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Electrochemical Reduction of Sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate in Aqueous and Aqueous Dimethyl Formamide Mixed Solvent: A Cyclic Voltammetric Study

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The electrochemical behavior of sodium 1,4-dihydroxy-9,10-anthraquinone-2- sulphonate (sodium quinizarin-2-sulphonate), an analogue of the core molecule of anthracycline antibiotics, was studied using cyclic voltammetry. In pure and aqueous dimethyl formamide quinizarin-2-sulphonate undergoes successive two one- electron reductions and there is comproportionation between the quinone and its dianion to form a semiquinone radical. The apparent comproportionation constants in pure and aqueous dimethyl formamide mixtures were calculated. It was found at acidic, neutral and alkaline pH, when cyclic voltammetry is carried out in pure aqueous buffer the reduction of sodium quinizarin-2-sulphonate follows a one step two- electron reduction. In acidic buffer, it was found that the reduction involves two protons along with two electrons but at neutral and alkaline pH it is free from protons. It was found that at pH 9.0 there is also a comproportionation reaction.

Keywords: Sodium quinizarin-2-sulphonate; cyclic voltammetry; formal reduction potential; pH dependence; DMF, comproportonation reaction

1. INTRODUCTION

Adriamycin and daunorubicin are anthracycline drugs widely used in the treatment of various human cancers. Since their discovery, studies on anthracycline antibiotics have been actively pursued for their anticancer activity and mechanism of drug action. Most of these studies on anthracyclines and its metal complexes concentrate on interaction with DNA [1-8].

The major limitations of the use of anthracycline drugs include their acute and chronic toxicities. The chronic total dose limiting toxicity is cardiotoxicity [9,10] and these drugs may also cause chromosomal damage. Cardiotoxicity [11] and chromosomal damage [12] are associated with several electron transfer processes involving the respiratory chain generating $H_2O_2/O_2^{\cdot-}/OH^-$, oxidative phosphorylation, complexation of phospholipid and may even initiate peroxidation of lipid, [13-18]. The behavior of these drugs have a good correlation with redox properties [19-22]. The quinone moiety present in these drugs after one electron reduction forms a semiquinone, which plays a major role in determining toxicities of these drugs in cellular systems [23, 24]. It is therefore, important to study the reduction behavior of such molecules under different conditions. Semiquinone radicals are short lived and readily undergo disproportionation [25, 26] generating a quinone and its corresponding dianion. Pulse radiolysis techniques [27-31] and electrochemical methods like cyclic voltammetry have been used to investigate redox behaviors of different quinone systems [32-39].

In aprotic media, the reductions of quinones take place by two successive one- electron reduction steps forming Q^- and then Q^{2-}. The formal potentials for these reduction steps depend upon the polarity of the solvent [32- 34]. In aprotic media the cation of the supporting electrolyte plays a vital role whether the reduction is two steps or one step [35,36]. The electrochemical behavior of the quinones may be altered significantly in presence of acidic additives [37]. Hydrogen bonding is also known to play an important role in determining redox behaviors of hydroxy quinone systems [38, 39].

The present study concentrates on the detailed electrochemical behavior of sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate (sodium quinizarin-2-sulphonate), an analogue of the core unit of anthracycline drugs using cyclic voltammetry. Sodium quinizarin-2-sulphonate is highly soluble in water and may therefore be used under physiological conditions. It was found that sodium quinizarin-2-sulphonate exhibits a wide range of phenomena, which are of interest both from the standpoint of contemporary electrochemistry as also from a biological point of view. Cyclic voltammetry study of sodium quinizarin-2-sulphonate was carried out both in aqueous and mixed aqueous dimethyl formamide solution at different pH. Several electrochemical parameters have been obtained under different conditions of experiment with the help of which a possible mechanism of the chemical processes taking place have been attempted.

2. EXPERIMENTAL PART

Sodium quinizarin-2-sulphonate was prepared by sulphonation of Quinizarin (Sigma-Aldrich) with aqueous sodium sulphite in the presence of cupric oxide [40]. Sodium quinizarin-2-sulphonate obtained was recrystalized from ethanol water mixtures. The quinone moiety being sensitive to light solutions were prepared just before the experiment and kept in dark. Tetrabutylammonium bromide (TBAB) (AR grade) obtained from Spectrochem, India and sodium chloride (AR grade) obtained from Merck, were used as supporting electrolyte in DMF-water and aqueous media respectively. All other reagents used were of AR grade. Acetate buffer and Britton- Robinson buffer was used to maintain pH. All solutions were prepared in triple distilled water. Cyclic voltammetry experiments were carried out using the conventional three- electrode system at 25^0C. The temperature was maintained at 25^0C using circulating water bath. A glassy carbon electrode of surface area $0.1257 cm^2$ served as the working electrode, a platinum wire acted as the counter electrode while Ag/AgCl was the reference electrode. Experiments were done using *EG & G* Potentiostat Model 263A. Cyclic voltammetric experiments of quinizarin- 2- sulphonate were done in pure aqueous buffer, pure and aqueous dimethyl formamide mixtures at different pH. In aqueous dimethyl formamide mixtures, the required pH was adjusted according to equation pH = $-\log C_{H}^{+} - \log \gamma_{H}$ [41]. Concentrations of experimental solutions were in the range 5×10^{-4} moldm^{-3} to 1.5×10^{-3} moldm^{-3}. All experimental solutions were degassed for 30 mins with high- purity argon gas, before any cyclic voltammetry of a sample was done. Simulation study was carried out using esp24b software.

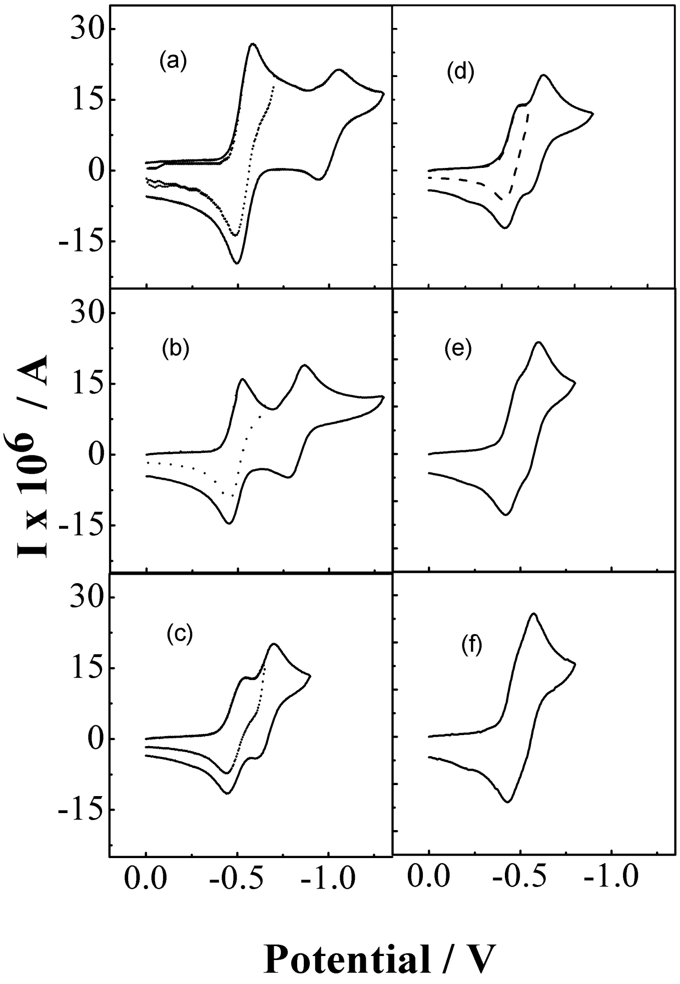


Figure 1. Cyclic voltammogram of 1mM sodium quinizarin-2-sulphonate showing two successive one- electron reduction in 0.1M TBAB in (a) pure DMF, (b) 80% aqueous DMF, (c) 60% aqueous DMF, (d) 40% aqueous DMF, (e) 20% aqueous DMF, (f) 10% aqueous DMF at pH 9.00 on glassy carbon electrode; scan rate 100mV/sec. Dotted lines show the voltammogram for the one- electron reduction when the scan is reversed before the second reduction starts.

3. RESULTS AND DISCUSSION

As was observed earlier in other quinone systems [32- 34], in pure DMF, sodium quinizarin-2-sulphonate undergoes successive two one-electron reduction to give Q^{-} (-530mV) and Q^{2-} (-970mV) showing two peaks which are well separated by 440mV. The first step is completely reversible while the second step is quasi- reversible at customary scan rates. When the scan is reversed at a potential well before the second reduction, the peak current of the anodic wave for the oxidation of $Q^{\cdot-}$ is comparatively less than that observed when the scan is reversed after the second reduction generating Q^{2-}. A typical cyclic voltammogram for sodium quinizarin-2-sulphonate in pure DMF is shown in Fig. 1(a). The formal potential, $E_{1/2}$ values of the respective reduction steps were calculated from the average of cathodic and anodic peak potentials and results are shown in Table-1.

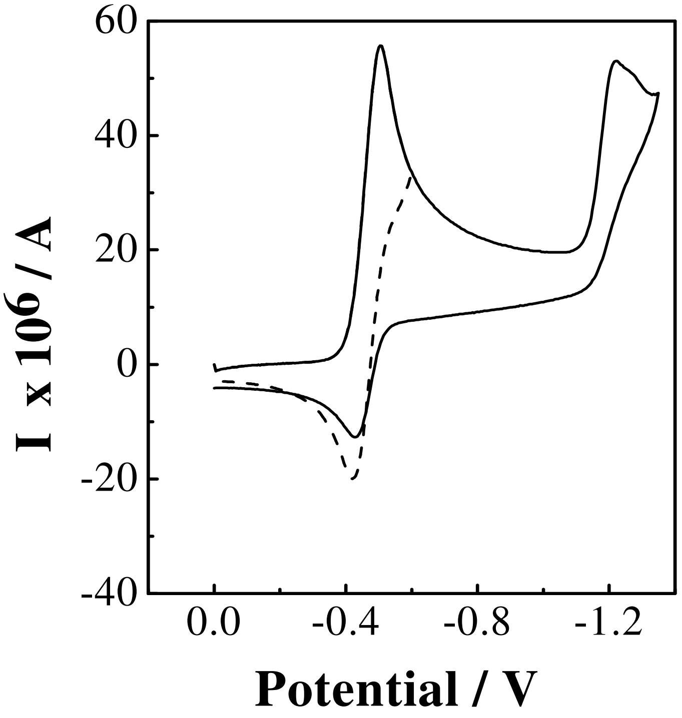


Figure 2. Cyclic voltammogram of 1mM of sodium quinizarin-2-sulphonate in pure water at pH 7.00. Dotted lines show the voltammogram for the two- electron reduction when the scan is reversed before hydrogen evolution starts.

In pure water, the cyclic voltammogram at neutral pH (Fig. 2) shows one reversible peak and one irreversible peak at –500mV and –1220mV respectively. The reversible peak is sharper and the peak current increases two fold in comparison to the two one- electron reduction in pure DMF indicating a merger of the two one- electron peaks in case of water. In contrast to that observed in pure DMF, the peak current for the anodic oxidation for the first wave in water, is comparatively higher than the peak current when the scan is reversed before the second reduction process in pure DMF. It is to be noted that the irreversible peak potential for the second wave occurs at a more negative potential than the successive second reduction peak potential in pure DMF. Thus it appears from the above experiments that the second irreversible wave found in pure water is not the same reduction step as that in pure DMF. Further, in alkaline pH this irreversible peak disappears. Therefore, it is not any adsorption peak that appeared in the reduction of anthraquinone in alkaline aqueous solution as has been observed in

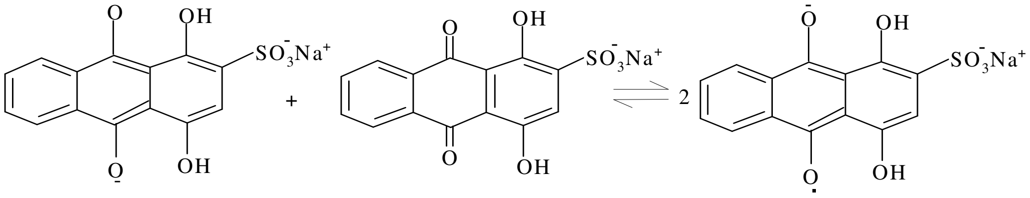
Table-1: Reduction potentials (E_1 and E_2), Comproportionation constants (K_{comp}) and Diffusion coefficients (D_0) at different percentage of DMF

% DMF	% H_2O	E_1 (mV)	E_2 (mV)	K_{comp}	D_0 ($cm^2 s^{-1}$)
100	0	-978	-530	3.81×10^7	5.40×10^{-6}
85	15	-819	-455	1.44×10^6	2.94×10^{-6}
80	20	-802	-470	4.15×10^5	2.87×10^{-6}
75	25	-754	-450	1.42×10^5	2.83×10^{-6}
70	30	-707	-456	1.79×10^4	1.36×10^{-6}
65	35	-688	-452	1.00×10^4	1.98×10^{-6}
60	40	-645	-455	1.66×10^3	1.96×10^{-6}
55	45	-640	-440	2.45×10^3	1.93×10^{-6}
50	50	-617	-458	4.95×10^2	1.92×10^{-6}
45	55	-604	-450	4.07×10^2	1.85×10^{-6}

*E_1 and E_2 denote the $E_{1/2}$ values of the first and second one-electron reduction steps

previous studies [42, 43]. Comparing the behavior of the present molecule with adriamycin and quinizarin it may be said that the first reversible peak arises due to two- electron reduction and the second irreversible peak might be due to hydrogen evolution. Similar hydrogen evolution was observed in earlier studies [44]. It was suggested that the presence of adjacent hydroquinone moieties in the molecule may catalyze the hydrogen evolution current and the irreversible peak is thus generated. To evaluate the number of electrons involved in the first reversible reduction step chronocoulometric studies were carried out in aqueous buffer of acidic, neutral and alkaline pH.

Results have shown that two electrons are involved in such reduction whatever be the pH of the solution. Results therefore suggest that the electrochemical reduction in protic and aprotic solvents differ appreciably.



Scheme I

To see the role of protic solvents studies were therefore extended to mixed aqueous DMF solutions at different pH. At neutral pH in 95% DMF, the two successive reduction waves observed in pure DMF did not appear and a single two- electron wave was observed. When pH was gradually increased the two separate waves did not appear until pH 9.0. At pH 9.0 two successive one-electron reduction waves were observed upto 40% DMF [Fig. 1a-d]. On further increasing concentration of water the two reduction peaks come closer and finally merge. The cyclic voltammograms are shown in Fig.1. The formal electrode potentials for the successive one- electron reduction of sodium quinizarin-2-sulphonate in different aqueous DMF buffer are shown in Table-1. The apparent comproportionation constants corresponding to the equilibrium, $Q^{2-} + Q \rightleftharpoons 2Q^{\cdot-}$ [Scheme- I], may be determined by equation (1) in pure and aqueous DMF and they are shown in Table- 1.

$$K_{comp} = \exp\left[-F/RT\,(E_2-E_1)\right] \qquad (1)$$

F = Faraday
R = Molar gas constant
T = Temperature
E_1 = Formal potential of first reduction
E_2 = Formal potential of second reduction

It is found that as water concentration increases K_{comp} decreases. This is an indication in favour of the fact that as water concentration increases there is some sort of a stability rendered to the Q^{2-} species by water as a result of which rate of comproportionation falls off. The comproportionation reaction is supported by the cyclic voltammogram in DMF and different aqueous DMF solutions [Fig.1a-d]. When the scan is reversed well after the second reduction then the anodic peak current is markedly increased than when the scan is reversed before the second reduction.

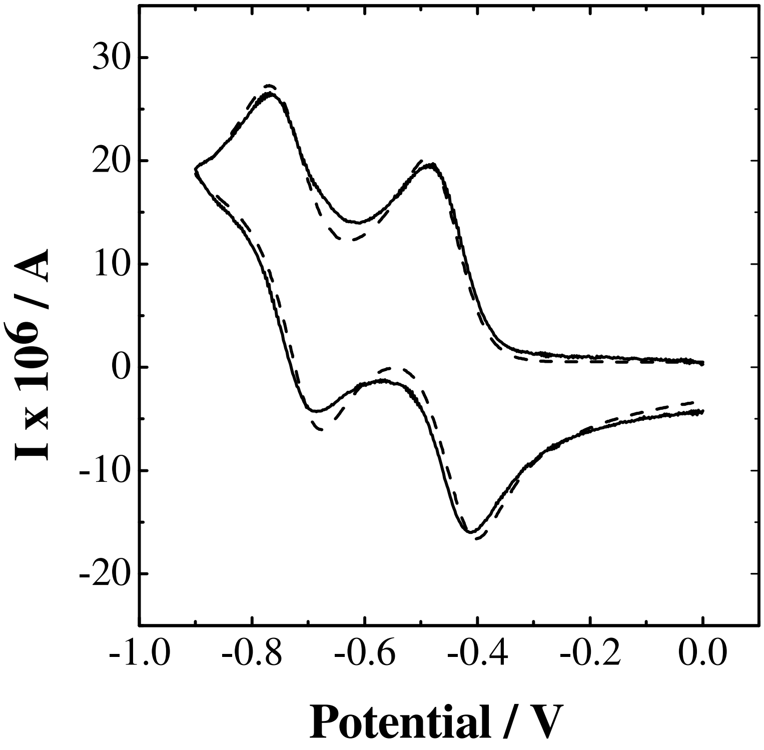


Figure 3. Cyclic voltammogram of 1mM of sodium quinizarin-2-sulphonate at 200 mV/s in 0.1M TBAB in 65% aqueous DMF at pH 9.00 on glassy carbon electrode. In simulation and experiment 425 Ω resistance was included. Other simulation parameters: $k_{s,1}$ = 0.065 cm s^{-1}, α_1 = 0.60, E_1 = -445 mV *vs*. Ag/AgCl saturated KCl; $k_{s,2}$ = 0.025 cm s^{-1}, α_2 = 0.30, E_2 = -722 mV *vs*. Ag/AgCl saturated KCl; D_0 = 6.5×10^{-6}, 6.7×10^{-6} and 8.5×10^{-6} for quinone, semiquinone and quinone di anion respectively; K_{comp} = 8×10^{3}, A = 0.1256 cm^2. Simulation was carried out in planar geometry. Cathodic currents were taken as positive.

Comproportionation reaction of the molecule in pure and aqueous DMF was also supported by the simulation study [Fig. 3]. Comproportionation reaction was included into the simulation study as homogeneous chemical reaction. It should be mentioned that only E_1 and E_2 are of quantitative significance, the other parameters simply being those that result in best fit of data. The values of E_1 and E_2 are –688 and –452 mV respectively. One can see that the agreement between the simulated data (----) and experimental data (—) is quite good.

From Fig.4, it is seen that the first peak current (I_{pc}) for the first reduction has linear relationship with square root of scan rates and it passes through the origin. This phenomenon suggests that the reduction is diffusion controlled with no adsorption on the electrode surface. The diffusion coefficient, D_0, of the sodium quinizarin-2-sulphonate was determined from the relation shown in equation (2).

$$I_{pc} = (2.69 \times 10^5)\, n^{3/2}\, D_0^{1/2}\, A\, C\, v^{1/2} \qquad (2)$$

Where,
I_{pc} = Cathodic peak current, μA
n = number of electron
A = Area of the electrode, cm^2
C = Concentration, $moles/cm^3$
v = Scan rate, V/s

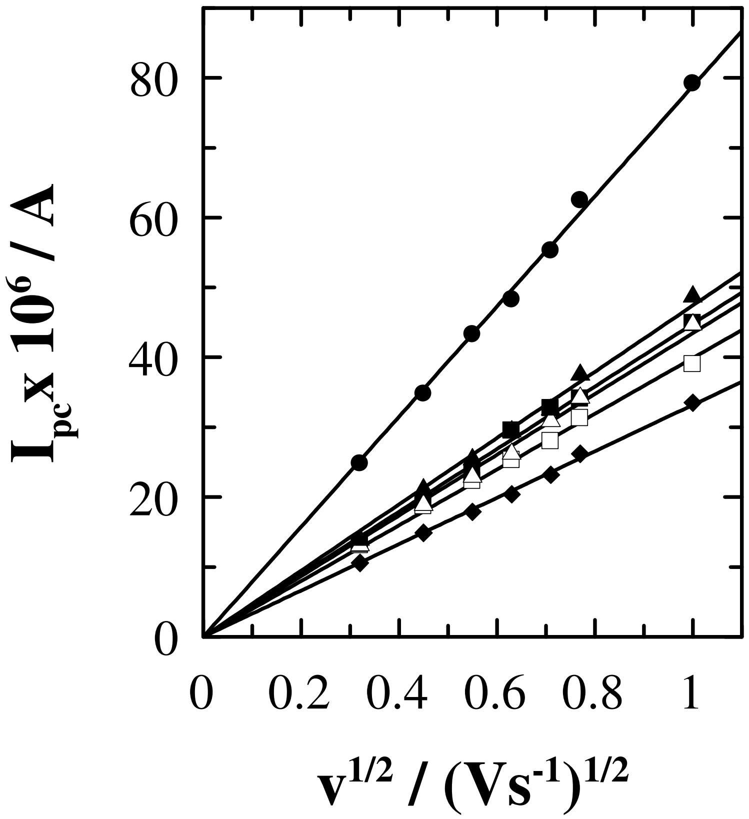


Figure 4. Dependence of cathodic peak current for the one- electron reduction of sodium quinizarin-2-sulphonate at different DMF- water mixtures at pH 9.00. (• = 100% DMF, ʌ = 80% DMF, = 70% DMF, ! = 60% DMF, 8 = 50% DMF, 7 = 40% DMF).

The determined formal electrode potentials of first and second reductions were plotted against DMF concentration and from an extrapolation of the straight lines [Fig. 5] the two reduction potentials E_1 and E_2 for the two successive reductions in pure water were obtained as –457 mV and –515 mV respectively. Due to such small difference in peak potentials (58 mV), the two one- electron waves merge to give a single wave and the reduction would be found to be like one step two- electron process [45]. The $E_{1/2}$ value calculated for one step two- electron reduction in aqueous solution at pH 9.0 from this data is –486 mV considering comproportionation reaction in between the quinone and its dianion to form semiquinone. The experimental determination shows that $E_{1/2}$ value for one step two- electron reduction is –485 mV at pH 9.0. Thus there is an excellent correlation between the two results suggesting that a comproportionation reaction in aqueous solution actually takes place at pH 9.0.

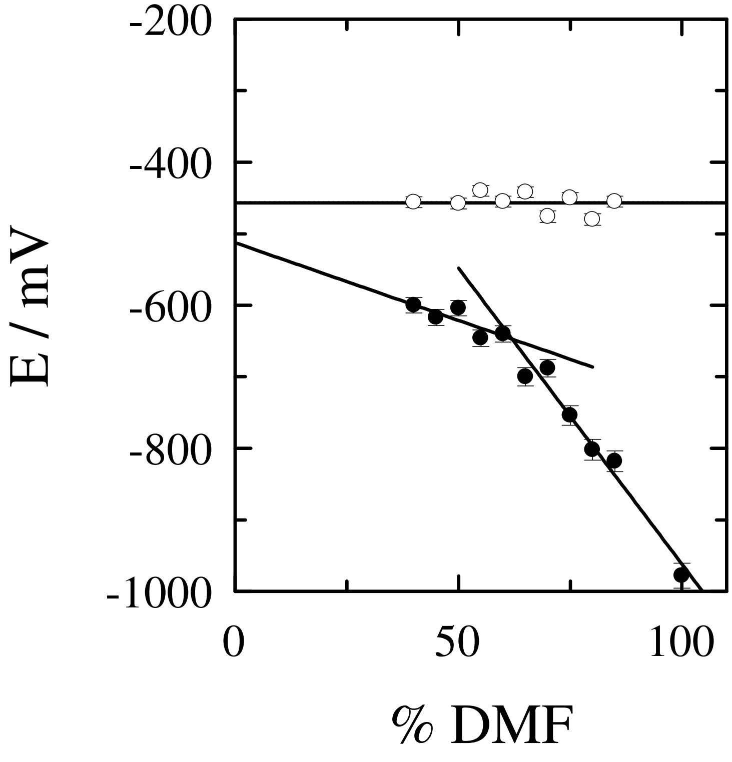


Figure 5. Change of formal electrode potential on solvent composition: First one- electron reduction potential, E_1 (o) and Second one- electron reduction potential, E_2 (•).

It is observed that in aqueous solution the dependence of peak potential E_{pc} with pH is linear in acidic pH until pH 6 with a slope of 61.33 mV/pH with correlation coefficient 0.9896 (Fig. 6). The formal electrode potential $E_{1/2}$ vs. pH plot also gives a slope of 62.01 mV/pH with correlation coefficient 0.9862. It thus confirms that the redox reaction is two- electron two- proton [Scheme-II]. After pH 6.0 $E_{1/2}$ values remain almost a constant till pH 9.0 (Fig. 7), which leads us to the conclusion that due to non-availablity of proton over this pH range there is no major reflection in $E_{1/2}$ values and the reduced form is chemically deprotonated. In the pH range, pH > pK_a of the newly formed phenolic –OH groups at 9- and 10- positions the molecule [46], exists as an unprotonated Q^{2-} [Scheme-III] and there are strong hydrogen bonding between anionic quinone oxygens and phenolic –OH protons of 1 and 4 positions respectively. After pH 9.0 the electrode potential further drops with pH and this is due to deprotonation of phenolic -OH at position 1 (pK = 9.0 determined by spectrophotometric titration) which disrupts the stabilizing influence of hydrogen bonding with the simultaneous onset of ionic repulsion between two negatively charged oxygen atoms at 1 and 9 respectively. Thus the product is less stable and this results in a decrease in the formal potential.

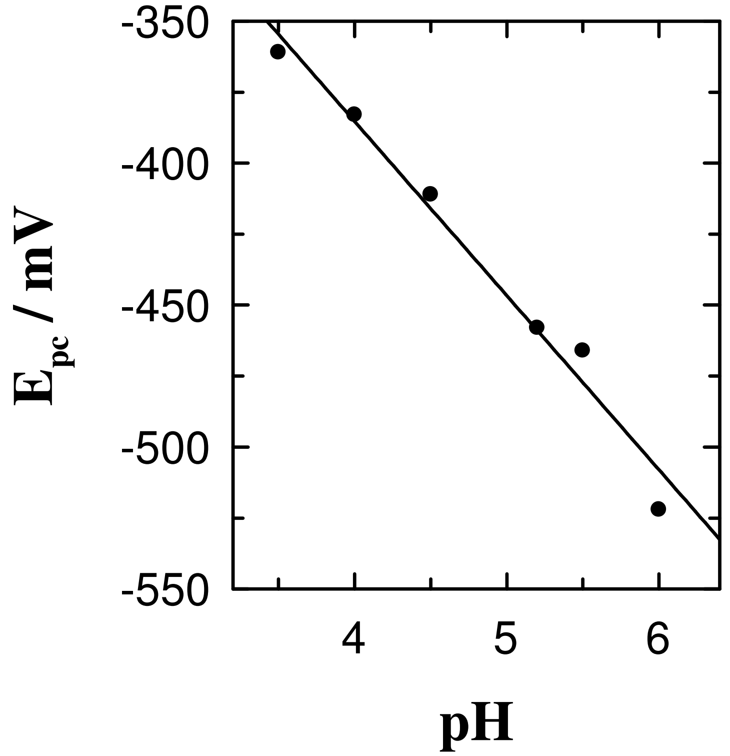


Figure 6. Change of cathodic peak potential (E_{pc}) for the one step two- electron reduction of sodium quinizarin-2-sulphonate with pH in aqueous buffer.

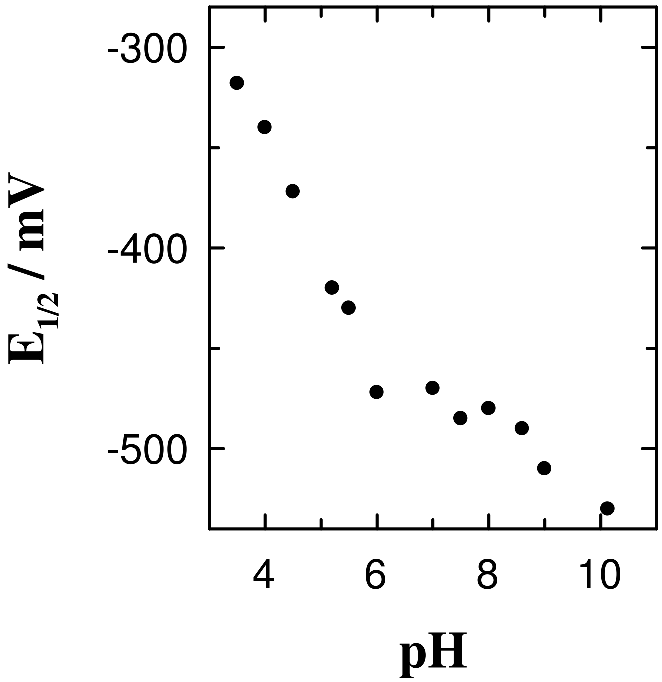
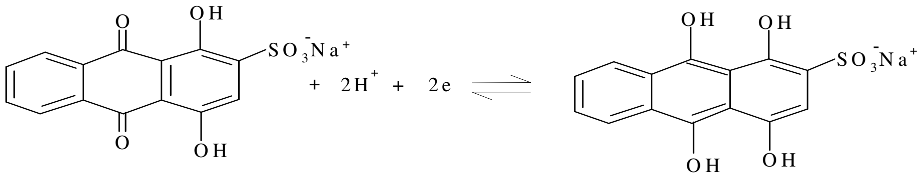
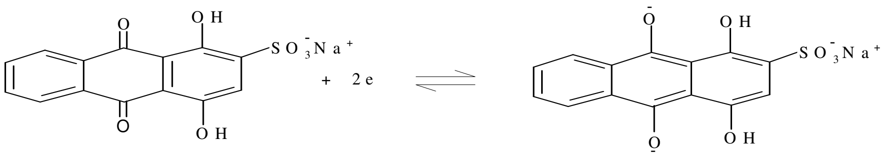


Figure 7. Change of formal electrode potential for the one step two- electron reduction of sodium quinizarin-2-sulphonate with pH in aqueous buffer.



Scheme II



Scheme III

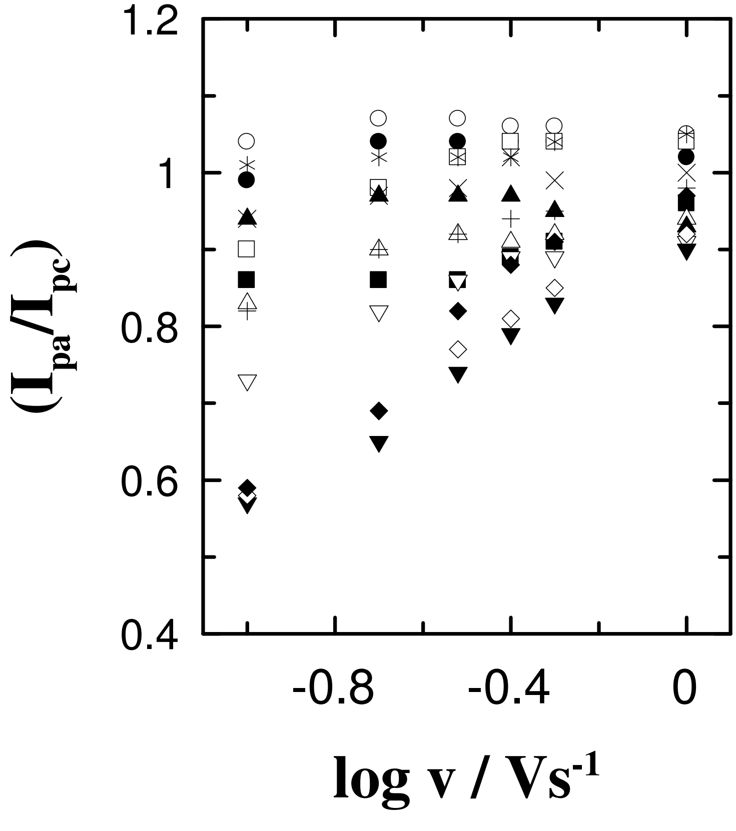


Figure 8. (I_{pa}/ I_{pc}) ratio dependence on scan rates in aqueous media at different pH values: o = pH 3.5, • = pH 4.0, □ = pH 4.5, ! = pH 5.2, 8 = pH 5.5, 7 = pH 6.0, X = pH 7.0, B = pH 7.5, M = pH 8.0, Λ = pH 8.6, + = 9.0, × = 9.5, ∗ = 10.1.

From Fig.8, it is found that till pH 6 (I_{pa}/ I_{pc}) (where I_{pa} and I_{pc} are anodic and cathodic peak current respectively) value is almost unity even in very slow scan rates and so it is a reversible two-electron two- proton reduction [Scheme-II] as reported earlier [25, 26, 44, 46- 49]. In neutral pH and pH less than 9.0, the (I_{pa}/ I_{pc}) value is less than unity in lower scan rates; however, it increases with increasing scan rate reaching unity. Further, it is observed that after pH 9.0, (I_{pa}/ I_{pc}) value again reaches almost unity even at smaller scan rates and the reaction becomes reversible.

4. CONCLUSIONS

In pure dimethyl formamide, sodium quinizarin-2-sulphonate undergoes successive two one-electron reduction to give mono and dianionic forms showing two peaks which are separated by 440mV corresponding to the formations of $Q^{-\cdot}$ and Q^{2-} respectively. The first step is completely reversible while the second step is quasi- reversible at customary scan rates. In pure water the cyclic voltammogram at neutral pH shows one reversible peak at –500mV due to two- electron reduction to Q^{2-} and one irreversible peak at –1220mV due to hydrogen evolution. In pure aqueous alkaline buffer, in pure and aqueous DMF solution there is a comproportionation between quinone and its dianion to form semiquinone.

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