

Anodic Oxidation of N-Substituted Phenothiazines in Aqueous Medium at Graphite Electrode

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The results of d.c. voltammetry and cyclic voltammetry of a number of N-substituted phenothiazines in acidic solutions as well as buffer solutions of pH range 2-8 reveal that the variable stability of the monocation of phenothiazines in acidic solutions is closely connected with the S-protonation of the monocation. In solutions of low acid concentrations, there is little or no S-protonation and the monocation permits, through resonance, delocalisation of the positive charge located at N atom, creating thereby a positive site, on sulphur atom which is amenable to hydrolytic attack. In solutions of high acid concentrations, there is restriction, due to S-protonation, on the delocalisation of this positive charge, as a result of which there is restriction on the hydrolytic attack. This restriction imparts stability to the monocation. In dication, the loss of second electron from sulphur atom, accompanied by deprotonation, creates the requisite positive site on sulphur atom which renders the dication vulnerable to hydrolytic attack irrespective of the acidity of the medium.

Chemical¹ or electrochemical²⁻⁴ oxidation of N-substituted phenothiazines in aqueous solutions has been shown to yield the corresponding sulfoxides through the formation of monocations which are prone to facile hydrolysis in neutral or less acidic as compared to that in more acidic media. However, no plausible explanation has been offered for the variable stability of the monocation in acidic media. The title investigation is an attempt to arrive at a satisfactory explanation for the phenomenon of variable stability of the monocation. In this investigation we have used d.c. voltammetry (d.c.v.) as well as cyclic voltammetry (c.v.). The anticipated products of oxidation have been prepared separately by exhaustive electrolysis at appropriate potentials and identified spectroscopically.

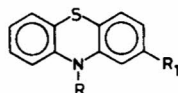
Materials and Methods

The hydrochlorides of promazine (1), chlorpromazine (2), trifluorpromazine (3), promethazine (4) and trifluoroperazine (5), sulphonate of prochlorperazine (6) and tartrate of trimeprazine (7) were procured commercially in pure form and used as such. Acid

solutions of different concentrations varying from 0.001 M to 4 M as well as buffers of different pH values varying from 2 to 8 were used as supporting electrolytes.

A conventional three-electrode assembly with a platinum counter electrode was used in all voltammetric measurements. The working electrodes were prepared from specpure compressed graphite rods (6.5 mm diam) obtained from M/s Johnson Matthey Chemicals Ltd, Royston, England and impregnated by ceresin wax following the procedure reported by Elving and Smith⁵. The d.c.v. measurements were made in hydrodynamic conditions using the tubular graphite electrode⁶ while c.v. measurements were made in stationary solutions using the plane graphite electrode. The other working parameters in various measurements were as follows:

- d.c.v. : Electrode length = 1.2 cm; inner diam = 1 mm; volumetric flow rate = 10 ml min⁻¹; and concentration of anolyte = 10⁻⁴ M
c.v. : Scan voltage = 0-2V (vs SCE); scan rate = 10-12 mV s⁻¹; electrode area = 0.377 cm²; and concentration of anolyte = 5 × 10⁻⁴ M.



R	R ₁
1 - (CH ₂) ₃ -N(CH ₃) ₂ ·HCl	-H
2 - (CH ₂) ₃ -N(CH ₃) ₂ ·HCl	-Cl
3 - (CH ₂) ₃ -N(CH ₃) ₂ ·HCl	-CF ₃
4 - CH ₂ CH(CH ₃)-N(CH ₃) ₂ ·HCl	-H
5 - (CH ₂) ₃ -N(CH ₂ CH(CH ₃)) ₂ ·HCl	-CF
6 - (CH ₂) ₃ -N(CH ₂ CH(CH ₃)) ₂ ·Sulphonate	-Cl
7 - CH ₂ ·CH(CH ₃)·CH ₂ ·N(CH ₃) ₂ ·Tartrate	-H

Results and Discussion

The d.c. voltammograms obtained for anodic oxidation of chlorpromazine hydrochloride as a representative in all the background solutions are presented in Fig. 1. Similar voltammograms were obtained for all other phenothiazines.

Similarly, cyclic voltammograms obtained only for promazine hydrochloride as a representative in

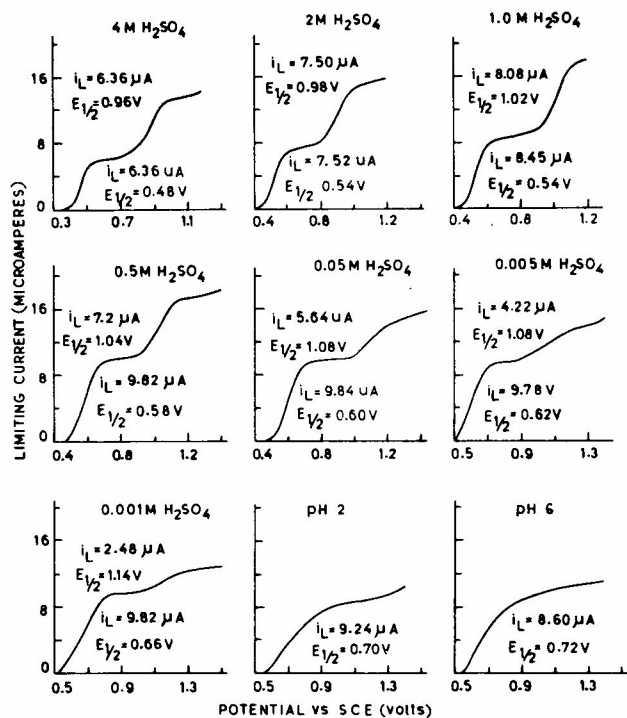


Fig. 1—DC voltammograms for the oxidation of chlorpromazine hydrochloride in H_2SO_4 solutions of different concentrations and buffers of pH 2 and pH 6

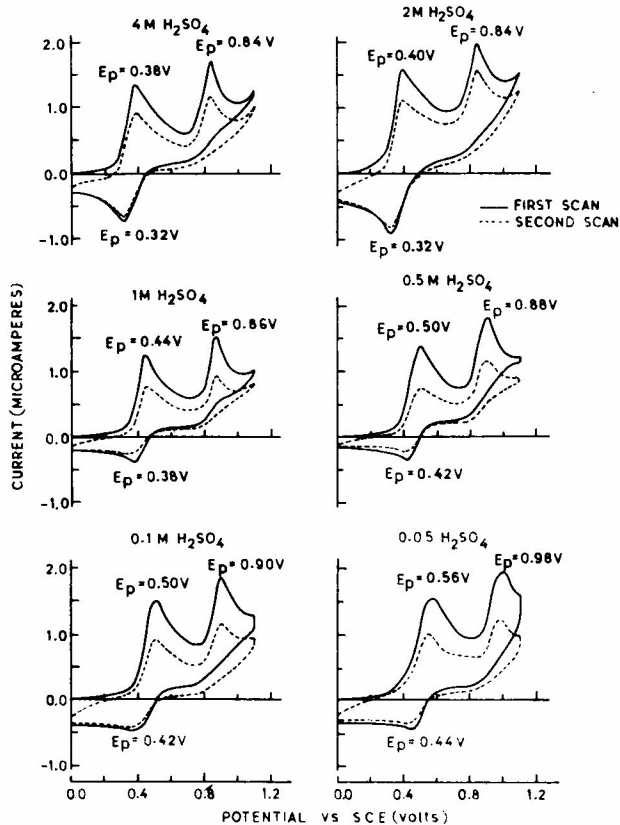


Fig. 2—Cyclic voltammograms for the oxidation of promazine hydrochloride in the potential range of 0-1.1 V (vs SCE) in various acid solutions

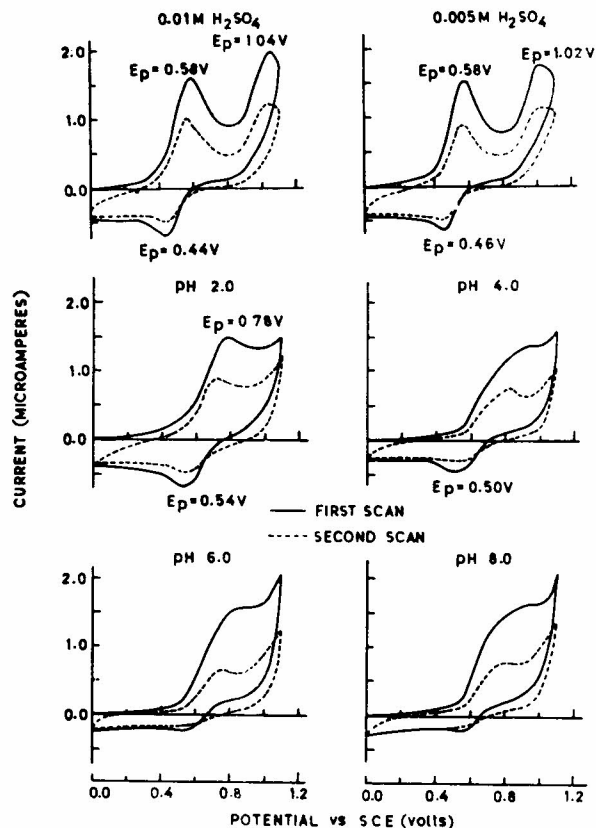


Fig. 3—Cyclic voltammograms for the oxidation of promazine hydrochloride in the potential range of 0-1.1 V (vs SCE) at low acidities and in various buffer solutions

various background solutions are presented in Figs 2 and 3. More or less similar cyclic voltammograms were obtained in all other cases.

The salient features of d.c.v. and c.v. may be summed up as follows:

(i) In buffer solutions of pH 2-8, each phenothiazine gives only one anodic wave in d.c.v. and only one anodic peak (that too not very well-defined) in c.v.

(ii) Unlike in buffer solutions, in 0.001 *M* sulphuric acid solution, each phenothiazine exhibits two anodic waves in d.c.v. and two anodic peaks in c.v. However, the height of the second wave in d.c.v. and that of the second peak in c.v., is considerably smaller than that of the first wave.

(iii) With increase in the concentration of the acid, there is progressive increase in the magnitude of the second step in d.c.v. as well as c.v., the height of the first step remaining more or less the same. Ultimately, when the concentration of the acid becomes 1 *M*, the heights of the two waves in d.c.v. and of the two peaks in c.v. become almost equal.

(iv) In solutions of higher acid concentrations (*viz* 1 *M*, 2 *M*, and 4 *M*), although the heights of the two steps remain almost equal, there is a distinct decrease in the absolute magnitude of the heights of both the steps (*cf.* Figs 1-3).

The above observations lead to the following conclusions:

(a) The formation of only one anodic wave in d.c.v. and one anodic peak in c.v. in buffer solutions of pH 2 to 8 indicates that the electrogenerated monocation is unstable in these solutions and undergoes hydrolysis instantaneously to give the corresponding sulphoxide, as postulated by Merkle and Discher² and supported by the observations made by Michaelis *et al.*¹. The electrode process in this case, evidently, involves a one-electron change. The electron liberated from hydrolysis is taken up by another molecule of the monocation to regenerate the original phenothiazine.

The magnitude of the limiting current, i.e. about 10 μ A, obtained in d.c.v., also supports the fact that the electrode process yielding the monocation involves one-electron change⁷⁻⁸.

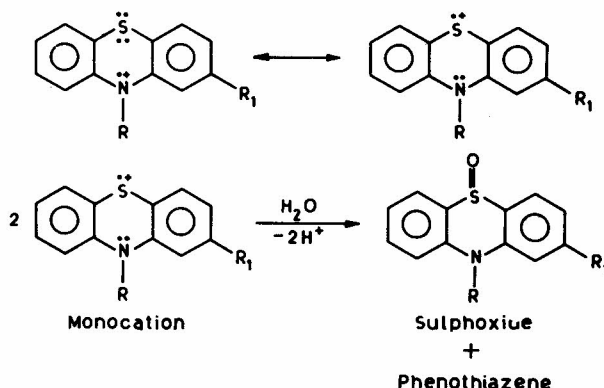
(b) The formation of a small second step in d.c.v. as well as in c.v. in 0.001 *M* acid solution indicates that at least a small fraction of the monocation formed in this solution is stable towards hydrolysis. The continuous increase in the magnitude of the second step with increase in the acid concentration till 1 *M* indicates formation of more and more of monocation not prone towards hydrolysis.

(c) The formation of two anodic steps of almost equal heights in d.c.v. and c.v. at [acid] > 1 *M* indicates that the monocation is almost stable in this acid range.

(d) A distinct decrease invariably observed in the absolute magnitude of the two steps in solutions of very high acid concentrations, viz., 1 *M*, 2 *M* and 4 *M* is probably due to an increase in the viscosity of the medium. The viscosities of 1 *M*, 2 *M* and 4 *M* solutions of sulphuric acid are 1.085, 1.298 and 1.724 poise, respectively at 25°C. The limiting currents calculated on the basis of diffusion coefficients corresponding to the above viscosity values have been found to be in excellent agreement with the values determined experimentally.

Our observations are distinctly different from those of earlier workers^{9,2}. For example, Merkle and Discher² did report stabilisation of the monocation (and two-step anodic oxidation of phenothiazines) but only in solution of very high acid concentration, viz. 12 *N*. Though voluminous work has been done on the anodic oxidation of phenothiazines in aqueous and non-aqueous media¹⁰⁻¹⁸, no satisfactory explanation has been offered so far for the variable stability of the monocation in the acid media. The results of the present investigation reveal that an essential pre-requisite for the hydrolysis of the monocation is the existence of a positive site at the sulphur atom. Any situation which inhibits the creation of this site would tend to impart stability to the monocation towards hydrolysis.

The monocation electrogenerated by the loss of electron from N atom⁹, permits through resonance the migration of the positive charge from N to S atom creating thereby a positive site which induces hydrolysis of the monocation, as illustrated in Scheme 1:

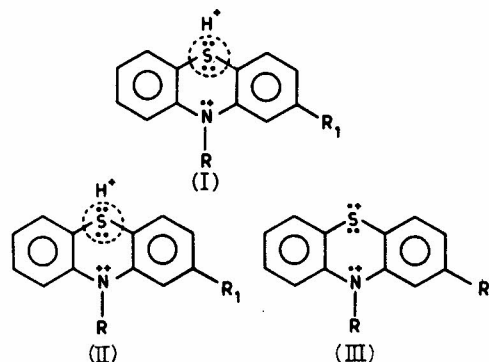


Scheme 1

This explains the instantaneous and complete conversion of the monocation formed in buffers or in acid solutions of very low acid concentrations into the corresponding sulphoxide.

In acid solutions of moderate and high concentrations, parent phenothiazines get protonated at N as well as at S sites. The degree or extent of protonation goes on increasing with increase in the acidity of the medium and ultimately when the concentration of the acid is 1 *M* and above, protonation is complete. A fully protonated phenothiazine when subjected to anodic oxidation, loses an electron from N atom (as already mentioned) forming the monocation. The loss of electron results in immediate deprotonation of the N atom as demanded by valency considerations. The monocation formed from a protonated phenothiazine may thus be represented by structure (I).

This structure does not permit the migration of the positive charge from N to S atom thus preventing the creation of the positive site and the subsequent hydrolysis of the monocation.



At intermediate acid concentrations (i.e., between 0.005 *M* and 1 *M*) there is understandably partial protonation of the original phenothiazine at the sulphur atom and hence there is only partial stabilisation of the monocation towards hydrolysis.

Another factor which may be responsible for the higher stability of the monocation in high acid concentration is the poor availability of the nucleophile in strongly acidic solutions.

The stability of the monocation in strongly acidic solutions is further proved by (i) the appearance of a reversible redox couple with almost exactly equal magnitude of oxidation and reduction peaks during c.v., of each phenothiazine carried out by restricting the potential to the first stage of oxidation and (ii) by the appearance of an intense ESR signal.

For the formation of the dication, the second electron may be lost either from nitrogen (see structure II) or from sulphur (see structure III):

However, the loss of second electron from nitrogen atom appears to be highly improbable because of the following reasons: (i) formation of a dication with two positive charges at the same atom would be less favoured thermodynamically; (ii) if at all the dication (II) is formed, it would be stable towards hydrolysis in highly acidic media due to complete S-protonation. But actually, it undergoes hydrolysis instantaneously to yield sulfoxide in spite of the high acidity of the medium; (iii) the dication (II) should be prone to easy electro-reduction. However, no such reduction is observed during the reverse scan in c.v. (Fig. 3), ruling out the possibility of formation of dication (II).

The only permissible structure for the dication is, thus, structure (III) which is vulnerable to hydrolytic attack due to the presence of the positive site on sulphur atom and yields sulfoxide instantaneously. In this case, the nucleophile (H_2O) is no doubt weak but since the substrate (the doubly positively charged species) is a strong electrophile, the hydrolytic attack is no less forceful.

The ultimate products of anodic oxidation of phenothiazines are thus the corresponding sulfoxides which (i) in solutions of very low acid concentrations result from the hydrolysis of the unprotonated monocation and (ii) in solutions of high acid concentrations these results from the hydrolysis of protonated dications. The oxidation process thus involves an *EC* mechanism in solutions of very low acid concentrations but an *EEC* mechanism in solutions of high acid concentrations.

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