

Behaviour of Thymoquinone & Its Derivatives at Dropping Mercury Electrode

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Thymoquinone and its derivatives, viz. semicarbazone, oxime, hydrazone, etc., have been studied polarographically in 5-8% ethanolic BR buffers. All the compounds give diffusion-controlled, reversible waves. The $E_{1/2}$ was found to lie in the potential range +0.40 to -1.60 V (vs SCE). A possible mechanism for the electrode processes has been put forward, and the polarographically determined values of pK from the $E_{1/2}$ versus pH plots are reported.

POLAROGRAPHIC behaviour of *p*-benzoquinone and its derivatives has been studied by several workers¹⁻⁵. Such studies have, however, not been undertaken in the case of thymoquinone. In this paper we report the results of systematic studies on the behaviour of thymoquinone and some of its derivatives at the d.m.e. in 7-8% ethanolic medium. Freshly synthesized samples were used throughout the investigation in spite of the inherent difficulties in their synthesis and purification. This was considered necessary to provide reliable polarographic data.

Materials and Methods

Thymoquinone (I), 3,6-dibromothymoquinone (II), thymohydroquinone (III), thymoquinhydrone (IV), thymoquinoneoxime-1 (V), nitrosothymol (VI), aminothymol (VII), thymoquinone hydrazone-1 (VIII), thymoquinone phenylhydrazone-1 (IX), thymoquinone *p*-nitrophenylhydrazone-1 (X), thymoquinone 2,4-dinitrophenylhydrazone-1 (XI), thymoquinone semicarbazone-1 (XII) and thymoquinone (bis)-semicarbazone (XIII) were prepared by the literature methods⁶⁻⁸ and crystallized from suitable solvents to get TLC pure products.

The buffer solutions were prepared from analar grade chemicals. Stock solutions of I-XIII were prepared in 75% spepure ethanol and later diluted by adding doubly distilled water to the requisite concentration (7-8% ethanol). Only in the case of XII and XIII 15% ethanol was employed to keep the substance in solution.

Polarograms were recorded on a Cambridge pen recording polarograph at $30^\circ \pm 0.1^\circ$. The capillary characteristic was $3.75 \text{ mg}^{\frac{1}{2}} \text{ sec}^{-\frac{1}{2}}$ ($h = 50 \text{ cm}$) at 0.0 V.

The pH of the solutions were checked up by means of Elico pH meter model LI-10 using an all purpose glass electrode. The instrument was previously standardized with phthalate and borate buffers.

Procedure—The buffer (9 ml) was mixed with 1.0 ml of 0.01M stock solution, and purified nitrogen passed for about 15 min before recording the polarograms. The millicoulometric method of DeVries and Kroon⁹ which is generally found to be quite satisfactory for determining the number of electrons involved in the reduction of organic compounds,

presented some difficulties while using CdSO_4 as the standard. This method, however, worked very satisfactorily when benzoquinone ($n = 2$) was used as the standard.

Results and Discussion

Amongst the thirteen thymoquinones studied polarographically, a single-step oxidation wave was obtained for thymohydroquinone (III) and aminothymol (VII), a composite wave for thymoquinhydrone (IV) and the rest of the compounds gave reduction waves. A few typical polarograms are depicted in Fig. 1.

The reduction was diffusion-controlled as shown by the linear plots of i_d versus h and i_d versus [depolarizer]. The temperature coefficient for all the compounds was found to be below 1.6% deg^{-1} . Their reversible character was confirmed by log plots using the value of n from millicoulometry. The diffusion current constant (I) is the same for all the compounds. However, a slight variation observed only in the case of nitrophenylhydrazone substituted thymoquinones (X and XI) can be attributed to the difference in the diffusion coefficients.

Mechanism—The reduction of thymoquinone (I) which involves two-electron transfer, results in the formation of a benzenoid structure (A).

The transference of one electron from (A) produces an anionic free radical called semiquinone (B) which

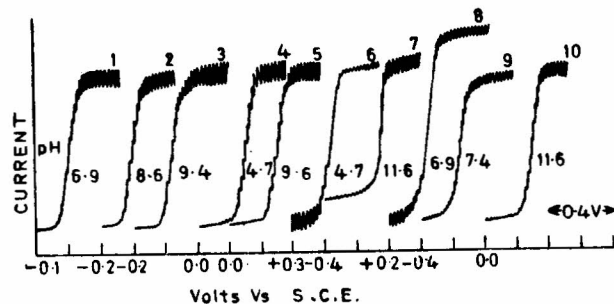


Fig. 1—Some typical polarograms of nitrosothymol (1, 2, 3), thymoquinone oxime-1 (4, 5), aminothymol (6), thymoquinone phenylhydrazone-1 (7), thymoquinhydrone (8), thymoquinone 2,4-dinitrophenylhydrazone-1 (9), and thymoquinone (bis)-semicarbazone (10) at 25° {[Depolarizer]=1 mM; $h=50 \text{ cm}$; $m^{2/3}t^{1/6}=3.75 \text{ mg}^{2/3} \text{ sec}^{-1/2}$ }

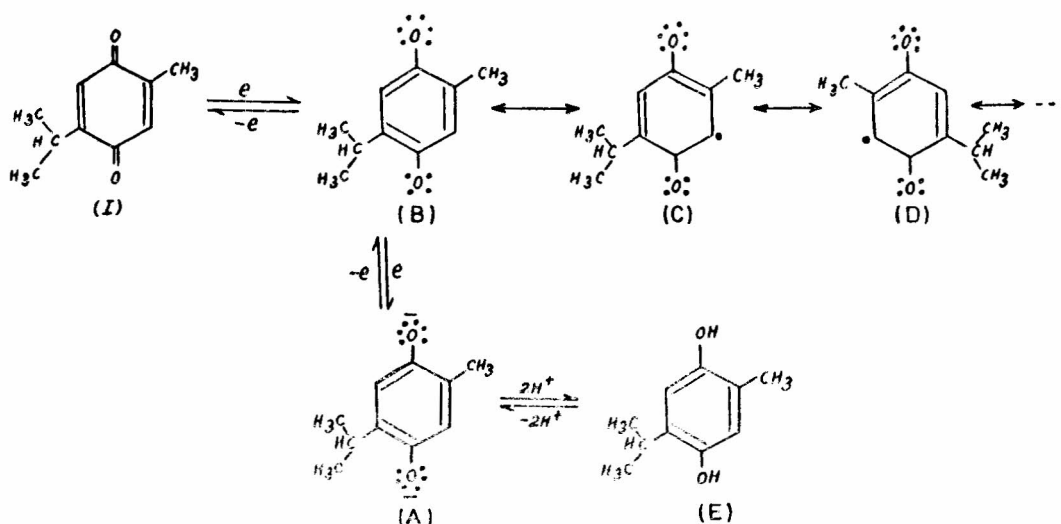


Chart 1

is stabilized by the canonical structures (C) and (D). The semiquinone adds another electron to give (A) as shown in Chart 1.

Stable free radicals of the type (B) have earlier been reported by Muller¹⁰ and Schafer¹¹, who also reported that free electron density is greater at *p*-position than at *o*-position while a small density almost approaching zero exists at *m*-position.

Effect of substituents — Thymoquinone (I) undergoes reduction with more difficulty than 3,6'-dibromothymoquinone (II) upto *pH* 7.4, but at higher *pH* its $E_{1/2}$ values are more positive than those of II (Table 1). This unusual behaviour can be attributed to the inductive effect of Br in II, which becomes more prominent at higher *pH*.

Thymohydroquinone (III) is the reduction product of I, hence $E_{1/2}$ of its oxidation wave is equal to the cathodic $E_{1/2}$ of I. This is evident from the data given in Table 1. Compound IV, which is an equimolecular mixture of I and III, undergoes dissociation into its components at equilibrium¹². In a properly maintained buffer solution a composite wave of quinhydrone has been reported by Muller and Baumberger¹ having $E_{1/2}$ at the same potential as that of quinone and hydroquinone in PO_4^{3-} buffer (*pH* 7.0). Our observations with compound-IV are exactly similar in the same buffer (*pH* 6.9).

Since V and VI are the tautomeric forms¹³, they would exert similar effects on the electron density of $-\text{C}=\text{O}$ group due to $-\text{NOH}$ and $-\text{NO}$ groups. Therefore, both the compounds give similar $E_{1/2}$ (Table 1).

Compounds VIII, IX and X are reduced only in the neutral *pH* range, viz. *pH* 6.4 to 7.4, giving high $E_{1/2}$ values as compared to that of I. This can be attributed to the electron withdrawing phenyl and nitro groups in these compounds. As X possesses a phenyl group and one nitro group, its $E_{1/2}$ is more negative at all *pH* than that of IX which possesses only a phenyl group. Similarly compound XI shows $E_{1/2}$ more negative as compared to that of X due to two nitro groups in the benzene ring.

Compounds XII and XIII possess semicarbazone group¹⁴, which is known to undergo reduction involving 4 electrons but in these compounds it has

been found that they undergo two-electron transfers reduction. This suggests that semicarbazone group in these compounds does not undergo reduction. The reduction of these compounds at comparatively higher negative potentials than I may be due to deactivation of the molecule by semicarbazone group.

Effect of pH on $E_{1/2}$ — The results on the variation of $E_{1/2}$ with *pH* are given in Table 1 and depicted graphically in Fig. 2. The curves consist of two intersecting linear segments and the points of intersection may be taken as corresponding to the dissociation constants¹⁵ of the reduced form of the depolarizers.

A critical examination of the curves would reveal that compounds I and III have identical *pK* values (6.9). This behaviour is understandable since I and III exist in redox equilibrium due to two-electron transfer (as confirmed by millicoulometry). This is further confirmed by the fact that compound-IV which is an equimolecular mixture of I and III gives a composite wave.

In the case of II, the bromo group should facilitate ionization and a *pK* value lower than that for the parent compound I should be obtained. However, due to the combined inductive and mesomeric effects a larger *pK* value (7.4) is obtained. This observation finds support from the $E_{1/2}$ value of this compound which is more negative than that of the parent compound-I (Table 1). Compounds V and VI are the tautomers and so they have, as expected, similar *pK* values (6.4).

The polarographically determined *pK* values for VII and VIII are found to be 7.3 and 7.4. In this connection it may be pointed out that VII can be chemically reduced to VII with the evolution of ammonia. On the other hand in the case of compounds XII and XIII, the *pK* values should slightly differ from each other as XIII has one more semicarbazone group. The points of intersection for compounds XII and XIII are found to be 7.4 and 7.5 respectively.

As already pointed out the compounds IX, X and XI do not undergo reduction either in highly acidic or highly alkaline medium. Hence a complete spectrum of the variation in $E_{1/2}$ with *pH* could not be

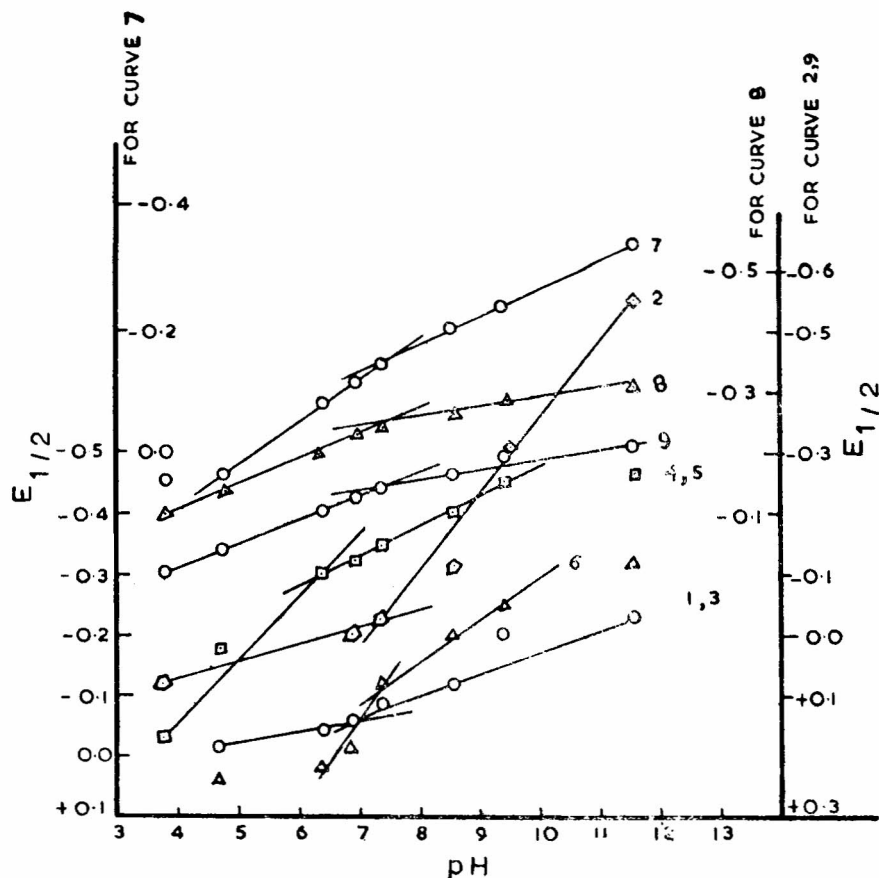


Fig. 2 — Plots of $E_{1/2}$ versus pH [(1) Thymoquinone, (2) 3,6-dibromothymoquinone, (3) thymohydroquinone, (4) thymoquinone oxime-1, (5) nitrosothymol, (6) aminothymol, (7) thymoquinone hydrazone-1, (8) thymoquinone semicarbazone-1, and (10) thymoquinone (bis)-semicarbazone]

TABLE 1 — VARIATION IN $E_{1/2}$ (V) WITH pH IN BRITTON-ROBINSON BUFFER AT $30^{\circ} \pm 0.1^{\circ}$

Compound	pH							
	3.8	4.7	6.4	6.9	7.4	8.6	9.4	11.6
I	—	-0.015	-0.04	-0.06	-0.08	-0.12	-0.20	-0.23
II	+0.08	+0.02	—	0.00	-0.03	-0.12	-0.30	-0.54
III	—	-0.015	-0.04	-0.06	-0.08	-0.12	-0.20	-0.23
IV	—	—	—	-0.06	Composite wave phosphate buffer			
V	-0.03	-0.18	-0.30	-0.32	-0.35	-0.40	-0.45	-0.46
VI	-0.03	-0.18	-0.30	-0.32	-0.35	-0.40	-0.45	-0.46
VII	+0.10	+0.06	+0.02	-0.02	-0.12	-0.20	-0.25	-0.32
VIII	+0.05	+0.06	-0.085	-0.11	-0.14	-0.20	-0.24	-0.34
IX	—	—	-0.70	-0.74	-0.78	—	—	—
X	—	—	-0.65	-0.66	-0.67	—	—	—
XI	—	—	-0.62	-0.63	-0.64	—	—	—
XII	-0.10	-0.16	-0.22	-0.27	-0.31	-0.34	-0.38	-0.39
XIII	-0.10	-0.14	-0.20	-0.23	-0.24	-0.26	-0.29	-0.31

studied. However, in the small pH range (6.4-7.4) the variations in $E_{1/2}$ with pH are very small and the plots are almost parallel to the pH axis. From this observation it may be concluded that the reduction of these compound is independent of pH .

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