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# Solvation of 1-Amino-4-Hydroxy-9,10-Anthraquinone Governs Its Electrochemical Behavior in Non-Aqueous and Aqueous Media: A Cyclic Voltammetry Study

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The electrochemical behavior of 1-amino-4-hydroxy-9,10-anthraquinone (1-AHAQ) was studied in acetonitrile, dimethyl formamide and dimethyl sulfoxide. In such solvents 1-AHAQ undergoes successive two one-electron reduction forming semiquinone and quinone dianion respectively in which the first step is completely reversible and the second step is quasi-reversible. The reduction and oxidation potentials are dependent on the polarity of the media. The electrochemical parameters are evaluated and correlated with the polarity index of the media. During such reductions a comproportionation reaction operates between the quinone (1-AHAQ) and its dianion ($1\text{-AHAQ}^{2-}$) to form a semiquinone radical ($1\text{-AHAQ}^{\bullet -}$). The apparent comproportionation constants are calculated to find a comparative account on the stability of the radical intermediate in such solvents. In the presence of benzoic acid the electrochemical behavior of 1-AHAQ is altered significantly which is determined in this study. Role of the polarity of the solvents, intra or intermolecular hydrogen bonding and acidic additives on the stability of the radical species is evaluated. In aqueous buffer the reduction of 1-AHAQ follows a one step two-electron process where a kinetic study was carried out to determine the apparent charge transfer rate constants at various scan rates. The results show that electrochemical behavior of 1-AHAQ in non-aqueous and aqueous media mimics the action of anthracycline anticancer drugs which may find a similarity in their biological activities at the cellular level.


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Anthracycline drugs such as doxorubicin, daunorubicin, carminomycin, aclacinomycin, nogalamycin, etc., are some of the important chemotherapeutic agents used in the treatment of various forms of human cancers.[1–4] 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 the interaction with DNA.[5–8] Some studies showed that the sugar moiety present in these drugs help in the recognition of cancer cells.[9,10] At the same time, the presence of the sugar moiety on the aliphatic side chain attached to the hydroxy-9,10-anthraquinone in these molecules makes them so costly that it is not always possible for many to continue treatment using this category of drugs. This is particularly true for the people affected with cancer residing in the developing countries. Though there is very wide application of anthracyclines in cancer chemotherapy the above mentioned aspects are very unfortunate and needs serious consideration. Efforts are therefore on to find out new but cheaper analogues and derivatives of anthracycline drugs. In several studies[11–16] we were able to show that much cheaper hydroxy-9, 10-anthraquinones mimic the behavior of anthracycline drugs. A very recent study by Rossi et al.[17] showed that 1, 4-dihydroxy-9, 10-anthraquinone and 1, 8-dihydroxy-9,10-anthraquinone have promising anticancer activity though they do not posses any sugar moiety. Mitoxantrone (1, 4-dihydroxy-5, 8-bis-[(2-[(2-hydroxyethyl) amino] ethyl) amino] -9,10-anthraquinone), an analogue of anthracyclines, was found to have better antineoplastic activity and less toxicity than adriamycin.[18] It is used for the treatment of breast cancer, prostate cancer, leukemia and lymphoma. Mitoxantrone induces compaction of isolated chromatin,[19] protein associated DNA cleavage[20] and inhibits DNA and RNA synthesis.

Although several studies on hydroxy-9, 10-anthraquinones[11–16] and mitoxantrone (an amino hydroxy-9, 10-anthraquinone)[18–22] were extensively carried out the other amino hydroxy-9,10-anthraquinones have not been seriously investigated as a possible substitute of anthracycline anticancer drugs.

However, the major limitation of the use of anthracycline drugs includes their acute and chronic toxicities, of which cardiotoxicity is an aspect that requires most attention.[23–25] Accumulating evidence indicates that formation of the semiquinone free radical intermediate by one-electron reduction of the quinone moiety present in these drugs is a requirement both for chemotherapeutic efficiency as well as toxicity. The aspects of therapeutic efficiency as well as toxicity have been seen to associate with redox properties of these drugs and the electrochemical parameters play an important role in determining the structure-activity relationship of such molecules.[26,27] It is therefore, important to study the electrochemical behavior of such molecules under different conditions. Semiquinone radicals produced by the one-electron reduction of the quinone unit are short lived in the presence of proton donors and readily undergo disproportionation[28,29] generating a quinone and its corresponding hydroquinone. Pulse radiolysis techniques[30–32] and electrochemical methods like cyclic voltammetry have been used to investigate redox behaviors of different quinone systems.[33–58] In aprotic media, the reduction of quinones (Q) takes place by two successive one-electron reduction steps forming $Q^{\bullet -}$ and then $Q^{2-}$. The formal potentials for these reduction steps depend upon the polarity of the solvent,[32–35] the nature of the cation of the supporting electrolyte[36,37] and the presence of acidic and basic additives.[38–50] The intra and intermolecular hydrogen bonding is also known to play very important role in determining redox behaviors of hydroxy quinones.[39–42,44–51] Previous studies showed that although the intramolecular stabilization mode is important for quinone molecules, in biological media there are some weak proton donors, which can also induce stabilization by intermolecular interactions.[43] Thus, considering the important correlation between the redox potential of quinones with their biologic activity, this work is focused on analyzing the effect of intramolecular and intermolecular hydrogen bonding interactions on the redox chemistry of 1-amino-4-hydroxy-9,10-anthraquinone having a phenolic group in the presence of benzoic acid. This proton donor is selected considering that it can induce either association or protonation processes. Furthermore, this proton donor could emulate carboxylic moieties present in bio-macromolecule such as proteins in the cell.

How the hydrogen bonding affects the stability of electrogenerated quinone radicals and hence mechanism of the electrochemical reaction were extensively investigated by I. González, F. González, N. Macias-Ruvalcaba and their groups in several studies.[39–42,44–51,54,58] A very recent study on some quinones by using an electrochemical, ESR-spectroelectrochemical, and computational analysis characterizes the charge and spin states of produced species which helps to understand the reduction mechanisms of this class of compounds.[51]

The focus of our study is to find out whether 1-amino-4-hydroxy-9, 10-anthraquinone which is much less costly, mimics the electrochemical behavior and hence the mechanism of drug action of the anthracyclines. The present study concentrates on the detailed electrochemical behavior of 1-amino-4-hydroxy-9, 10-anthraquinone (1-AHAQ), an analogue of the core unit of anthracycline drugs, using cyclic voltammetry in non-aqueous and aqueous solvents. The

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role of the polarity of the solvents, intra and intermolecular hydrogen bonding, role of acidic additives, kinetics of the charge transfer, etc., are analyzed during the course of electrochemical reduction of 1-amino-4-hydroxy-9, 10-anthraquinone using cyclic voltammetry and other electrochemical methods. Several electrochemical parameters are evaluated under different experimental conditions in order to help determine a possible mechanism for the electrochemical and chemical processes taking place. It is found that 1-AHAQ exhibits a wide range of phenomena, which are of great interest both from the standpoint of contemporary electrochemistry and also from a biological point of view. Finally the evaluated electrochemical parameters of 1-amino-4-hydroxy-9,10-anthraquinone in non aqueous and aqueous solvents are compared with the results of anthracyclines studied earlier[59–64] in order to see whether this molecule has the potential to mimic the action of anthracycline drugs.

## Experimental

1-amino-4-hydroxy-9, 10-anthraquinone (96%) purchased from Alfa Aesar, Germany was recrystalized from ethanol -methanol mixture. For characterization purposes $^1$H NMR was done and the responses for the aromatic –$NH_2$ and phenolic –OH protons were found in the characteristic region of 0.87 to 4.37 ppm. The aromatic protons were found in the region 6.91 to 8.37 ppm. Elemental analysis of the compound was carried out on a 2400 Series II CHN Analyzer, Perkin Elmer. Elemental analysis shows the contents of C, H and N as 70.27, 3.81 and 5.87 wt% respectively (calculated C: 70.29%, H: 3.77% and N: 5.88%).The quinone moiety being sensitive to light, solutions were prepared just before the experiment and kept in the dark. NaOH (AR Grade) purchased from Merck, India was used in spectrometric titration. Spectrophotometric studies were carried out using UV-Vis spectrophotometer, Model: MECASYS OPTIZEN POP. Tetrabutylammonium bromide (TBAB) (AR grade) obtained from Spectrochem, India and potassium chloride (AR grade) obtained from Merck, India, were used as supporting electrolyte in organic and aqueous media respectively in the electrochemistry experiments. Dimethylsulfoxide (DMSO) (99.0%, Spectrochem) was first dried over fused $CaCl_2$ for 3–4 days, decanted and then distilled under reduced pressure.[65] The distilled sample was preserved in a well stopper Jena bottle in desiccators and redistilled before use.

Acetonitrile (ACN) (99.8%, GR, Merck) was purified[65,66] by refluxing with KOH (Merck) for several hours followed by fractional distillation and then again refluxing with $CaH_2$ (Merck) for several hours followed by fractional distillation. Only the middle fraction was collected from each distillation, ensuring removal of all ammonia evolved during the alkali treatment. The solvent was stored as described above.

*N, N*-dimethyl formamide (DMF) (99.5%, Spectrochem) (LR, BDH) was purified[67] first by distilling under reduced pressure in $N_2$ atmosphere and preserving the distillate over dry $K_2CO_3$ (Merck) for a week or so. The solvent was then decanted off and treated with pure $P_2O_5$ (Riedel) and finally distilled under reduced pressure. The water content of the solvents were determined by Karl-Fisher titration[68] and found to be less than 0.02-mol $dm^{-3}$ in each case.

Hepes buffer (AR Grade, Spectrochem, India) was used to maintain the pH of aqueous media. All other reagents used were of AR grade. Aqueous solutions were prepared in triple distilled water. Since 1-AHAQ is almost insoluble in water, a stock solution of 1-AHAQ in ethanol of strength $10^{-3}$ mol $\cdot$ $dm^{-3}$ was prepared by weighing of an exact amount of 1-AHAQ and for the experiments in aqueous media, the solutions were prepared by an exact dilution of a stock solution ($10^{-3}$ mol $\cdot$ $dm^{-3}$) in ethanol with water. Cyclic voltammetry experiments were carried out using the conventional three-electrode system at 298.15 K. The temperature was maintained at 298.15 K using circulating water bath. A glassy carbon electrode of surface area 0.07065 $cm^2$ served as the working electrode, a platinum wire acted as the counter electrode while Ag/AgCl, saturated KCl was used as the reference electrode. Electrochemical experiments were done using *Digi-Ivy* Potentiostat (Model DY2312). To clean the glassy carbon electrode surface two successive steps were made such as abrasion with emery paper and polishing with alumina-water suspensions with particle size 0.5 μm. The electrode was cleaned with water carefully in between and after these steps. To ensure the removal of adsorbed species, the electrode surface was then washed with chloroform. Finally the activation of the glassy carbon electrode surface was made when the potential was cycled at intermediate scan rates (typically 0.1 $Vs^{-1}$) in between a moderately negative potential and more positive potential (−0.5 and +1.50 V). Concentrations of experimental solutions were in the range $5 \times 10^{-5}$ mol $\cdot$ $dm^{-3}$ to $1.5 \times 10^{-3}$ mol $\cdot$ $dm^{-3}$. All experimental solutions were degassed for 30 min. with high- purity argon gas, before any cyclic voltammetry of a sample was done.

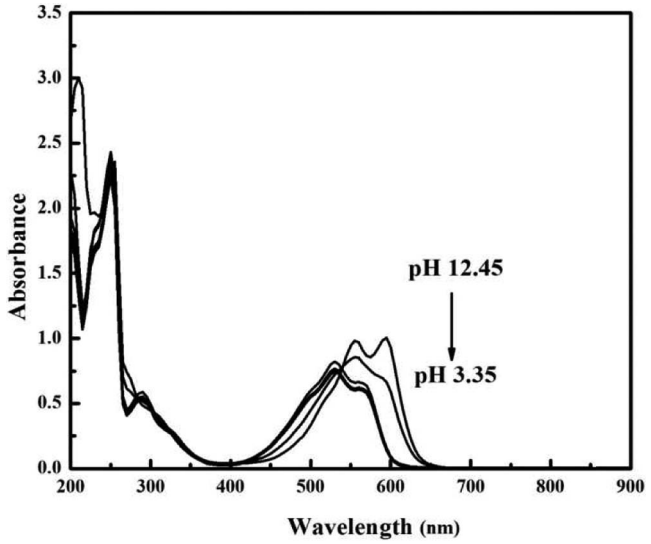



**Figure 1.** Absorption spectra of 1-AHAQ at different pH: 12.45 (1), 10.83 (2), 9.40 (3), 7.62 (4) 5.94 (5) and 3.35 (6) at a fixed 1-AHAQ concentration. [1-AHAQ] = $5 \times 10^{-5}$ mol $\cdot$ $dm^{-3}$, [NaCl] = 0.01 mol $\cdot$ $dm^{-3}$, T = 298.15 K.

## Results and Discussion

*Determination of pK of 1-amino-4-hydroxy-9,10-anthraquinone.*— To observe the role of intra-molecular hydrogen bonding in between the reduced quinone i.e. semiquinone or quinone dianion and the phenolic–OH during the course of electrochemical reduction it is essential to determine the pK value of the phenolic -OH. In order to evaluate the pK for the phenolic –OH of 1-AHAQ, spectrometric titration was carried out. At first $5 \times 10^{-5}$ mol $\cdot$ $dm^{-3}$ aqueous solution of 1-AHAQ was acidified to pH 3.1 and it was then titrated slowly with 0.01 mol $\cdot$ $dm^{-3}$ NaOH solution keeping the concentration of 1-AHAQ fixed and absorption spectra at various pH values were measured. In such titration it was found that after pH 9.5 the peaks at 530 and 560 nm shift to 555 and 594 nm respectively and the intensity of the peaks increase with an increase in pH (Figure 1). Change in the absorbance at 555 nm indicates a release of the phenolic proton in the pH range 9.5 - 11.5. The absorbance $A_{obs}$ at 555 nm is fitted according to equation 1 against pH of the solution (Figure 2) and the p$K$ of phenolic-OH proton is determined as (10.52 ± 0.10).

$$A_{obs} = \frac{A_1}{1 + 10^{(pH-pK)}} + \frac{A_2}{1 + 10^{(pK-pH)}} \quad [1]$$

where, $A_{obs}$ is the overall absorbance of the solution at 555 nm at different pH values; $A_1$ and $A_2$ refer to the absorbance of 1-AHAQ and its phenoxide ion respectively.

*Electrochemical reduction in non aqueous organic solvent.*— As was observed earlier in other quinones and anthracyclines,[32–34,69, 70]

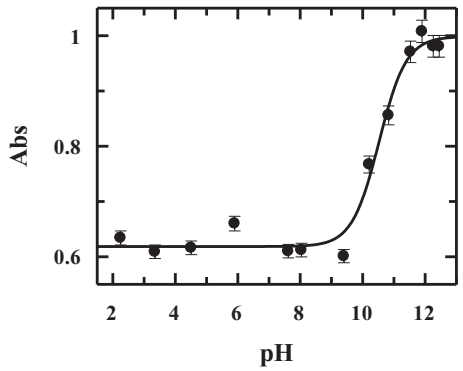



**Figure 2.** Spectrophotometric titration of 1-AHAQ, shown by the variation of absorbance at 555 nm; [1-AHAQ] = $5 \times 10^{-5}$ mol · dm$^{-3}$, [NaCl] = 0.01 mol · dm$^{-3}$, T = 298.15 K.

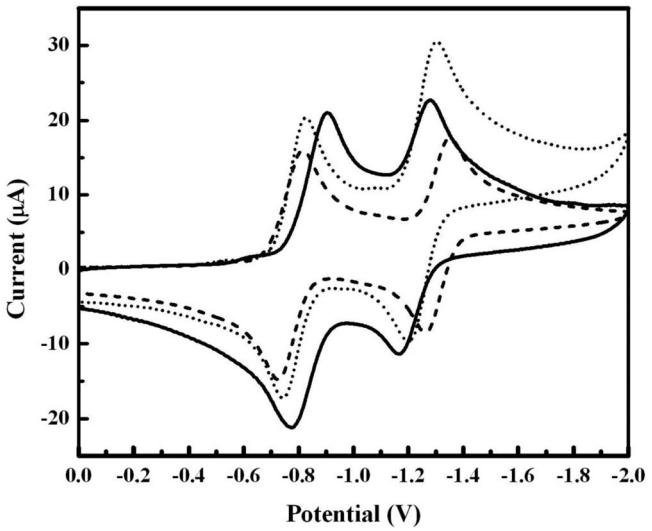



**Figure 3.** Cyclic voltammogram of 1-AHAQ in ACN: (—), DMF ( · · · · ) and DMSO: (- - -). Scan rate: 0.10 Vs$^{-1}$. [1-AHAQ] = $8.5 \times 10^{-4}$ mol · dm$^{-3}$, [TBAB] = 0.1 mol · dm$^{-3}$, T = 298.15 K.

in organic polar solvents[71] such as dimethyl formamide (DMF), acetonitrile (ACN) and dimethyl sulfoxide (DMSO) media, 1-amino-4-hydroxy-9, 10-anthraquinone (1-AHAQ) undergoes successive two one-electron reduction to give semiquinone (1-AHAQ$^{\bullet -}$) and then quinone dianion (1-AHAQ$^{2-}$) showing two reversible peaks (Figure 3).

The number (n) of electron involved in the first reduction is determined by linear sweep voltammetry (Figure 6) using the following eq. 2.[72,73]

$$E_{pc} - (E_{pc})_{1/2} = -56.5\,(mV)/n \qquad [2]$$

where $E_{pc}$ = cathodic peak potential, $(E_{pc})_{1/2}$ = the potential where the current is at half the peak value. Putting the value of $E_{pc}$ and $(E_{pc})_{1/2}$ the value of n for the first reduction of 1-AHAQ is evaluated in ACN, DMF and DMSO medium and it is found to be 1.

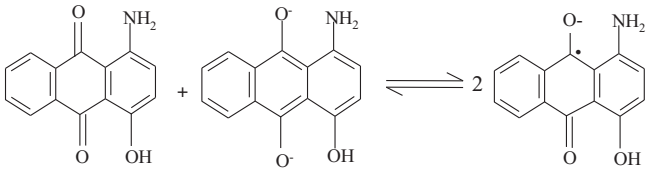
In this case the first step is completely reversible while the second step is quasireversible at different scan rates.[43,54–57,69] The formal potential ($E_{1/2}$) values of the respective reduction steps are calculated from the average of cathodic and anodic peak potentials. The results are shown in Table I and correlated with the polarity index of the solvents which is a relative measure of the degree of interaction of the solvent with various polar solutes.[71] The results show that the electrochemical parameters are dependent on the solvent polarity index (Table I). The formal potential values for the first one-electron reduction ($E_1$) of 1-AHAQ are −0.840, −0.785 and −0.770 V vs. Ag/AgCl, saturated KCl in ACN, DMF and DMSO respectively while the formal potential values for the second one-electron reduction ($E_2$) are −1.220, −1.258 and −1.308V vs. Ag/AgCl, saturated KCl respectively in ACN, DMF and DMSO. The polarity of these solvents increases as: ACN < DMF < DMSO.[71] Thus with increasing the polarity of the medium the first formal reduction potential ($E_1$) increases which means that the stability of the formed semiquinone (1-AHAQ$^{\bullet -}$) is increased with the increase in the polarity of the medium. The stabilization of the semiquinone (1-AHAQ$^{\bullet -}$) is also reflected in the formal reduction potential of second one-electron reduction ($E_2$) which actually decreases with increasing polarity of the medium. Greater the polarity of the medium greater is the stability of the semiquinone. Due to such stabilization in polar media the reduction of semiquinone to quinone dianion becomes difficult. In their pioneering work Lehmann and Evans[69] observed that in case of reduction of quinone in anhydrous aprotic polar solvent where the second electron reduction occurs (1-AHAQ$^{\bullet -}$ → 1-AHAQ$^{2-}$) with a higher difficulty than the first reduction (1-AHAQ → 1-AHAQ$^{\bullet -}$), the comproportionation reaction (1-AHAQ + 1-AHAQ$^{2-}$ → 2 1-AHAQ$^{\bullet -}$) is favored. At the potential where 1-AHAQ$^{2-}$ is formed at the electrode, incoming 1-AHAQ will react with electrogenerated 1-AHAQ$^{2-}$ in the diffusion layer forming semiquinone radical 1-AHAQ$^{\bullet -}$. It is important to note that comproportionation has no effect in the voltammetry for the case of mass transport by diffusion only, equal diffusion coefficients for all three species (1-AHAQ, 1-AHAQ$^{\bullet -}$, 1-AHAQ$^{2-}$), reversible electrode reactions, and the absence of other chemical reactions involving the three species in the EE (Electrochemical–Electrochemical) system. In a case where one or more of these conditions is not followed, the effect of comproportionation reaction would be observed in the voltammetry experiment. In the present study it is clear from the first and second reduction potential data (Table I) that the second reduction is quite difficult for 1-AHAQ in all the three non aqueous solvents.

Further it is interesting to note that in the current study the first step is completely reversible while the second step is quasireversible at different scan rates similar to earlier results.[43,54–57,69] The semiquinone (1-AHAQ$^{\bullet -}$) formed in the first reduction step is stabilized in the polar solvent and reduction of it (1-AHAQ$^{\bullet -}$) to quinone dianion (1-AHAQ$^{2-}$) becomes difficult which is evident from the second reduction potential data (Table I). This may probably be the reason behind the quasireversible nature of the second reduction step. Due to different solvent – solute (1-AHAQ, 1-AHAQ$^{\bullet -}$ and 1-AHAQ$^{2-}$) interaction the diffusion coefficients for 1-AHAQ, 1-AHAQ$^{\bullet -}$ and 1-AHAQ$^{2-}$ should be different. Comparing the present results with earlier[43,54–57,69] it can be said that a comproportionation reaction is operating as a homogeneous chemical reaction along with the electrochemical process. Further the ratio of the second to the first reduction

**Table I. Electrochemical parameters of 1-AHAQ in non-aqueous media with different solvent polarity index.[71] Scan rate: 0.100 Vs$^{-1}$.**

| Media | $E_{pc\text{-}1}$ (V) | $E_{pa\text{-}1}$ (V) | $E_1$ (V) | $E_{pc\text{-}2}$ (V) | $E_{pa\text{-}2}$ (V) | $E_2$ (V) | $D_O$ (cm$^2$s$^{-1}$) | $K_{comp}$ | Polarity Index |
|---|---|---|---|---|---|---|---|---|---|
| ACN | –0.904 | –0.776 | –0.840 | –1.270 | –1.170 | –1.220 | $1.74 \times 10^{-5}$ | $2.69 \times 10^{6}$ | 5.8 |
| DMF | –0.832 | –0.738 | –0.785 | –1.309 | –1.207 | –1.258 | $1.52 \times 10^{-5}$ | $1.04 \times 10^{8}$ | 6.4 |
| DMSO | –0.816 | –0.724 | –0.770 | –1.355 | –1.261 | –1.308 | $1.02 \times 10^{-5}$ | $1.27 \times 10^{9}$ | 7.2 |

(Potentials are measured against Ag/AgCl, saturated KCl reference electrode).



**Scheme I.** Comproportionation of 1-AHAQ and 1-AHAQ$^{2-}$ to 1-AHAQ$^{\bullet -}$.

peak current $(I_{pc})_2$ /$(I_{pc})_1$ is found to be less than expected for a simple EE reaction (Electrochemical–Electrochemical).[70] This suggests a reaction following the second reduction step, such as comproportionation reaction involving quinone dianion and quinone.[70] The apparent comproportionation constants ($K_{comp}$) corresponding to the equilibrium 1-AHAQ$^{2-}$ + 1-AHAQ ⇌ 2 (1-AHAQ$^{\bullet -}$) [Scheme I] are then determined by equation 3[13] in different solvents and the values are summarized in Table I.

$$K_{comp} = 10^{\frac{nF(E_1-E_2)}{2.303\,RT}} \quad [3]$$

where, F = Faraday, R = molar gas constant, T = 298.15 K, n = number electron transferred in this reaction = 1, $E_1$ = formal potential of first reduction, $E_2$ = formal potential of second reduction. The values of apparent comproportionation constants ($K_{comp}$) are found to be $2.69 \times 10^6$, $1.04 \times 10^8$ and $1.27 \times 10^9$ in ACN, DMF and DMSO respectively (Table I) indicating that semiquinone formation is enhanced with the increase in polarity of the medium. In other word one can say the stability of the semiquinone is higher than quinone dianion in organic polar solvents.

It is seen that in ACN, DMF and DMSO media the first reduction peak current ($I_{pc}$) for the reduction of 1-AHAQ has a linear relationship with the square root of scan rate and it passes through the origin (Figure 4). This phenomenon suggests that the reduction is diffusion controlled and there is no adsorption onto the electrode surface. The diffusion coefficient ($D_O$) for the first reduction of 1-AHAQ (Q) is then determined by the relation as shown in eq. 4[72,73] and summarized in Table I.

$$I_{pc} = \left(2.69 \times 10^5\right) n^{3/2} D_O{}^{1/2} A\, C\, v^{1/2} \quad [4]$$

where, $I_{pc}$ = cathodic peak current (A), n = number of electron involved in the reduction, A = area of the electrode ($cm^2$), C = concentration (moles · $cm^{-3}$) and $v$ = scan rate ($V \cdot s^{-1}$).

It is evident from the values of diffusion coefficients ($D_0$ ) in different solvents (Table I) that $D_0$ increases as the polarity of the solvent decreases, clearly indicating that greater solvation of 1-AHAQ in more polar solvent causes a lower rate of diffusion to the electrode surface. The diffusive characteristic of a solute in a solvent is also affected by the solvent dipolar relaxation. Solvent dipolar relaxation depends upon solute-solvent shell formation which results in concentration change and change in macroscopic viscosity of the system. The

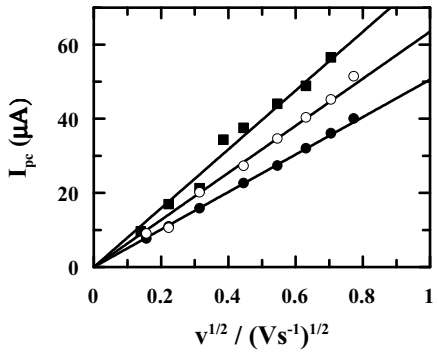
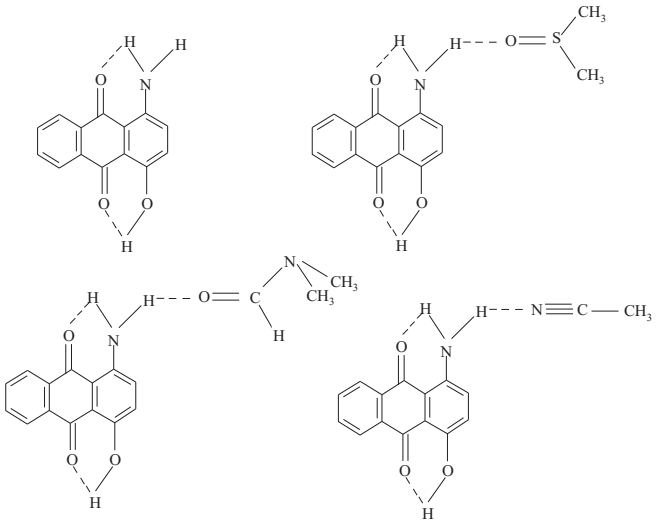



**Figure 4.** Plot of the peak current for the first reduction of 1-AHAQ vs. the square root of the scan rate in ACN (■), DMF(O) and DMSO (●) media fitted according to eq. 4.



**Scheme II.** Hydrogen bonding between 1-AHAQ and DMSO DMF or ACN molecules.

dipolar interaction or polarizability of a solvent influences the solvent effects on kinetics of electron transfer during the course of electrochemical reduction making the measurement of diffusion coefficient to be important. Thus 1-AHAQ is most solvated in DMSO while it is least solvated in ACN which is due to hydrogen bonding and other electrostatic forces between 1-AHAQ and solvent molecules. Intermolecular hydrogen bonding between one of the two hydrogens of aromatic amino group (-$NH_2$) of 1-AHAQ and negatively charged oxygen the solvent DMSO molecule (Scheme II) is very strong. This type of hydrogen bonding would definitely be weak in case of DMF since in this solvent oxygen has a less partial negative charge than that present on the oxygen of DMSO molecules. However, this type of hydrogen bonding would be weak in case of ACN since the nitrogen is less electronegative than oxygen, the nitrogen in ACN is *sp*-hybridized and the negative charge on this nitrogen is very small. Here one of the two hydrogens of aromatic amino group (-$NH_2$) of 1-AHAQ is considered for the formation of hydrogen bonding with the solvent ACN molecules[74,75] since another hydrogen of the –$NH_2$ group and hydrogen of phenolic –OH group are involved in intramolecular hydrogen bonding in 1-AHAQ (Scheme II).

*Electrochemical reduction in non-aqueous medium in presence of benzoic acid.*— In presence of benzoic acid in ACN, DMF and DMSO media the cyclic voltammogram of 1-AHAQ shows one reversible peak (I) along with two small shoulders (II and III) (Figure 5) which are summarized in Table II. It is interesting to note that the first reduction peak observed in pure ACN, DMF and DMSO media at −0.904, −0.832 and −0.816 V vs. Ag/AgCl, saturated KCl (Table I) respectively remain almost unaltered in the presence of benzoic acid. However, the second one-electron reduction peak observed in pure ACN, DMF and DMSO at –1.270, –1.309 and –1.355 V vs. Ag/AgCl, saturated KCl (Table I) respectively vanishes in the presence of

**Table II. Electrochemical parameters of 1-AHAQ in non-aqueous media in the presence of benzoic acid. Scan rate: 0.100 $Vs^{-1}$.**

| Medium | $E_{pc-1}$ (V) | $E_{pa-1}$ (V) | $E_1$ (V) | $E_{pc-2}$ (V) | $E_{pc-3}$ (V) |
|---|---|---|---|---|---|
| ACN | –0.804 | –0.628 | –0.716 | –1.459 | –1.696 |
| DMF | –0.807 | –0.697 | –0.752 | –1.467 | –1.676 |
| DMSO | –0.812 | –0.678 | –0.745 | –1.486 | –1.682 |

(Potentials are measured against Ag/AgCl, saturated KCl reference electrode).

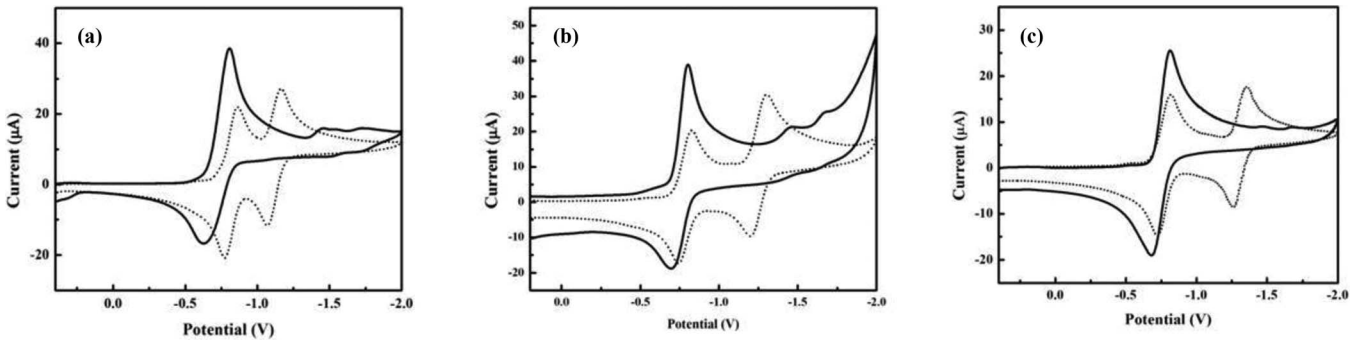



**Figure 5.** Cyclic voltammogram of 1-AHAQ in the absence (- - - -) and in the presence (—) of benzoic acid in (a) ACN (b) DMF (c) DMSO media. [1-AHAQ] $= 8.5 \times 10^{-4}$ mol · dm$^{-3}$, [Benzoic acid] = 0.03 mol · dm$^{-3}$, [TBAB] = 0.1 mol · dm$^{-3}$, T = 298.15 K.

benzoic acid. This is in accordance to the earlier reports by Eggins and Chambers[76] and Gómez et al.[45] A comparison of the present study with the earlier[45,76] it can be said that the formal reduction potential of the second one-electron reduction in the present study is increased and this peak therefore moves towards the first one-electron reduction peak and finally merge to produce a single wave at −0.804, −0.807 and −0.812 V vs. Ag/AgCl, saturated KCl in ACN, DMF and DMSO media respectively (Figure 5). Thus the single wave reversible reduction (I) (Figure 5) would be found to be like one step two-electron process.[76] This increases the reduction peak current at −0.804, −0.807 and −0.812 V vs. Ag/AgCl, saturated KCl in ACN, DMF and DMSO media respectively in the presence of benzoic acid almost twice the value of reduction peak current in the same media in the absence of benzoic acid.

Further from Figure 5 and Table II, it is clear that the oxidation potential of the first one-electron reduction of 1-AHAQ in different media in the presence of benzoic acid move to a more positive potential. Results of Table II show that the formal potential values for the reversible reduction decreases in the medium as ACN > DMSO > DMF which means that the reduction is comparatively most difficult in DMF while it would be the most facile in ACN medium. Thus in the presence of benzoic acid ACN would be least polar solvent while DMF would be most polar solvent. This is why the quinone molecule is most solvated in DMF media and least solvated in ACN media resulting in a gradual decrease in the above mentioned formal potential values from ACN to DMF through DMSO (Table-II).

To find whether the small shoulders (II) and (III) appear due to some electroactive species on the GC surface whose reduction is shifted positive due to the presence of benzoic acid, background scans are taken with the 0.03 mol · dm$^{-3}$ benzoic acid in DMSO, DMF and ACN containing 0.1 mol · dm$^{-3}$ TBAB' (Figure 6). The cyclic voltammograms (Figure 6) clearly show that there are no reduction or oxidation peaks in the potential range 0.4 to –2.0 V. This clearly shows that benzoic acid does not induce the small shoulders (II) and (III) (Figure 5) and these are definitely due to some other electrogenerated species.

*Electrochemical reduction in aqueous medium.*— In neutral aqueous medium, the cyclic voltammogram of 1-amino-4-hydroxy-9,10-anthraquinone shows one quasireversible peak (I) at –685 mV and another irreversible peak (II) at −1325 mV vs. Ag/AgCl, saturated KCl (Figure 7). A plot of the ratio of anodic to cathodic peak current ($I_{pa}/I_{pc}$) of the quasireversible peak (I) vs. the logarithm of scan rate (log v) (Figure 8a) shows that at both lower and higher scan rates the ($I_{pa}/I_{pc}$) values lie in the range 0.30 - 0.37 which is much smaller than unity establishing the fact that the electrochemical reaction is quasireversible. In the presence of NaOH the irreversible peak (II) (Figure 7) disappears indicating that it is not an adsorption peak that appeared in the reduction of anthraquinone in alkaline aqueous solution.[77,78] Comparing the behavior of the present molecule with adriamycin, quinizarin and sodium quinizarin-2-sulfonate[13,59] it can be said that the first quasireversible peak (I) arises due to two-electron reduction and the second irreversible peak (II) (Figure 7) is due to hydrogen evolution from adjacent phenolic –OH group at C-4 position of the molecule. 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.[13,59] To evaluate the number of electrons involved in the first quasireversible reduction step chronocoulometric studies were carried out in aqueous solution at neutral pH. The result shows that two electrons are involved in such reduction. A plot of cathodic peak ($I_{pc}$) current of the quasireversible peak (I) vs. the square root of the scan rate ($v^{1/2}$) (Figure 8b) does not show a linear relationship thereby establishing the quasireversible nature of this reduction. At pH 7.0 the phenolic-OH proton [(pK = 10.52 ± 0.10) as determined in Determination of pK of 1-amino-4-hydroxy-9,10-anthraquinone section] and –$NH_2$ group proton remain un-dissociated which form strong hydrogen bonding (Scheme III) with the reduced anionic quinone oxygen thereby stabilizing semiquinone and quinone dianion species.

In the quasireversible reduction of 1-AHAQ in the aqueous medium, it is interesting to note that both the cathodic and anodic peak potentials ($E_{pc}$ and $E_{pa}$ respectively) vary with scan rate (Figure 9) which indicates that a kinetic effect is operating during the charge transfer at the electrode surface. The kinetic analysis for the charge transfer in the quasireversible two-electron reduction of 1-amino-4-hydroxy-9, 10-anthraquinone is carried out by the most widely used method of Nicholson[79] and Perone.[80] For a

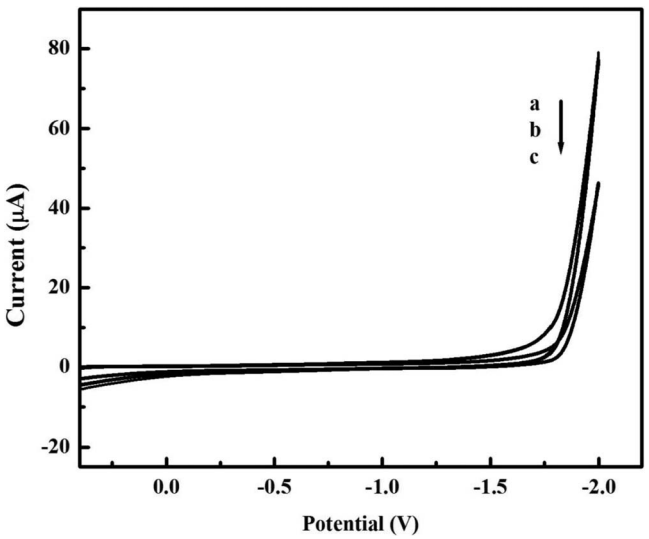



**Figure 6.** Cyclic voltammogram of 0.03 mol · dm$^{-3}$ benzoic acid in (a) DMSO (b) DMF (c) ACN media. [TBAB] = 0.1 mol · dm$^{-3}$, T = 298.15 K. Scan rate: 0.1 Vs$^{-1}$ (In this figure Curves- (a) and (b) overlap).

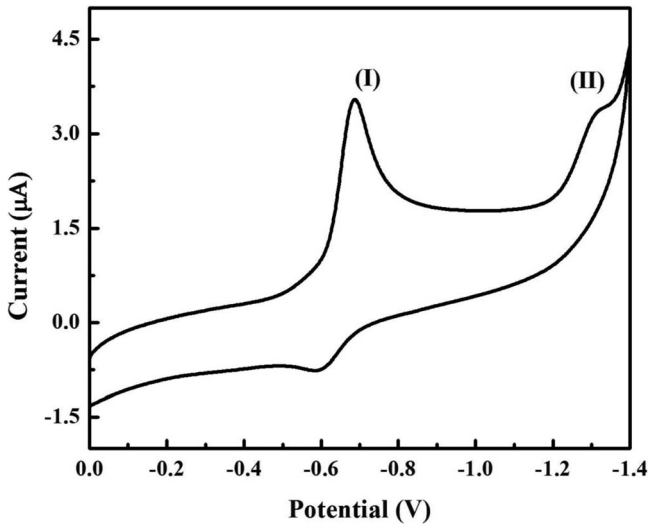



**Figure 7.** Cyclic voltammogram of 1-AHAQ in aqueous solution. Scan rate: 0.10 $Vs^{-1}$. [1-AHAQ] = $10^{-3}$ mol · $dm^{-3}$, [KCl] = 0.5 mol · $dm^{-3}$, T = 298.15 K, pH = 7.0.

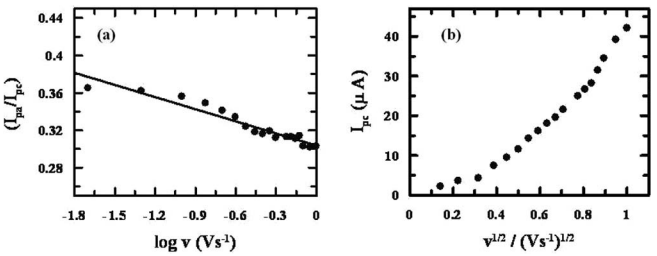
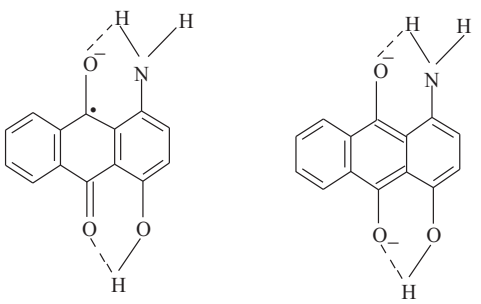



**Figure 8.** (a): Plot of the ratio of anodic to cathodic peak current ($I_{pa}/I_{pc}$) of the quasireversible peak (I) vs. the logarithm of scan rate (log v) for the reduction of 1-AHAQ in aqueous medium. (b): Plot of cathodic peak ($I_{pc}$) current of the quasireversible peak (I) vs. the square root of the scan rate ($v^{1/2}$).

quasireversible electrochemical reduction the wave shape and the peak potential separation $\Delta E_p = (E_{pa} - E_{pc})$ are functions of $v$, $k_s$, α and $E_\lambda$ [where $v$ = scan rate in V · $s^{-1}$, $k_s$ = standard rate constant for charge transfer (cm · $s^{-1}$), α = the transfer coefficient and $E_\lambda$ = switching potential in V]. However, if $E_\lambda$ is at least 90/n mV (i.e. it should be 45 mV in our experiment as here n = 2) beyond the cathodic peak the effect $E_\lambda$ is small. In the present cyclic voltammetry experiment of 1-AHAQ, $E_\lambda$ is separated from the cathodic peak by ≈ 200 mV and therefore our experimental results are free from the effect of $E_\lambda$. In this case the curves are the functions of the dimensionless parameters



**Scheme III.** Intramolecular H-bonding in semiquinone and quinone dianion.

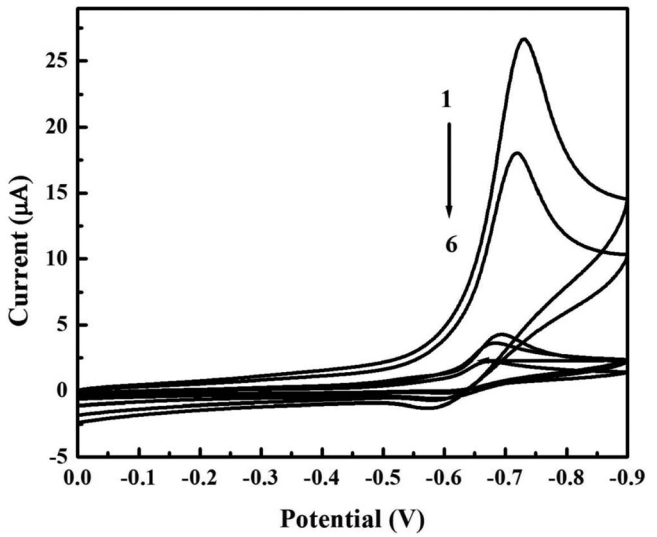



**Figure 9.** The cyclic voltammograms of 1-AHAQ in aqueous solution showing the variation of peak potentials ($E_{pc}$ and $E_{pa}$) with different scan rates: (1) 0.65 $Vs^{-1}$, (2) 0.40 $Vs^{-1}$, (3) 0.20 $Vs^{-1}$, (4) 0.10 $Vs^{-1}$, (5) 0.05 $Vs^{-1}$, (6) 0.02 $Vs^{-1}$. [1-AHAQ] = $10^{-3}$ mol · $dm^{-3}$, [KCl] = 0.5 mol · $dm^{-3}$, T = 298.15 K, pH = 7.0.

α and Ψ which is defined by eq. 5

$$\Psi = \frac{\gamma^{\frac{\alpha}{2}} k_s}{(\pi a D_O)^{\frac{1}{2}}} \qquad [5]$$

$$\text{where } \gamma = \frac{D_O}{D_R}, \quad a = \frac{nFv}{RT},$$

$D_O$ and $D_R$ are the diffusion coefficients of oxidized and reduced species in $cm^2 \cdot s^{-1}$, F = Faraday, R = Molar gas Constant, T = 298.15 K, $n$ = number electrons involved in the reduction.

It has been observed that for $0.3 < \alpha < 0.7$ the $\Delta E_p$ values are independent of α depend only on Ψ.[79] If $\Delta E_p$ is determined from the cyclic voltammetry experiments and the values of $D_O$, $D_R$ and $n$ of a redox couple are known then the corresponding Ψ value can be evaluated from Table III.[79,80] Knowing the value of Ψ one can determine the value of the standard rate constant for the charge transfer ($k_s$) in quasireversible systems. Even if both the values of $D_O$ and $D_R$ are not available, apparent values of $k_s$ are determined assuming γ = 1 i.e. $D_O = D_R$.[73] In the present study assuming the value of γ to be unity and $D_O$ to be $1 \times 10^{-5}$ $cm^2 \cdot s^{-1}$ for 1-AHAQ since the diffusion coefficient 1-AHAQ in various solvents lies in this range [Table I], the values of $k_s$ at various scan rates are determined using equation 5. The variation of peak potentials ($E_{pc}$ and $E_{pa}$) with different scan rate

**Table III. Determination of standard rate constant for charge transfer ($k_s$) from the values of Ψ, and $\Delta E_p$ at various scan rates in aqueous medium at neutral pH.**

| Scan Rate ($Vs^{-1}$) | $(\Delta E_p) \times n$ (mV) (Here n = 2) | Ψ | $k_s$ (cm $s^{-1}$) |
|---|---|---|---|
| 0.020 | 140 | 0.260 | 0.0114 |
| 0.050 | 160 | 0.200 | 0.0138 |
| 0.100 | 200 | 0.120 | 0.0117 |
| 0.200 | 212 | 0.100 | 0.0138 |
| 0.400 | 244 | 0.074 | 0.0144 |
| 0.650 | 290 | 0.048 | 0.0119 |

(Potentials are measured against Ag/AgCl, saturated KCl reference electrode).

**Table IV. Comparison of electrochemical parameters of 1-amino-4-hydroxy-9,10-anthraquinone with anthracyclines.**

| Name of the compound | Formal Potentials ($E_1$ and $E_2$ are the formal potentials for the first and second reduction of the quinone in non aqueous solvents while "E" corresponds to the formal potential of the two electron reduction of quinone in aqueous media) | Media | $K_{comp}$ |
|---|---|---|---|
| 1-Amino-4-hydroxy-9,10-anthraquinone | $E_1 = -840$ and $E_2 = -1220$ mV* | ACN | $2.69 \times 10^6$ |
| | $E_1 = -785$ and $E_2 = -1258$ mV* | DMF | $1.04 \times 10^8$ |
| | $E_1 = -770$ and $E_2 = -1308$ mV* | DMSO | $1.27 \times 10^9$ |
| | E = –685 mV* | Aqueous buffer at neutral pH | – |
| Adriamycin (Doxorubicin Hydrochloride) | E = – 435 mV*,[60] | Aqueous buffer at pH 4.50 | – |
| | E = –450 mV** at pH 4.54 and –333 mV** at pH 2.69[59] | Aqueous buffer at acidic pH | 0.138 at pH 4.54 and 0.148 at pH 2.69 |
| | E = $-665 \pm 5$ mV*,[61] | Aqueous buffer at neutral pH | Comproportionation was established but $K_{comp}$ was not determined. |
| Daunorubicin | E = – 730 mV**,[62] | Aqueous buffer at pH 9.18 | – |
| Idarubicin | E = –450 mV*,[63] | Aqueous buffer at pH 4.5 | – |
| Nogalamycin | E = –520 mV*,[64] | Aqueous buffer at pH 7.1 | – |
| Quinizarin (1,4-dihydroxy-9,10-anthraquinone) | E = –418 mV**,[59] | Aqueous buffer at pH 4.54 | 0.178 |
| 1,4-dihydroxy-9,10-anthraquinone | $E_1 = -568$ and $E_2 = -1118$ mV**,[71] | DMSO | Comproportionation was observed but $K_{comp}$ was not determined. |
| 1,5-dihydroxy-9,10-anthraquinone | $E_1 = -485$ and $E_2 = -920$ mV**,[71] | DMSO | |
| 1,8-dihydroxy-9,10-anthraquinone | $E_1 = -525$ and $E_2 = -1085$ mV**,[71] | DMSO | |

*Potentials are measured against Ag/AgCl, saturated KCl reference electrode.
**Potentials are measured against saturated calomel electrode.

is shown in Fig. 9. The values of $\Delta E_p$, $\Psi$ and $k_s$ are summarized in Table III. The values of $k_s$ evaluated here in the electrochemical reduction of 1-AHAQ lie in the range of $k_s$ values mentioned in the literature.[73]

Finally the electrochemical parameters of 1-amino-4-hydroxy-9,10-anthraquinone in non aqueous and aqueous solvents evaluated in the present study are compared with the earlier results of some anthracyclines[59–64] which are summarized in Table IV. Considering the entire aspects as discussed above one can say that there is a good similarity in electrochemical behavior between 1-amino-4-hydroxy-9,10-anthraquinone and anthracyclines in aqueous and non-aqueous solvents. In non-aqueous polar organic solvents such as acetonitrile, dimethyl formamide and dimethyl sulfoxide 1-AHAQ and anthracyclines undergo two one-electron reductions forming semiquinone and quinone dianion respectively [Table IV]. The cathodic peak potentials are dependent on the polarity of the solvent which is owing to the stability of the reduced species by intra and intermolecular hydrogen bonding.[39–53] In such solvents 1-AHAQ and anthracycline drugs undergo homogeneous chemical reaction along with the electrochemical reduction [Table IV]. However, in the presence of benzoic acid in the same solvents the two one-electron steps observed in pure organic solvent merge giving rise to a single step two-electron reduction like other quinones.[45,76] Similar to the anthracycline drugs 1-AHAQ undergoes one reversible two-electron reduction in aqueous media with one hydrogen evaluation peak.[13,59] Thus these entire behaviors hint at a possible similarity between 1-AHAQ and an anthracycline in their actions when such molecules would interact at the cellular level, since the electrochemical behavior of these molecules determines their therapeutic efficiency and toxic side effects.[26,27] This keeps open a possibility that 1-amino-4-hydroxy-9,10-anthraquinone which is much cheaper than established anthracycline anticancer drugs can be utilized in cancer chemotherapy in near future.

## Conclusions

In acetonitrile, dimethyl formamide and dimethyl sulfoxide, 1-amino-4-hydroxy-9,10-anthraquinone undergoes successive two one-electron reduction to give semiquinone and quinone dianion showing two cathodic peaks. The first step is completely reversible while the second step is quasireversible at customary scan rates. During the course of the reduction in these media quinone (1-AHAQ) and generated quinone dianion ($1\text{-AHAQ}^{2-}$) combine to form a semiquinone ($1\text{-AHAQ}^{\bullet-}$) leading to a comproportionation reaction. The apparent comproportionation constants are evaluated and the stability of the species is analyzed. Various electrochemical parameters evaluated are observed to be dependent on the polarity of the medium and therefore, these are correlated with the polarity index of the media. The intra and intermolecular hydrogen bonding is observed to play a great role in stabilizing the quinone (1-AHAQ) and its radical intermediates ($1\text{-AHAQ}^{\bullet-}$ and $1\text{-AHAQ}^{2-}$). In such media in the presence benzoic acid, the two one-electron steps observed in pure solvent merge giving rise to a single step two-electron reduction along with two small peaks. In aqueous media the cyclic voltammogram at neutral pH shows one quasireversible peak due to two-electron reduction of the quinone (1-AHAQ) to quinone dianion ($1\text{-AHAQ}^{2-}$) and one irreversible peak. In aqueous medium a kinetic study was carried out to determine the apparent charge transfer rate constants at various scan rates. Comparing the results and considering the entire aspects of electrochemical behaviors one can say that 1-amino-4-hydroxy-9,10-anthraquinone mimics the action of anthracycline drugs which may be extrapolated to say that their activity at the cellular level would be similar.

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