have been published previously.[25] UV–vis spectra of the electrolysis products of both 3,7-diOH-CPZ and 3-OH-CPZ were obtained in the pH region 2–7 and compared with the spectra of the electrolysis products of 3,7,8-trihydroxychlorpromazine and 2,3-dihydroxypromazine, respectively. From pH 3–7, the electrolysis products of 3-OH-CPZ and 2,3-dihydroxypromazine have identical UV–vis spectra, with peaks at 258 and 505 nm, and shoulders at 285 and 530 nm. The spectra are very similar to that of 7,8-dioxo-CPZ, the only difference being a 3–4 nm hypsochromic shift relative to 7,8-dioxo-CPZ. The electrolysis products of 3,7,8-triOH-CPZ and 3,7-diOH-CPZ have qualitatively similar spectra in the pH range 2–7. In the pH range 3–6, both spectra are characterized by a broad, pH-dependent, visible band with λ_{max} 538–547 nm.

Attempts to isolate intermediates and products were frustrated by the limited amounts of starting materials and the instability of many of the species of interest. Identification of products depended on voltammetric and spectroscopic characteristics and on deductions from the quantitative coulometry and chronoamperometry results.

Discussion

It is apparent from the results that under the proper conditions, 3-OH-CPZ, 7-OH-CPZ, and 3,7-diOH-CPZ may lose either 1 electron or 2 electrons to form either radical or quinone imine species. As is evident from the potential vs. pH plots, the ability to form radicals is present only in certain pH regions, as discussed in greater detail below. In addition, the doubly oxidized forms (loss of 2 electrons) are unstable on a time scale of a few seconds or less, necessitating the use of a dynamic technique such as cyclic voltammetry rather than an equilibrium approach such as potentiometry. The chemistry of the singly oxidized radicals will be discussed separately from that of the doubly oxidized quinone imines.

Generation and Characteristics of Radicals. Below pH 2, cyclic voltammetry, chronoamperometry, and coulometry indicate that all three compounds studied can lose 1 electron per molecule to form a radical which is stable on a time scale of several tens of minutes. If the initial 1-electron transfer is not accompanied by proton loss, the resulting radical ion could be considered either a protonated semiquinone imine cation radical or a hydroxy substituted phenothiazine cation radical. Protonated semiquinones are well known, and phenothiazine radicals have been examined quite extensively in recent years. A simple 1-electron oxidation without proton loss would require a pH-independent peak potential in region I of all three plots of Figure 2. The unusual positive slopes in this region result from a significant decrease in the activity of the cation radicals in regions of high ionic strength. As reviewed by Clark,[29] the potential of a redox reaction accompanied by proton loss depends both upon pH and ionic strength:

$$\text{red} \rightleftharpoons \text{ox} + ne^- + qH^+$$

$$E = E^0 + \frac{RT}{nF} \ln \frac{a_{ox}(a_{H^+})^q}{a_{red}}$$

$$E = E^0 + \frac{RT}{nF} \ln \left(\frac{[ox]}{[red]}\right) + \left(\frac{q}{n}\right)\frac{RT}{F} \ln (a_{H^+}) + \frac{RT}{nF} \ln \left(\frac{\gamma_{ox}}{\gamma_{red}}\right)$$

where γ_{ox} and γ_{red} denote activity coefficients. Because of protonation of the side-chain nitrogen, the oxidized forms of region I are dications, and their activity coefficients depend more heavily on ionic strength than those of the reduced forms. As the acidity increases, the ratio of γ_{ox} to γ_{red} decreases and the potential decreases. It is very difficult to assess this effect quantitatively for lack of an accurate means to estimate activity coefficients in solutions of high ionic strength. The −0.060 V/pH unit peak shift for the second 1-electron oxidation (region II) indicates a loss of single proton and is not severely distorted by activity effects because both ox and red are dications, and will be affected equally by ionic strength. Thus the loss of the only ionizable proton must occur in region II, and region I involves only loss of an electron to form a protonated cation radical.

The UV–vis absorption maxima for the three cation radicals are listed in Table II, and are consistent with the spectra of other phenothiazine radicals. Absorption maxima for $CPZ^{+\cdot}$ are included in the table for comparison and show that the visible absorption maximum is shifted to longer wavelengths by hydroxylation. The molar absorptivities are from electrogenerated cation radical solutions. Those values in most cases are more accurate than the corresponding values from chemical oxidation because of the selectivity in oxidiing potential.

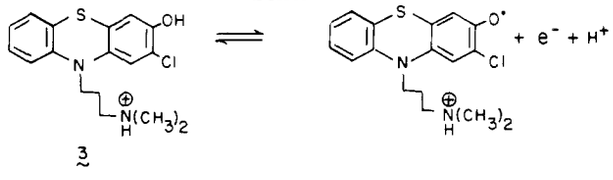
Two 1-electron/molecule waves in the voltammograms of 3-OH-CPZ at values of pH greater than 6, combined with chronoamperometric data, indicate the formation of a radical with moderate stability (Figure 3C). The slope of the pH profile for the first oxidation (region IV, Figure 2B) is −0.070 V/pH unit, which indicates that the number of protons and electrons involved in the initial oxidation are equal. The ring system of the resulting radical must therefore be neutral, having lost 1 electron and 1 proton, as shown in Scheme I.

The proton dissociation constant of the cation radical of 3-OH-CPZ may be determined from the slopes of the potential curves (dashed lines in Figure 2B) utilizing the methods reviewed by Clark.[29] The second oxidation potential curve (Figure 2B) was used to obtain the pK_a, which is indicated by the change in slope from −0.060 to 0 V/pH unit at pH 3.8. Because of the distorted slope in region I, the radical pK_a was determined from extrapolations of regions II and V. The pK_a for the 3-OH-CPZ cation radical determined in this fashion is 3.8 ± 0.2. Since no wave splitting was observed for 7-OH-CPZ and 3,7-diOH-CPZ above pH 6, the pK_a of the cation radicals of these compounds cannot be determined using this method.

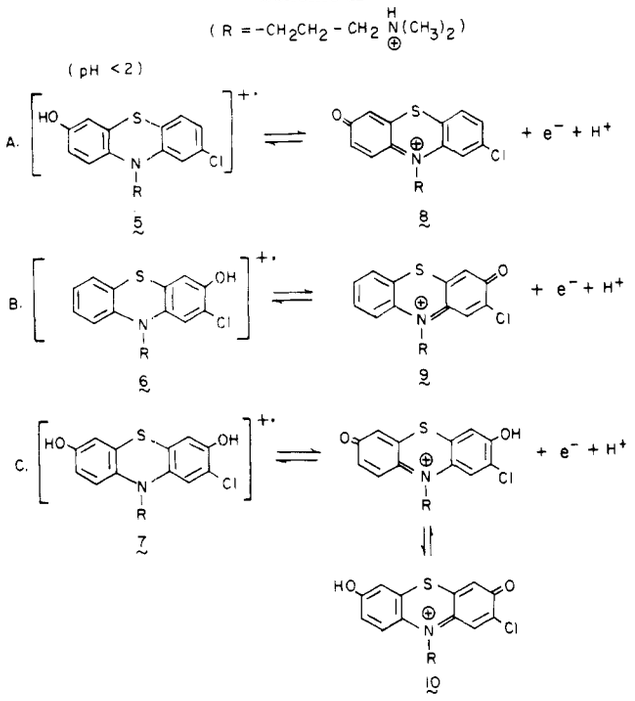
Generation and Characteristics of Quinone Imines. The 2-electron/molecule oxidized species of 3-OH-CPZ, 7-OH-CPZ, and 3,7-diOH-CPZ in each case is the corresponding quinone imine, which can be formed by further oxidation of a stable radical or by 2-electron oxidation of the fully reduced parent material. At low pH, the E_p of the second voltammetric wave for each compound has a pH dependence of −0.060 ± 0.005 V/pH unit, since the protonated radical loses 1 electron and 1 proton to form the quinone imine (region II, Figure 2, and Scheme II). The second wave E_p for 3-OH-CPZ in the neutral pH range is pH independent, as indicated by the zero slope in region V of Figure 2B. One electron is lost from the radical to form the quinone imine (Scheme III).

In the pH range of region III of Figure 2, for all three compounds chronoamperometry indicates that 2 electrons are lost in the initial oxidation. The observed E_p vs. pH curve for 3-OH-CPZ in this region falls between the two single-electron potential curves (dashed lines in Figure 2B) and is somewhat distorted from a 2 electron, 1 proton (−0.030 V/pH unit) slope by the fast reactions subsequent to charge transfer. Region

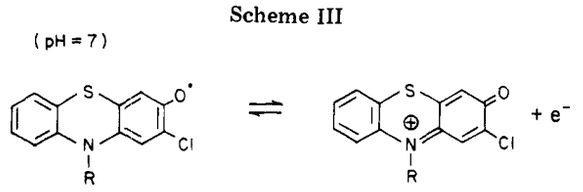
Scheme I



Scheme II



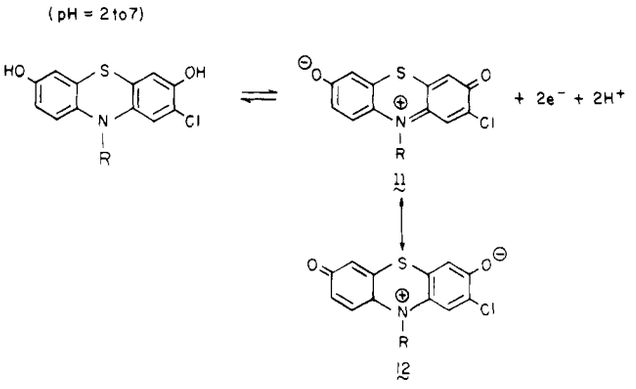
Scheme III



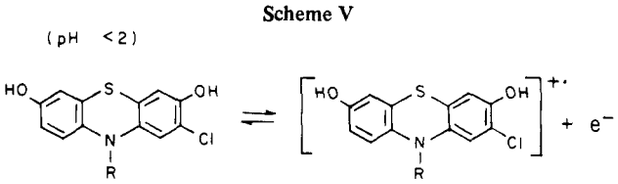
III for 7-OH-CPZ (Figure 2A) is similar, with more distortion since the quinone imine reactions are faster. The spectrum of the quinone imine of 3-OH-CPZ, with λ_{max} 440 nm, is typical of those of other quinone imines.[30] The quinone imine of 7-OH-CPZ could not be observed spectroscopically because of its short lifetime.

The data of Figure 2 indicate that the oxidation potentials for the 2-electron oxidations of 3-OH-CPZ and 7-OH-CPZ are very close (region III), with 3-OH-CPZ having a potential 35 mV lower than its isomer. While this similarity was expected on structural grounds, it is also apparent that 3,7-diOH-CPZ is significantly (>0.1 V) easier to oxidize than the monohydroxy derivatives. The pH dependence of the oxidation potential for 3,7-diOH-CPZ has a −0.059 V/pH unit slope in region III, indicating that the number of protons lost equals the number of electrons in this region. Since coulometry and chronoamperometry establish this process to involve 2 electrons, the oxidation of 3,7-diOH-CPZ must be that of Scheme IV, with both hydroxyl protons being lost. The quinone imine of 3,7-diOH-CPZ can be represented as a resonance hydrid of structures **11** and **12**. Given the extensive conjugation of this system one would expect a less reactive species, as indicated by the quinone imine lifetimes (Table II) and the large reverse wave in Figure 4. In addition, the visible λ_{max} for the 3,7-diOH-CPZ quinone imine (601 nm) is much higher than that of 3-OH-CPZ quinone imine (440 nm) or other non-phenothiazine quinone imines. This change in spectral characteristics presumably results from greater electron delocalization. The behavior of the E_p vs. pH profile form 3,7-diOH-CPZ below pH 2 can be explained by assuming that the quinone imine form has a pK_a of about 2. Thus region I corresponds to loss of a single electron to yield diprotonated radical (Scheme V), and region II corresponds to loss of a second

Scheme IV



Scheme V



electron and one proton yielding a protonated quinone imine and exhibiting a −0.060 V/pH unit slope (Scheme II). In the apparent region of discontinuity between regions II and III in Figure 2C, the pH profile has a steeper slope than the −0.060 V/pH unit, corresponding to loss of 2 protons and 1 electron from the radical, and resulting in a nonprotonated quinone imine.

Reactions of Cation Radicals. Once the cation radicals were generated by chemical or electrochemical oxidation, the time dependence of their concentrations was monitored with spectroscopy and voltammetry. In the case of electrochemical generation, the circuit was opened after the 1-electron oxidation to the radical. The radicals of all three compounds studied are quite stable in strong acid, although a slow (on a time scale of hours) degradation occurs to as yet unidentified products. In less acidic media (H_0 −0.2 to 2) the products of decomposition of **5**, determined voltammetrically and spectroscopically, are 7,8-dioxo-CPZ and 7-OH-CPZ, the same products reported for the 7-OH-CPZ quinone imine decomposition at pH 2.[25] A probable mechanism is disproportionation of the radical (reaction 1) followed by hydrolysis of the quinone imine and eventual formation of 7,8-diozo-CPZ.[25] The products of decomposition of **6** in the pH range −0.2 to 2 are 2,3-dioxopromazine and 3-OH-CPZ and can also be accounted for by disproportionation (reaction 2) followed by further reaction of the quinone imine. Spectroscopic and voltammetric results indicate that the products of decomposition of **10** are also those of reactions of its quinone imine. Again, disproportionation is a probable mechanism (reaction 3).

$$2(\mathbf{5}) \rightarrow \mathbf{8} + \mathbf{2} + H^+ \quad (1)$$

$$2(\mathbf{6}) \rightarrow \mathbf{9} + \mathbf{3} + H^+ \quad (2)$$

$$2(\mathbf{7}) \rightarrow \mathbf{10} + \mathbf{4} + H^+ \quad (3)$$

The rate of disappearance of **5** is much faster than the rates for disappearance of **6** and **7** in the pH range −0.2 to 2, because of the very large difference in lifetimes of the corresponding quinone imines (Table I). A direct reaction of cation radicals with solution components cannot be ruled out by the present data, but a disproportionation mechanism is thermodynamically likely, and leads to the observed products.

The surprising stability of the 3-OH-CPZ neutral radical at a pH greater than 6 results from the relative stability of the

associated quinone imine. The equilibrium constant for disproportionation in this region is less than one, and the quinone imine concentration will be low. For the case of 7-OH-CPZ, the quinone imine is much more reactive (Table I), and therefore the radical, should it form at pH ~7, will have a shorter lifetime than the 3-OH-CPZ radical. Thus the 7-OH-CPZ radical could not be observed at neutral pH on a voltammetric time scale.

Reactions of Quinone Imines. Quinone imines should react in aqueous solution by two possible routes: hydrolysis to the corresponding quinone, a reaction studied in some detail;[31,32] or hydroxylation or other nucleophilic addition reaction, such as those observed for quinones.[33,34] Both of these possibilities have been observed during studies of the oxidation of 7-OH-CPZ, 3-OH-CPZ, and 3,7-diOH-CPZ, with the nature and rate of the reaction dependent on the quinone imine structure and pH.

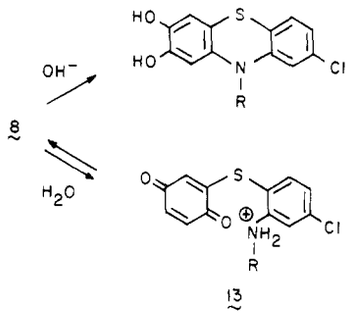
The reactions of oxidized 7-OH-CPZ in aqueous media have been reported previously[24,25] and include hydrolysis at pH 2 and both hydrolysis and hydroxylation from pH 3–7 (Scheme VI). The cyclic voltammogram at pH 3 (Figure 1A) shows redox waves for the products of both reactions, with the hydroquinone form of **13** oxidizing at a more positive potential than 7,8-diOH-CPZ. 7,8-Dioxo-CPZ accounts for all or a large part of the products in the pH range 2–7 and can be formed by either route. The quinone **13** in Scheme VI can react further to eventually form 7,8-dioxo-CPZ by a mechanism reported earlier.[25] 7,8-Dioxo-CPZ can also be formed via oxidation of 7,8-diOH-CPZ at an electrode or by solution components. Either route requires 4 electrons per molecule for the overall oxidation process.

Chronoamperometry and coulometry indicate that 2 electrons per molecule are involved in both the initial and overall oxidation processes of 3-OH-CPZ in the pH range 3–7. The electrolysis products of 3-OH-CPZ are voltammetrically and spectroscopically identical to 2,3-dioxopromazine (**14**). This product identification, along with the coulometric data, indicates that 3-OH-CPZ quinone imine undergoes nucleophilic substitution of the chlorine by hydroxide (Scheme VII). Examination of Figure 3A shows that in addition to the followup wave for 2,3-dioxopromazine, there is another followup wave at +0.27 V, which is due to the hydrolysis product, quinone **15**, shown in Scheme VII. The $E^{0'}$ at pH 3 for a similar compound, 1,4-dihydroxy-2-chlorobenzene, is +0.286 V vs. SCE.[35] Quinone **13**, the 7-OH-CPZ quinone imine hydrolysis product, undergoes intramolecular addition of the aromatic amine to form 6,9-diOH-CPZ.[25] The possibility of intramolecular michael addition of aromatic amine in quinone **15** may be ruled out by the lack of spectroscopic and voltammetric evidence for such a process and by the 2-electron per molecule stoichiometry. The intramolecular addition rate apparently cannot compete with the rate of reverse hydrolysis (ring closure), and any **15** formed eventually cycles through the quinone imine to yield 2,3-dioxopromazine.

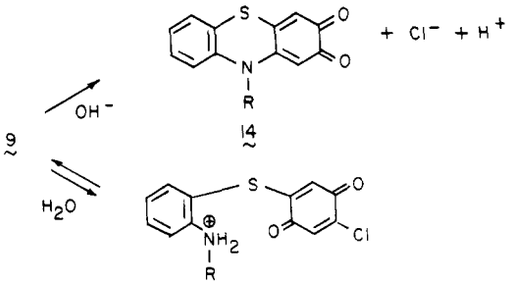
3,7-diOH-CPZ shows the same 2-electron/molecule stoichiometry upon oxidation as 3-OH-CPZ. The voltammograms and spectra of oxidized 3,7-diOH-CPZ are consistent with the formation of 2,3-dioxo-7-hydroxypromazine (**16**) by nucleophilic substitution (Scheme VIII). Formation of 3-hydroxy-7,8-dioxochlorpromazine cannot be ruled out by voltammetry and spectroscopy but is not consistent with the observed stoichiometry, requiring an overall 4-electron rather than 2-electron oxidation.

The data in Table I show that oxidized 3-OH-CPZ has a shorter half-life than oxidized 3,7-diOH-CPZ. This can be accounted for by the greater partial positive charge on the C_2 of 3-OH-CPZ quinone imine, making it more susceptible to nuleophilic attack at that position. The C_2 of 3,7-diOH-CPZ quinone imine has a smaller positive charge since both benzene rings have partially oxidized character and are involved in the resonance hybrid. Oxidized 7-OH-CPZ reacts more quickly than either of the other compounds. At pH 5 this difference in rate can be accounted for by the fact that 7-OH-CPZ quinone imine can be hydroxylated at the 8 position. 3-OH-CPZ does not have this opportunity, and the partial positive charge of C_8 for oxidized 3,7-diOH-CPZ is apparently not large enough for rapid nucleophilic attack at this position.

Scheme VI



Scheme VII

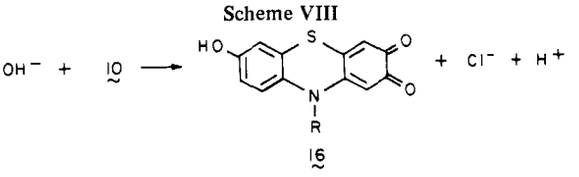


Conclusion

At pH values below 2, all three hydroxylated CPZ derivatives form relatively stable radical cations, due to protonation of the usually unstable semiquinone imine radical. In the case of 3-OH-CPZ, a neutral radical could be formed above pH 6, but its lifetime was on the order of a few seconds. Formation of a similar radical from 7-OH-CPZ was not observed, although such a process could be predicted on structural grounds. The voltammetry of 7-OH-CPZ in the pH 6–8 region was rather poorly defined, and it is possible that evidence of radical formation was missed due to more rapid reactions following charge transfer.

Once a quinone imine is formed during the oxidation process, either by radical disproportionation or direct electrochemical oxidation, it may react by one of three routes. Hydroxylation (Scheme VI, top), hydrolysis (Scheme VI, bottom), or nucleophilic substitution of chloride (Scheme VIII) can occur, depending upon the identity of the quinone imine and the pH. For quinone imine **8**, derived from 7-OH-CPZ, both hydroxylation and hydrolysis were observed, with no loss of chloride. For **9**, derived from 3-OH-CPZ, primarily substitution of chloride was observed, leading to 2,3-dioxopromazine (**14**) and requiring 2 faradays/mol for complete oxi-

Scheme VIII



dation. Similarly, quinone imine 11, derived from 3,7-diOH-CPZ, lost its chloride through substitution, requiring 2 electrons for oxidation.

The importance of radical ion or quinoneimine formation to the biological activity of the hydroxylated chlorpromazines is difficult to assess, but the present results allow some insight into their possible involvement in pharmacological effects. First, radical formation from 3-OH-CPZ is very likely at physiological pH, and it is also probable that 7-OH-CPZ undergoes a similar reaction, although it was not observed explicity here. While electrochemical generation of radicals is not possible in the region denoted III in Figure 2, homogeneous generation of radicals is possible if one-electron oxidants are used. This aspect is potentially important in vivo, where 1-electron oxidants are widespread, and the concentration of radical would be sufficiently low to prevent rapid disproportionation.

The likelihood of generation and the fate of the quinone imines are also difficult to evaluate. However, significant pharmacological evidence indicates the importance of oxidation of hydroxylated CPZ metabolites to the drugs' side effects, and the oxidation products and intermediates observed electrochemically are likely to be formed in vivo, if oxidation does indeed occur.

Acknowledgment. The authors thank Dr. A. A. Manian for gifts of compounds and helpful discussions. This work was supported by NIMH through Grant No. MH 28412.

References and Notes

(1) H. N. Blount, *J. Electroanal. Chem.*, **42**, 271 (1973).
(2) J. Evans and H. Blount, *J. Org. Chem.*, **41**, 516 (1976).
(3) V. D. Parker and L. Eberson, *J. Am. Chem. Soc.*, **92**, 7488 (1970).
(4) U. Svanholm and V. D. Parker, *J. Am. Chem. Soc.*, **98**, 997 (1976).
(5) B. K. Bandlish, S. R. Mani, and H. J. Shine, *J. Org. Chem.*, **42**, 1538 (1977).
(6) J. Evans, J. Lenhard, and H. Blount, *J. Org. Chem.*, **42**, 983 (1972).
(7) J. Evans and H. Blount, *J. Org. Chem.*, **42**, 976 (1977).
(8) H. Y. Cheng, P. H. Sackett, and R. L. McCreery, *J. Am. Chem. Soc.*, **100**, 962 (1978).
(9) L. Levy, T. Tozer, L. Tuck, and D. Loveland, *J. Med. Chem.*, **15**, 989 (1972).
(10) D. Thompson, C. Veneziani, and H. Shine, *J. Heterocycl. Chem.*, **4**, 517 (1967).
(11) D. E. Green and I. S. Forrest, *J. Forensic Sci.*, **17**, 592 (1972).
(12) G. Bulow, I. Yamazaki, and L. Piette, *Biochem. Biophys. Acta*, **88**, 120 (1964).
(13) S. Ohnishi and H. McConnell, *J. Am. Chem. Soc.*, **87**, 2293 (1965).
(14) T. Akera and T. Brody, *Biochem. Pharmacol.*, **21**, 1403 (1972).
(15) T. Akera and T. Brody, *Biochem. Pharmacol.*, **25**, 1751 (1976).
(16) P. Turano, W. Turner, and A. Manian, *J. Chromatogr.*, **75**, 277 (1973).
(17) J. Buckley, M. Steenberg, H. Barry, and A. A. Manian, *J. Pharm. Sci.*, **62**, 715 (1973).
(18) H. Y. Meltzer et al., *Eur. J. Pharm.*, **41**, 431 (1977).
(19) A. Mackay, A. Healey, and J. Baker, *Br. J. Clin. Pharm.*, **1**, 425 (1974).
(20) G. Sakalis et al., *Psychopharmacologia*, **32**, 279 (1973).
(21) T. L. Perry, C. A. Culling, K. Berry, and S. Hanson, *Science*, **146**, 82 (1964).
(22) M. H. Woert, *Nature (London)*, **219**, 1054 (1968).
(23) H. R. Adams et al. in "Phenothiazines and Structurally Related Drugs", I. S. Forrest, C. J. Carr, and E. Usdin, Eds., Raven Press, 1974, p 281.
(24) R. L. McCreery, *J. Pharm. Sci.*, **66**, 357 (1977).
(25) M. Neptune and R. L. McCreery, *J. Med. Chem.*, **21**, 362 (1978).
(26) T. A. Grover, L. H. Piette, and A. A. Manian, ref. 23, p 561.
(27) R. N. Adams, "Electrochemistry at Solid Electrodes", Marcel Dekker, New York, N.Y., 1976.
(28) Z. Galus, "Fundamentals of Electrochemical Analysis", Wiley, New York, N.Y., 1976.
(29) W. M. Clark, "Oxidation Reduction Potentials of Organic Systems", Krieger, New York, N.Y., 1972.
(30) D. L. Forster et al., *J. Chem. Soc. C*, 993 (1971).
(31) Reference 27, p 336.
(32) J. F. Corbett, *J. Chem. Soc. B*, 213 (1969).
(33) L. Papouchado, G. Petrie, J. Sharp, and R. N. Adams, *J. Am. Chem. Soc.*, **90**, 5620 (1968).
(34) M. F. Marcus and M. D. Hawley, *J. Electroanal. Chem.*, **18**, 175 (1968).
(35) Reference 29, p 368.

Notes

Selective Transformations of Sugar Tosylhydrazones to Deoxy and Unsaturated Sugars[1]

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Received December 12, 1977

In many areas of synthesis of natural products and especially in carbohydrate chemistry, there is occasionally need for deoxygenation of a secondary hydroxyl group selectively and quantitatively. In connection with some work in our laboratory on the synthesis of nucleoside antibiotics, we needed a relatively simple, high yielding, synthetic accessibility to the naturally occurring pentose 3-deoxy-D-*erythro*-pentose.[2] The existing methods of synthesis of 3-deoxypentoses are in general cumbersome, involved procedures which have limitations due to low product yields, complexity of product mixtures, and difficulties associated with obtaining starting compounds.[2-7] The major difficulty in deoxygenation of secondary hydroxyl groups in carbohydrate chemistry arises because S_N2 processes are generally hindered at these carbons both sterically and through dipolar effects.

The availability of mild and specific oxidation methods in carbohydrate chemistry suggested the desirability of deoxygenation via keto sugars. Recent reports[8] suggest that a wide variety of aldehydes and ketones can be deoxygenated via their tosylhydrazones with sodium cyanoborohydride ($NaBH_3CN$) under acidic conditions. Noteworthy features of $NaBH_3CN$[9] which are of particular interest to carbohydrate chemistry include its acid stability[10] and its reported ability to reduce tosylhydrazones selectively to methylene derivatives without the formation of side products in the presence of a host of otherwise sensitive functional groups. These observations are significant in view of the fact that glycofuranosidulose and glycopyranosidulose derivatives can be produced in high yields, and these in turn, we have found, can be converted to the corresponding crystalline tosylhydrazones almost quantitatively. In this report we wish to describe a mild and high yielding procedure for the synthesis of protected 3-deoxy sugars from their tosylhydrazones. We also developed in the process one of the most efficient methods for the introduction of 3,4 unsaturation in furanoid sugars.[3,11]

The keto sugar 1 served as the source for our starting compound 2. This ketone can be prepared in high yield from D(+)-xylose.[12] In order that the final product be produced in

0022-3263/78/1943-5013$01.00/0