# Substituent Effects on Oxidation and Stabilization of Phenothiazine Semiquinone Free Radicals

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**Rates of decay of semiquinones of certain derivatives of phenothiazine were measured in aqueous acetic acid solution using electron spin resonance spectroscopy and visible absorption spectrophotometry. Like that of phenothiazine itself, the semiquinones of the derivatives decayed by a second-order process with a rate constant inversely proportional to acid concentration. The rate results were consistent with a mechanism for the decay process as follows. Semiquinone undergoes rapid one-electron disproportionation by oxidation and reduction. The product of the oxidation (analog of phenazothionium ion) is unstable and is involved in two competing reactions. One is hydrolysis to sulfoxide, which is completely reversible to addition of acid. The other is a two-electron disproportionation producing the corresponding 3-hydroxyphenothiazine. In derivatives substituted on the nitrogen, the 3-hydroxy substitution is highly inhibited. The decay rates of the 3-substituted derivatives obey a Hammett relationship using *para*-substituent constants, while the 2,10-substituted derivatives obey a Hammett relationship using *meta*-substituent constants. An interesting relationship involving midpoint electrode potentials upon oxidation of certain 3-substituted phenothiazine derivatives is demonstrated.**

COMPOUNDS formed by substitution of halogens and other functional groups onto phenothiazine vary greatly in type of pharmacologic activity and potency (1), especially when the substitution is made on the nitrogen bridge atom. However, there are many physicochemical properties common to all of the compounds which are characteristic of phenothiazine itself. Bernthsen (2) first described the synthesis of phenothiazine, but interest in the electron donor propensity of the compound and its derivatives was not prevalent until the theory of univalent oxidation–reduction was propounded by Michaelis (3).

Chemical interest in phenothiazine and many of its derivatives stems from the fact that their oxidations occur in distinct univalent steps, especially in highly acidic solutions. The odd-electron intermediate or free radical resulting from the first oxidation is called a "semiquinone," based on its structural similarities with the free radical intermediate in the hydroquinone-quinone oxidation–reduction system (4). Until the last decade, when the technique of electron spin resonance (ESR) spectroscopy was developed (5), methods of study of odd-electron intermediates were limited to potentiometric titration, paramagnetic susceptibility, and spectrophotometry. Semiquinones of members of the phenothiazine family of compounds, generated by various methods, have been detected and studied by ESR (6–10).

Some suggestions have been made that there is a direct correlation between the stability of the free radical intermediate in the oxidation of these phenothiazine derivatives and the intensity of the biological action (11). The present research is a fundamental chemical study of the effect of substituents on the kinetic and thermodynamic stability of the first oxidation product of the phenothiazine derivatives. The techniques of electron spin resonance spectroscopy and absorption spectrophotometry are utilized.

The oxidation of phenothiazine and several of its derivatives in acidic media proceed univalently through two successive distinct steps, as has been shown by Michaelis (12) using potentiometric titration. The chemical equations of these steps are

$$H^+ + R = S^+ + e^- \text{ and } S^+ = T^+ + e^-$$

where R, S, and T, respectively, represent the reduced form (phenothiazine), the semiquinone intermediate, and the totally oxidized form (phenazothionium). The stability of the semiquinone may be expressed by the semiquinone formation equilibrium constant, $K = (S^+)^2/(R)(T^+)(H^+)$, corresponding to the chemical equation, $H^+ + R + T^+ = 2S^+$. In the absence of complicating reactions, upon mixing equivalent amounts of oxidizing agent and reduced form, the semiquinone concentration has its maximum value, and (R) will be equal to $(T^+)$. This 1:1

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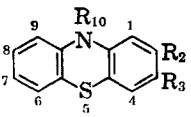
equivalent condition is studied in this paper and will be understood unless otherwise stated.

It was the initial intent of this research to determine the semiquinone formation constants of a series of substituted phenothiazines from semiquinone concentrations measured by ESR and optical photometry. This proved to be impracticable. Equilibrium cannot be established owing to the continuous decay of the semiquinone by another route, except when the disproportionation is suppressed; therefore, our studies have yielded primarily rate data. These data have shown some interesting dependencies on the nature and site of the phenothiazine substitution.

The following is a generalized structure of the phenothiazine derivatives studied in this investigation:




## EXPERIMENTAL

**Apparatus.**—The electron spin resonance spectrometer previously described (6), was altered for improved sensitivity by addition of a Varian 100-Kc. field modulation and control unit and a multipurpose cavity. A Varian flat cell with a volume of 0.04 ml. within the microwave cavity was used. For all ultraviolet and visible absorption spectra the Cary model 11 spectrophotometer was used. All measurements were made at room temperature.

**Materials.**—The phenothiazine derivatives used in this research include the following in which the substitution is made in the 3-position,[1] synthesis and purification procedures for which have been described (13): 3-methoxy-, 3-methyl-, 3-phenyl-, 3-chloro-, 3-bromo-, and 3-iodophenothiazine. A few of the compounds required purification by sublimation to obtain proper melting points. The following phenothiazines substituted in the 10- and 2,10-positions were investigated: acepromazine hydrochloride, chlorpromazine hydrochloride, ethopropazine hydrochloride, fluphenazine dihydrochloride, mepazine acetate, methoxypromazine maleate, perphenazine dihydrochloride, prochlorperazine ethanedisulfonate, promazine hydrochloride, promethazine hydrochloride, pyrathiazine hydrochloride, thiopropazate dihydrochloride, trifluoperazine dihydrochloride, triflupromazine hydrochloride, and trimeprazine tartrate.[2]

Phenothiazine was obtained commercially from Eastern Chemical Corp.; it was recrystallized twice from benzene–petroleum ether. A sample sublimed under reduced pressure had the same melting point (182°) and ESR spectrum as the freshly recrystallized sample.

The compound, 1,1-diphenyl-2-picrylhydrazyl, used as a free radical standard was prepared from the hydrazine by the method of Goldschmidt and Renn (14). Solutions of ceric ammonium sulfate (obtained from the G. Frederick Smith Co.) were standardized by potentiometric titration with oxalic acid (15). All other reagents and solvents were of C.P. grade.

**Experimental Procedure.**—Semiquinone free radicals were formed by oxidation of the phenothiazine derivatives to the one equivalent point. The free radical was prepared in a solvent mixture described below, and its concentration was followed with time by the height of the ESR signal. For each sample a control in 3 *M* sulfuric acid, referred to as the acid-stabilized solution, was used as a comparison standard of fixed concentration. With exceptions mentioned below, the acid-stabilized free radical was invariant with time and constituted 100% of the available phenothiazine derivative.

With phenothiazine and promazine, an additional experiment was performed. As the reaction proceeded, aliquots were withdrawn from the reaction vessel and acidified at successive times, and the resulting free radical concentrations were measured. These compounds thus yielded two sets of data, one representing the free radical as it decayed *in situ*, the other a reconstituted free radical concentration.

Ceric ammonium sulfate was used as oxidizing agent because of the high value of its electrode potential, the univalency of its reduction, and the absence of ring substitution side reactions. Its standardized solutions were made up to contain 0.2% sulfuric acid to prevent hydrolysis. The different solubility characteristics of ceric ammonium sulfate and the phenothiazine derivatives (together with their reaction products) dictated a compromise solvent system, which was 60% (v/v) aqueous solution of acetic acid for the 3-substituted derivatives and 50% for the 10-substituted derivatives.

The preparation of the semiquinone for each rate experiment was accomplished by the immediate addition of a measured quantity of aqueous ceric solution to a glacial acetic acid solution of the phenothiazine. The order of mixing of the reagents was designed to minimize the possibility of oxidation of the phenothiazine derivative past the semiquinone stage. The concentrations of the phenothiazine derivatives and the oxidizing agent upon mixture were 0.002 *M*, and the resulting average oxidation state corresponded to that of the semiquinone free radical. The pH was approximately 2. The acid-stabilized control solutions were prepared by the addition of an acidified ceric reagent to an acetic acid solution of the phenothiazine derivative. The final volume of 12 ml. contained 2 ml. of concentrated sulfuric acid and was 0.0017 *M* in the phenothiazine derivative and ceric ion. A factor of 6/5 was used in comparing the stabilized to the unstabilized solutions.

Separate rate studies using visible spectrophotometry were performed for promazine and four of its 2-substituted derivatives. Promazine and methoxypromazine semiquinones decayed slowly enough that successive passes through the visible region of the spectrum (400 to 700 mμ) could be made and the progress of the entire spectrum studied with time, as shown in Fig. 1. For the other derivatives, the spectrophotometer was set on the wave-

[1] The authors thank Dr. J. Cymerman Craig for purified samples of the 3-substituted phenothiazines.

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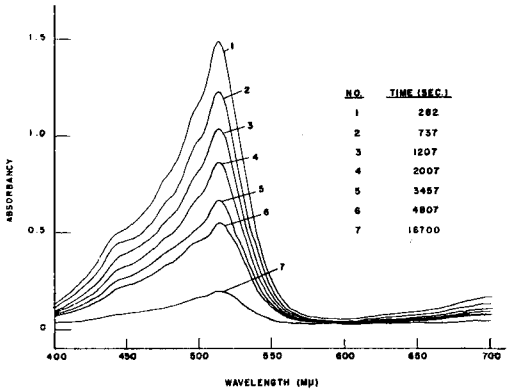



Fig. 1.—Change with time of the visible absorption spectrum of promazine semiquinone. The times at which the maximum absorption wavelengths were recorded are tabulated on the figure.

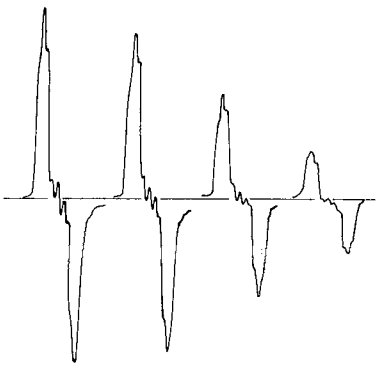


Fig. 2.—ESR spectra of promazine semiquinone showing its change with time. The largest spectrum is that of the acid-stabilized control. The other spectra were made at 9, 30, and 90 min.

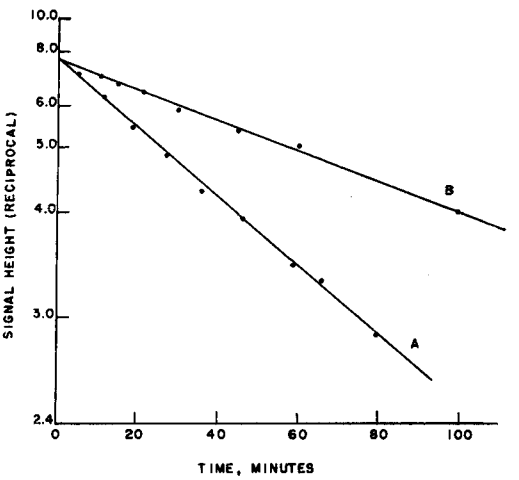



Fig. 3.—Reciprocal of ESR signal height of phenothiazine semiquinone plotted against time. The mixture is initially 0.002 *M* in phenothiazine and ceric ion. Key: A, decay *in situ* in sulfuric acid; B, reconstituted samples plotted against time at which acidification occurred.

length of maximum absorption previously determined for the respective semiquinone, and the time dependence of the absorbance was recorded directly.

**Concentration Determination.**—An acid-stabilized control sample of each compound, as described above, served as a reference standard of concentration (0.002 *M*) of semiquinone, and the proportionality of ESR signal height to free radical concentration provided a means of concentration measurement accurate to within 2 or 3%. At small semiquinone concentrations (less than about $10^{-5}$ *M* under experimental conditions prevailing in this research) the signal-to-noise ratio approaches unity, and concentration measurements become quite inaccurate. Detailed hyperfine structure, which is characteristic of the molecular structure, was intentionally suppressed by the adjustment of the field modulation amplitude in order to produce spectra of common shape according to the class of the derivative. The spectra of the phenothiazine semiquinone and of other derivatives not substituted in the 10-position consisted of the four hyperfine lines produced by nitrogen with an attached proton. That of each 10-substituted derivative consisted of a single line (with minor hyperfine lines) with a width of about 20 gauss. Typical ESR recordings for promazine are shown in Fig. 2.

An absolute determination of the semiquinone concentration based on a benzene solution of 1,1-diphenyl-2-picrylhydrazyl, standardized by its 520 mμ absorbance (16), showed that within the accuracy of the method the acid-stabilized control was entirely in the free-radical form. For the present purposes, a more convincing confirmation of this assumption is the fact that acid-stabilized control samples of each compound studied in this research yielded an ESR spectrum having the same second integral (5).

## RESULTS

The experimental data, consisting of ESR signal heights at successive times, were plotted to determine the order and the rate constants of the reactions. For each of the 22 substances studied, the data produced a straight line in a plot of the reciprocal of signal height against time, indicating a second-order decay process with respect to the semiquinone. The slope of this plot, supplemented by the initial semiquinone concentration, was used to compute the rate constant. The initial concentration was computed from the ratio of the zero time intercept of the ESR signal to the signal obtained from the acid-stabilized control of the respective phenothiazine derivative. Evidence outlined above justifies the assumption that in the control sample the phenothiazine derivative is completely in the semiquinone form.

When phenothiazine is oxidized with one equivalent of oxidizing agent at an acid concentration of 7 *N* or greater, the semiquinone free radical is formed instantaneously, and its concentration remains constant for several days. At an acid concentration less than 2 *N*, the same procedure produces an immediate free radical concentration nearly equal to that in the 7 *N* acid, but it proceeds to decay by a second-order process, as shown as curve A of Fig. 3. When aliquots of a solution which had undergone partial decay were acidified, the free radical concentration immediately increased to a new value and

TABLE I.—SECOND-ORDER DECAY RATE CONSTANTS AND ELECTRODE POTENTIALS OF THE SEMIQUINONES FROM PHENOTHIAZINE SUBSTITUTED IN THE 3-POSITION

| Compd. | Rate Constant, 1/mole/min. | Electrode Potential, mv.[a] | $\sigma_p$ |
|---|---|---|---|
| 3-Methoxyphenothiazine | .65 | 590 | −.27 |
| 3-Methylphenothiazine | 3.2 | 651 | −.17 |
| 3-Phenylphenothiazine | 18.6 | 679 | +.01 |
| Phenothiazine | 58 | 696 | 0.00 |
| 3-Chlorophenothiazine | 302 | 763 | +.23 |
| 3-Bromophenothiazine | 385 | 766 | +.23 |
| 3-Iodophenothiazine | 597 | 758 | +.28 |

[a] *Reference 22.* Values at 20° in 80% v/v acetic acid, pH = 2. [b] Substituent constants from Jaffe, H. H., *Chem. Rev.*, **53**, 191(1953).

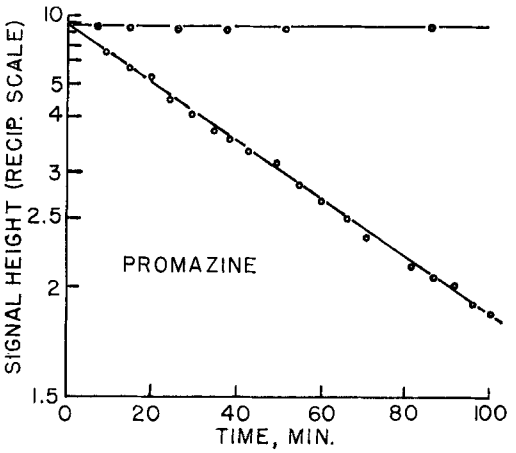
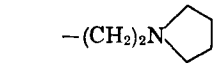
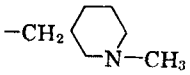
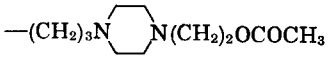
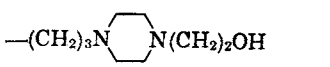
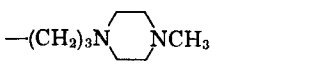
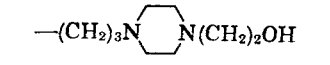
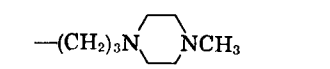



Fig. 4.—Reciprocal of ESR signal height of promazine semiquinone plotted against time. The mixture is initially 0.002 *M* promazine and ceric ion in 50% acetic acid. The upper curve is the ESR signal height after acidification.

remained constant thereafter. The new concentration, plotted against the length of time the solution had been at the lower acid concentration, is shown as curve B of Fig. 3. From this graph it appears that two second-order decay processes are proceeding simultaneously, one of which is reversed by an increase in the acid concentration. The mechanism proposed for this reaction is discussed briefly below. These data for phenothiazine, though carried out in 1 *N* sulfuric acid instead of the acetic acid solution used generally in this paper, are used in Fig. 3 because of the completeness of the experiment. Simi

TABLE II.—SECOND-ORDER DECAY RATE CONSTANTS OF THE SEMIQUINONES OF PHENOTHIAZINE SUBSTITUTED IN THE 2- AND 10-POSITIONS

| Parent Compd. | Substituents: 2-Position | Substituents: 10-Position | Rate Constant, 1/mole/min. |
|---|---|---|---|
| | | **Phenothiazine Series** | |
| Promazine | H | $-(CH_2)_3N(CH_3)_2$ | 12.3 |
| Pyrathiazine | H |  | 308 |
| Ethopropazine | H | $-CH_2CH(CH_3)N(C_2H_5)_2$ | Very weak signal |
| Promethazine | H | $-CH_2CH(CH_3)N(CH_3)_2$ | Very weak signal |
| Mepazine | H |  | 24 |
| Trimeprazine | H | $-CH_2CH(CH_3)CH_2N(CH_3)_2$ | 115 |
| | | **2-Chlorophenothiazine Series** | |
| Chlorpromazine | Cl | $-(CH_2)_3N(CH_3)_2$ | 168 |
| Thiopropazate | Cl |  | 109 |
| Perphenazine | Cl |  | 304 |
| Prochlorperazine | Cl |  | 243 |
| | | **2-Trifluorophenothiazine Series** | |
| Triflupromazine | $-CF_3$ | $-(CH_2)_3N(CH_3)_2$ | 870 |
| Fluphenazine | $-CF_3$ |  | 1100 |
| Trifluoperazine | $-CF_3$ |  | 1280 |

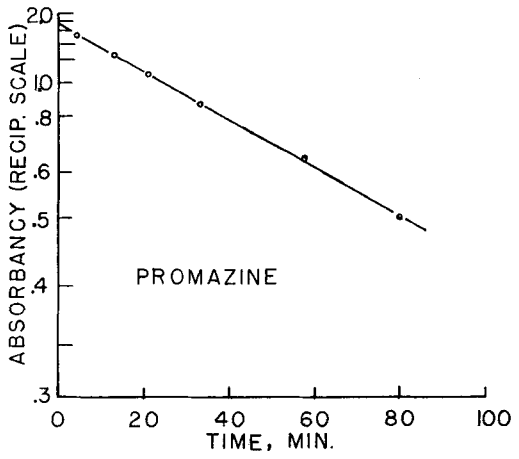



Fig. 5.—Reciprocal of the absorbance of promazine at 513 mμ using the data from Fig. 1.

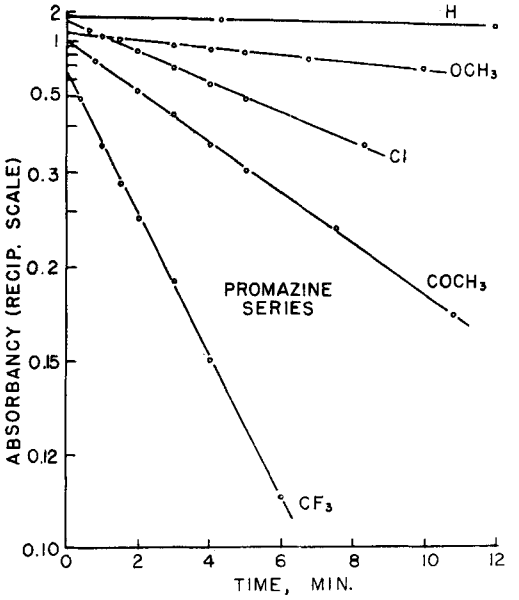



Fig. 6.—Reciprocal of the maximum absorbance for the promazine series. The uppermost curve, of promazine itself, is from the same data as Fig. 5 to a different scale, included here for comparison.

TABLE III.—SECOND-ORDER DECAY RATE CONSTANTS OF PROMAZINE SERIES FROM ESR AND VISIBLE ABSORPTION SPECTRA

| Compd. | Rate Constant, 1/mole/min. From ESR | From Absorption | λ (mμ) |
|---|---|---|---|
| Promazine | 12.3 | 14.8 | 513 |
| Methoxypromazine | 29 | 49 | 570 |
| Chlorpromazine | 168 | 286 | 528 |
| Acepromazine | 320 | 340 | 516 |
| Triflupromazine | 870 | 1060 | 502 |

lar results with the lower rate constant given in Table I are obtained when the pH 2 condition prevails.

The principal results of this study are the effects on the semiquinone decay rate of various substituents at various positions in the phenothiazine molecule. Column 2 of Table I contains the second-order decay rate constants of the semiquinones of phenothiazine and six 3-substituted phenothiazines in 60% acetic acid. The chemical behavior of these compounds is similar to that of phenothiazine. No systematic study of their acid-reconstituted free radical concentrations were carried out except to note that they were similar in character to that of phenothiazine.

The effect on the decay process of substitution on the nitrogen is of particular interest. When subjected to 1 *N* acid, the *N*-substituted derivatives undergo much slower semiquinone decay than does phenothiazine, while at a pH of approximately 2 (no acid added to the 50% acetic acid solvent) their decays are only slightly faster than that of phenothiazine in 1 *N* acid. This behavior is shown for promazine in the lower curve of Fig. 4. As the upper curve of Fig. 4 shows, subsequent acidification reestablishes the original concentration regardless of the amount of decay which has already occurred. The results with 10-methylphenothiazine (not reported here) and other *N*-substituted derivatives are similar. Certain exceptional members of the series, however, such as triflupromazine, undergo slow decay of the free radical with time even in high concentrations of acid. The rate constants for the second-order decay of the semiquinones of the 10-substituted phenothiazines are listed in Table II. The compounds chosen for this study include only those containing aliphatic amino groups, which are of general biological interest. They are classified into three series characterized by the substituent in the 2-position.

Absorption spectrophotometric studies of promazine and four of its 2-substituted derivatives were carried out for confirmation of the ESR studies. The second-order plots of the decay are shown in Figs. 5 and 6, in which reciprocal of absorbance is plotted against time. As Table III shows, the rate constants determined therefrom are in good agreement with those determined from ESR data. This table contains two compounds which are not included in the ESR data of Table II, methoxypromazine and acepromazine. The wavelengths of the peaks of the visible absorption bands for the respective semiquinones are also tabulated.

## DISCUSSION

The stable oxidation products of phenothiazine furnish the key to the decay process of the semiquinone. Phenothiazine-5-oxide is known to be one of the first and most stable oxidation products of phenothiazine (17). In acidic solution 3-hydroxyphenothiazine is formed, even in an acid as weak as acetic acid (18). The phenothiazines substituted in the 10-position are known to be primarily oxidized to their corresponding sulfoxide (19), even under mildly acidic conditions, by electrochemical oxidation (20).

The oxidation mechanism of phenothiazine and its derivatives based on the kinetics of intermediate

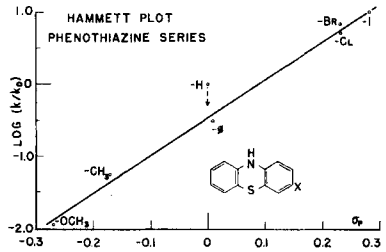



Fig. 7.—Hammett plot of the decay rate constants of the 3-substituted phenothiazine semiquinones, using the *para*-substituent constants. The arrow indicates the shift of the unsubstituted phenothiazine point to correct for the fact that both the 3- and 7-positions are free to be attacked.

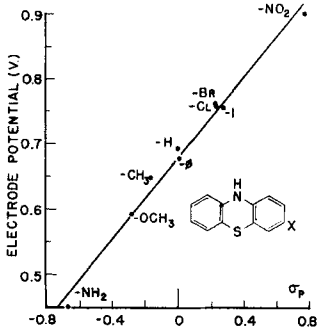



Fig. 8.—Midpoint electrode potentials (22) of the 3-substituted phenothiazines as a function of the Hammett *para*-substituent constants.

semiquinone free radicals is a subject of a separate publication (21). It is there shown that disproportionation of the semiquinone and subsequent hydrolysis and disproportionation of the totally oxidized form occur by the following chemical reactions:

$$2S^+ = R + T^+ + H^+ \quad \text{Reaction } 1$$

$$T^+ + H_2O = SO + H^+ \quad \text{Reaction } 2$$

$$2T^+ \rightarrow R + RO + 2H^+ \quad \text{Reaction } 3$$

The SO represents phenothiazine sulfoxide; RO, 3-hydroxyphenothiazine; the other symbols are defined above. Disproportionation of the semiquinone by Reaction *1* is suppressed by acid, which explains the stability of the free radical in the acid-stabilized control. Decay by Reactions *2* and *3* proceeds to the degree that the unstable phenazothionium form, $T^+$, is available from the disproportionation. The sulfoxide formation (Reaction *2*) is reversed by addition of acid, whereas the 3-hydroxy formation (Reaction *3*) is not. This explains the tendency for the final product to be the sulfoxide at higher pH conditions and 3-hydroxy phenothiazine at low pH. The 10-substituted compounds are oxidized with greater difficulty to the 3-hydroxide derivative and are therefore more stable.

Under the conditions prevailing in these experiments, the semiquinone concentrations of all the phenothiazine derivatives at the one-equivalent point constituted close to 100% of the reduced form originally present, as based on ESR and on optical absorption spectrophotometry. Integration of the ESR spectra of the 3-substituted phenothiazines yielded concentration values of semiquinones corresponding to between 70 and 110% of the total phenothiazine. Several of the 10-substituted derivatives yielded similar values. Analyses of the ultraviolet spectra of the 10-substituted compounds, similar to that described by Borg and Cotzias (9), confirmed the ESR results. The reduced forms of these derivatives have strong absorption maxima between 255 and 260 mμ, while the semiquinones have strong maxima between 265 and 280 mμ. The calculated concentrations of the semiquinones of promazine, chlorpromazine, and methoxypromazine were between 80 and 100% of the total compound present. Accurate absolute values are not directly determinable from the spectra due to overlap of lines and other complications.

In the less acidic conditions, while the percentages of semiquinone are undoubtedly smaller, the measurements are even less certain because of the rapidity of semiquinone decay at lower acid concentration. Extrapolation of the decay curves to zero time would in principle yield a meaningful stability constant, as there is evidence to indicate that the reversible oxidation–reduction processes are extremely rapid compared to the decay processes. However, to the degree that the initial semiquinone concentration is decreased to a value measurably different from 100%, the rate of decay is correspondingly increased, with the result that uncertainties in the time of mixing and reading contribute additional errors to the extrapolated values. This would appear to confirm the interpretation that the phenazothionium form is the unstable link in the chain. In all the semiquinones studied at the pH 2 conditions, the extrapolated initial concentrations were between 30 and 70% of the acid-stabilized values.

**3-Substituted Phenothiazine Derivatives.**—It is of considerable interest and of predictive value that the rates of decay of the 3-substituted derivatives yield a linear correlation in a Hammett plot using the *para*-substituent constants, as shown in Fig. 7. All of the points fall very near the line except that for phenothiazine. If the major decay product is the 3-hydroxy derivative, the fact that the 3- and 7-positions are identical gives phenothiazine two positions for the appropriate attack. On the other hand, in the 3-substituted derivatives, one of these positions is blocked, and other things being equal, one would expect the phenothiazine to be twice as reactive as the derivative. If the value of the rate constant for phenothiazine is decreased on the plot by a factor of 2 (or 0.301 is subtracted on the logarithmic scale), all of the points fit a linear Hammett relationship.

Craig *et al.* (22) have measured values of the midpoint electrode potentials for the univalent oxidation of a number of compounds of this series. These values (not their logarithms), when plotted against the *para*-substituent constants (Fig. 8), yield a linear plot, indicating a possible logarithmic Hammett relationship involving the semiquinone formation constants. (This follows from the logarithmic relation between the standard electromotive force and the equilibrium constant.)

**10- and 2,10-Substituted Phenothiazine Derivatives.**—In the tranquilizer series of phenothiazines, the substituents on the 2-position have a more

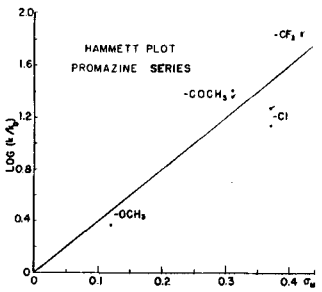



Fig. 9.—Hammett plot of the decay rate constants of the 2,10-substituted phenothiazine semiquinones (promazine series) using the *meta*-substituent constants. The points with tails represent the values calculated from spectrophotometric data; the plain points are from the ESR data.

predictable effect on the semiquinone decay rate than does the tertiary alkylamine group at the 10-position. Table II lists the second-order decay rate constants as determined from ESR data for 13 members of this series. The principal effect of the 10-substituent, as mentioned earlier, is the inhibition of the acid-irreversible decay of the semiquinone as compared with the unsubstituted derivative. As to the relative rates of the various compounds listed, certain tentative effects are noted which may arise from the length or the branching of the chains. Further compounds must be studied before definitive relationships are established. It is presumed that the very weak signal obtained from the semiquinones of ethopropazine and promethazine is the result of a decay rate too rapid to observe in its measurable stages by the technique used in this research. In this table the compounds are grouped according to their 2-position substituent for comparison.

The subseries containing as its 10-substituent the 3-dimethylaminopropyl group is referred to here as the promazine series. Semiquinone decay rates of this series are listed in Table III as measured independently by ESR and optical spectrophotometric methods. The two methods show agreement within the order of magnitude of the expected accuracies. For purposes of correlation, they are plotted on a Hammett plot in Fig. 9, using as abscissa the *meta*-substituent constants. In this figure the points with the tails represent the calculations from the spectrophotometric data. Promazine itself is not shown on this plot because, as the reference substance, it determines the origin. It is to be noted that though the points do not fall as close to a straight line as do those for the 3-substituted series, there is an unmistakable trend, with only the chlorpromazine departing appreciably from the proper sequence.

The results of these free radical studies are presented here in the hope that they will further understanding of the mechanism or mechanisms by which members of this important class of therapeutic agents act. If the free radical represents the active form, then information by which its concentration may be modified has been presented. Moreover, if the Hammett relation is generally applicable, it furnishes a mode of calculation useful in predicting the chemical, and perhaps the therapeutic, behavior of these compounds.

It was hoped that pharmacological results could be correlated with the physical data presented here. Unfortunately, such data are not available in quantitative terms. However, it is hoped that this presentation will contribute to the knowledge of phenothiazine derivatives and to the development of experimental techniques for the correlation, quantitation, and prediction of their pharmacological effects.

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