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Review Article

Electrochemical Reduction of Quinones in Different Media: A Review

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The electron transfer reactions involving quinones, hydroquinones, and catechols are very important in many areas of chemistry, especially in biological systems. The therapeutic efficiency as well as toxicity of anthracycline anticancer drugs, a class of anthraquinones, is governed by their electrochemical properties. Other quinones serve as important functional moiety in various biological systems like electron-proton carriers in the respiratory chain and their involvement in photosynthetic electron flow systems. The present paper summarizes literatures on the reduction of quinones in different solvents under various conditions using different electrochemical methods. The influence of different reaction conditions including pH of the media, nature of supporting electrolytes, nature of other additives, intramolecular or intermolecular hydrogen bonding, ion pair formation, polarity of the solvents, stabilization of the semiquinone and quinone dianion, catalytic property, and adsorption at the electrode surface, are discussed and relationships between reaction conditions and products formed have been presented.

1. Introduction

Quinone-hydroquinone couples are the prototypical examples of organic redox systems and the research on the electrochemical behavior of these compounds has been actively pursued for many decades starting from the beginning of the twentieth century [1]. The electrochemical behavior associated with electron-proton transfer equilibrium and kinetics provides information on molecular structure [2–5] and the environment of the basic process [6–9]. To find out their mode of action, evaluation of reaction mechanisms and determination of physicochemical parameters, studies on the reduction of these molecules under different conditions were carried out [6–17]. Besides chemical aspects, quinones play important roles in the biochemistry of living cells [18–35]. Anthracyclines, a class of anthraquinones are used as medicine in several types of human cancer [36–63] where it has been observed that their biological activities are associated with their redox behavior [18–63]. Thus it becomes necessary to understand the environmental factors

which regulate the potentials and reaction pathways of various species that appear in the quinone-hydroquinone systems in biology. Pulse radiolysis techniques [64–68], electron spin resonance [64, 65, 69], and electrochemical methods like polarography, cyclic voltammetry, square wave voltammetry and so forth, have been used to investigate redox behavior of different quinone systems [70–109].

In aqueous buffer, at acidic, neutral, and alkaline pH anthracyclines, anthraquinones, and other *para*-quinones undergo reversible two-electron reduction in which the reduction potential varies with pH in a straightforward Nernstian manner. At acidic pH, the reduction is a single step two-electron two-proton process while in alkaline pH the reduction does not involve proton and is only a case of two-electron reduction [77, 86–89]. At neutral pH, the reduction is either one proton two-electron or only two-electron without the participation of proton [77, 86–89].

In neutral aprotic media, the quinones (Q) undergo two successive one-electron reduction steps to produce semiquinone ($Q^{\bullet-}$) and quinone dianion (Q^{2-}) generating

two separate cathodic waves in which the first step is completely reversible and the second step is quasireversible at customary scan rates [110–122]. Electron spin resonance has been used to demonstrate the presence of quinone radicals as intermediates in the redox processes [64, 65, 69]. The potentials of these redox systems depend on the stability of the reduced species. Polarity of the solvents, nature of the supporting electrolyte, intra or intermolecular hydrogen bonding, presence of acidic or basic additives, ion pairing and protonation-deprotonation equilibrium play a crucial role in stabilizing reduced forms of quinones. Cation of the supporting electrolyte forms an ion pair with semiquinone and quinone dianion while acidic additives form hydrogen bond with the reduced species that stabilizes semiquinone and dianion. Many studies have been devoted to the ion pair formation processes between electrochemically reduced quinones and cationic species [7, 123]. The shift of polarographic half-wave potentials provide useful information to determine the association constant and stoichiometry of the ion pair formed in the vicinity of the electrode. In hydroxy quinones, the presence of the hydroxy functionality seems to be related to the biological activity of this kind of compound [124–128] and the position of this functional group can alter the typical redox behavior of the quinonoid moiety [129–131] owing to the formation of intramolecular hydrogen bonds in the reduced species. This is relevant, considering that most of the biological activity of quinonoid systems is related to their capacity to carry out free radical generation via redox reactions. Previous results for hydroxy substituted anthraquinones and naphthoquinones have been compared with that of 9,10-anthraquinone and 1,4-naphthoquinone to find out effect of hydroxy substitution on the geometry and electronic structure of anthraquinone and naphthoquinone.

This paper covers an area of research on electrochemical behavior of quinones from chemical to the biochemical domain. The aim of this paper is to provide an in-depth understanding on specific aspects of the reduction of quinones at different electrodes using different solvents, electrolytes, experimental conditions by using different electrochemical methods.

2. Electrochemical Aspects of Quinones

2.1. Biological Aspects of Quinones. Anthracycline drugs, a class of anthraquinones used as anticancer drugs [36] are effective against acute leukemia, malignant lymphomas and also active in solid tumours, particularly in case of breast cancer [36–45]. To decrease toxicity and increase therapeutic action new analogues and derivatives of these drugs are being formulated and tried clinically [36–38]. The cardiotoxicity [45–47] and chromosome damaging property [48] of the anthracyclines limit their use in cancer chemotherapy. Both cardiotoxicity and chromosomal damages are associated with several electron transfer processes involving the respiratory chain generating $\text{H}_2\text{O}_2/\text{O}_2^{\bullet-}/\text{OH}^-$. Participating in radical reactions anthracycline drugs initiate oxidative phosphorylation, complexation of phospholipid, and peroxidation of several lipids [49–54]. Several studies have shown that both therapeutic efficiency and toxicity of such drugs have

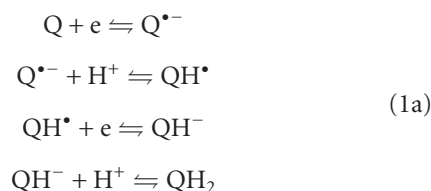
good correlation with redox properties [55–58]. The quinone moiety present in these drugs after one electron reduction forms semiquinone that plays a major role in determining toxicities of these drugs in cellular systems [59, 60]. Other quinones such as ubiquinones, are well-known important functional moiety in various biological systems acting as an electron-proton carrier in respiratory assemblies and in photosynthetic electron flow systems [18]. These *para*-quinones are reduced to semiquinones by mitochondrial NADH dehydrogenase [23–31, 40, 62, 63]. The reoxidation of semiquinone leads to the production of $\text{O}_2^{\bullet-}$ from where hydrogen peroxide and hydroxyl radical (HO^\bullet) arise and these active species are reported to degrade DNA by abstracting hydrogen from the deoxyribose residues [23, 24, 30–35, 40, 62, 63].

2.2. Electrochemical Reduction in Aqueous Media

2.2.1. Electrochemical Reduction in Buffered Aqueous Media.

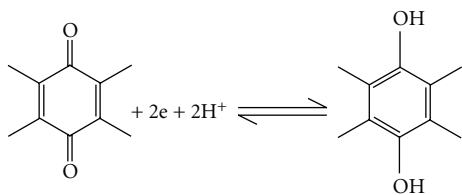
In buffered aqueous media (including mixtures with ethanol, methanol, etc.) quinone-hydroquinone couples provide familiar single step two-electron redox systems in which potentiometric or polarographic potentials vary with pH in a straightforward Nernstian manner [132]. This behavior was conveniently summarized in E-pH diagrams (Pourbaix diagrams), showing regions of existence of various redox and protonated species and their respective pK_a values [2, 3, 70, 71, 133]. It was shown that in aqueous buffer, at acidic, neutral and alkaline pH anthracyclines, anthraquinones, and other *para*-quinones are reduced by two electrons generating one reversible wave in cyclic voltammetry. At acidic pH the reduction is a single step two-electron two-proton process (Scheme 1) [72–77] and in alkaline pH the reduction does not involve proton and is only a case of two-electron reduction (Scheme 2) [77, 86–89]. At neutral pH, the reduction is either by one proton two electrons or only two electrons without the participation of proton [77, 86–89].

The reduction of *para*-benzoquinone in aqueous solution was studied by different workers [99, 100] and the mechanism of such reduction in aqueous solution was summarized as follows:

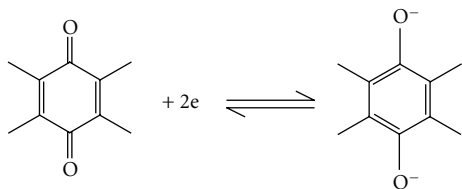


The sequence of the reactions is described as two rounds of electron-transfer coupled with proton acceptance (chemical reaction) that is ECEC or EHEH mechanism. In absence of protons the *para*-benzoquinone is reduced to its dianion, Q^{2-} . When the acidity of the medium is high, the two protonation steps can be so fast that the whole reaction affords directly hydroquinone QH_2 as product





SCHEME 1: Two-electron two-proton reduction of quinone in aqueous buffer.

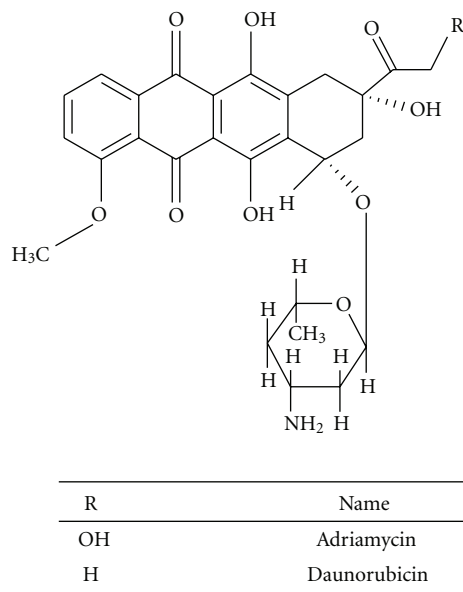


SCHEME 2: Two-electron reduction of quinone in aqueous buffer.

This reaction forms the basis of what is known as a “quinone/hydroquinone electrode” used in pH measurements.

At acidic and neutral pH in addition to a reversible reduction peak corresponding to two-electron reduction an irreversible reduction peak has been observed for anthracyclines and hydroxy-9,10-anthraquinones. Several studies on the electrochemical behavior of adriamycin (doxorubicin hydrochloride) and daunorubicin (daunomycin) (Scheme 3) by different researchers have been extensively carried out over a few decades [72–76, 78–86]. Rao et al. [72] and Molinier-Jumel et al. [73] have discussed the mechanism involved in the reduction of anthracyclines at mercury electrodes and attempted to correlate the observed behavior with their therapeutic actions. In both studies two reduction peaks are observed; one approximately at -600 mV versus saturated calomel electrode that is completely reversible and involves two-electron reduction of the quinone to hydroquinone while the second reduction is irreversible and occurs at more negative potential assigned to the irreversible reduction of the side chain carbonyl adjacent to the anthraquinone nucleus of adriamycin.

At carbon paste electrode, at pH 4.5, adriamycin shows two sets of waves one at a positive ($+500$ mV) and another at a negative (~ -600 mV) potential [74]. The oxidation peak at $+500$ mV is reversible and involves the oxidation of the hydroquinone group of the dihydroxy-9,10-anthraquinone moiety. The reduction peak at negative potential (~ -600 mV) was similar to the previously reported reduction of anthracycline quinones to hydroquinone [72, 73]. This reduction peak at negative potential shifted anodically by approximately 60 mV/pH unit as the pH was decreased and appeared to be reversible in more acidic condition (pH 2.3). This suggests that at acidic pH adriamycin is reduced by the mechanism of two electrons and two protons. Thus at carbon

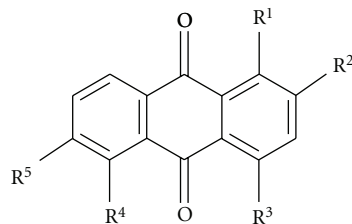


SCHEME 3: Structure of adriamycin and daunorubicin.

paste electrode at pH 4.5 two distinct sets of waves were observed for adriamycin which corresponds to two types of redox processes as mentioned above. However, at more acidic and neutral pH only one peak was observed which indicates that under such conditions both redox processes mentioned above take place at nearly the same potential.

The electrochemical reduction at carbon paste electrode is adsorption controlled. In order to establish the adsorption Chaney and Baldwin [75] carried out differential pulse voltammetry of extraordinarily low concentration (1.0×10^{-8} M) of adriamycin at pH 4.5 and observed a well-defined peak clearly indicating that electrochemical reduction in the carbon paste electrode is adsorption controlled. The peak at $+0.5$ V in square wave voltammetry was successfully utilized for the quantitative determination of adriamycin in unknown samples.

Kano et al. [76] studied the electrochemical properties of adriamycin and one of its simple analogue quinizarin (1,4-dihydroxy-9,10-anthraquinone) (Scheme 4) at pH 4.54 by cyclic a.c. and d.c. voltammetry using a hanging mercury drop electrode. It has been established that under such experimental conditions the electrochemical reaction is purely adsorption controlled with diffusion being negligible. The cyclic d.c. voltammetry shows two reduction peaks, one at -450 mV and another at -1130 mV. The first reduction is completely reversible while the other is irreversible. The pH dependence of the first peak is 60 mV/pH unit in the pH range of 2 to 6 indicating a two-electron two-proton redox process. The nature of the a.c. and d.c. voltammogram is almost similar. The peak potential of the second reduction shifts by about 50 mV for a 10-fold increase in scan rate in the range 10 to 500 mV/s. Further, they showed peak current grows parabolically with scan rate and the temperature coefficient of this peak current is 6.3% in the temperature range 10°C to 40°C . These indicate that the reduction



R ¹	R ²	R ³	R ⁴	R ⁵	Name
OH	H	OH	H	H	Quinizarin
OH	SO ₃ ⁻	OH	H	H	Quinizarin-2-sulphonate
SO ₃ ⁻	H	H	H	H	Anthraquinone-1-sulphonate
H	SO ₃ ⁻	H	H	H	Anthraquinone-2-sulphonate
SO ₃ ⁻	H	H	SO ₃ ⁻	H	Anthraquinone-1,5-disulphonate
H	SO ₃ ⁻	H	H	SO ₃ ⁻	Anthraquinone-2,6-disulphonate
COOH	H	H	H	H	Anthraquinone-1-carboxylic acid

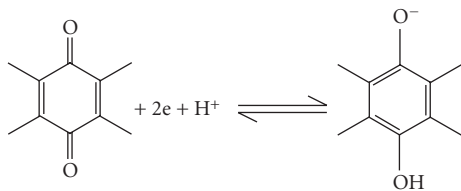
SCHEME 4: Structures of different anthraquinones.

is kinetic or catalytic in character. Similar second reduction peak was observed in quinizarin (1,4-dihydroxy-9,10-anthraquinone) [76] and sodium quinizarin-2-sulphonate (sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate) [77] (Scheme 4), but such reduction peak was not observed in case of pure anthraquinone. From these observations, it was suggested that the presence of two adjacent hydroquinone moieties is essential for such a reduction peak and was proposed to be due to hydrogen evolution. Addition of dimethylformamide or alkali to the reaction media makes such irreversible peak very small or it completely vanishes [77]. Since DMF has proton abstracting power [134–137] therefore, it reduces or vanishes hydrogen evolution peak [76]. Kano et al. clearly showed that 20% DMF completely vanishes the hydrogen evolution peak of adriamycin and quinizarin [76]. This supports the fact that the reduction peak is actually due to hydrogen evolution current, which is catalyzed by two hydroxy groups adjacent to benzene rings containing the quinone [76, 77]. Rao et al. [72] described the second reduction as an irreversible reduction of the side chain carbonyl adjacent to the anthraquinone nucleus on the basis of its similarity to the reduction processes of acetophenone and 1'-acetophenone. However, the side chain carbonyl of adriamycin is aliphatic and is not conjugated to the aromatic ring like the carbonyl of acetophenone. Therefore, it is difficult to reduce such aliphatic carbonyl group of adriamycin. In general, the reduction of aliphatic ketone was not observed in the usual buffer solution [73]. Further, Rao's assignment cannot explain the second irreversible reduction peak for quinizarin and quinizarin-2-sulphonate which do not possess the side chain carbonyl group [76, 77].

The electrochemical behavior of doxorubicin hydrochloride (adriamycin) using cyclic and square wave voltammetry in acetate buffer at different pH values using hanging mercury drop electrode was studied by Hahn and Lee [80]. They established that doxorubicin hydrochloride is reduced by two

electrons and two protons at hanging mercury drop electrode at acidic pH and that the reduction is quasi-reversible. The peak current is directly proportional to the concentration of doxorubicin and using this linear relation concentrations of doxorubicin in the unknown sample has been determined with very high precision [80]. El-Hady et al. [81] studied the electrochemical behavior of Cu(II) complex of adriamycin (adriamycin or doxorubicin hydrochloride) and its interaction with DNA by square wave voltammetry. They were able to show that the electrochemical reduction of such a complex is reversible but irreversibility increases with increase of pH.

Zhang et al. [82] analyzed the electrochemical behavior of adriamycin at carbon paste electrode in presence of cationic surfactant cetyltrimethylammonium bromide (CTAB). Adriamycin adsorbed strongly at the electrode surface assisted by CTAB thereby affecting the peak current and reduction potentials. In presence of CTAB the reduction at -0.500 V was seen to be irreversible and was used to determine the concentration of adriamycin in practical determinations [82]. Hu and Li [83] studied electrochemical property of adriamycin using CH₃COOH-CH₃COONa as supporting electrolyte at glassy carbon (GC) electrode and Ni ion-implanted glassy carbon electrode (Ni/GC) by linear sweep voltammetry. They performed experiments with different electrolytes like 0.05 M H₂SO₄, 0.1 M HCl, 0.1 M CH₃COOH-CH₃COONa, 0.1 M KCl, 0.1 M NH₃-NH₄Cl, 0.1 M NaOH and found that with 0.1 M CH₃COOH-CH₃COONa peak shape and size was good and sensitivity was reasonably high. It was found that as the pH was increased the peak current also increased tending to stabilize to a certain value for pH in the range 3.72–5; for all pH beyond 5.0 the peak current decreased. Due to this reason, 0.1 M CH₃COOH-CH₃COONa (pH 4.62) was chosen for this experiment and the concentration of adriamycin was determined quantitatively. They established that determination of adriamycin at low concentration is



SCHEME 5: Two-electron one-proton reduction of quinone in aqueous buffer.

more effective using a Ni/GC than GC electrode illustrating higher catalytic activity of Ni/GC than the glassy carbon (GC) electrode for the reduction of adriamycin. Using this method adriamycin was determined in urine samples of patients undergoing active adriamycin chemotherapy. In the same study it was found that the cathodic peak current has a linear relationship with the square root of the scan rate indicating that the reaction is diffusion controlled and that there is no adsorption at the electrode surface.

Electrochemical behavior of adsorbed daunomycin on hanging mercury drop electrode (HMDE) was studied in aqueous buffer at pH 9.18, and it was observed that the compound undergoes two-electron reduction following ECE pathway [84]. The result corroborates previous results [85].

Several researches [77, 86–109, 137, 138] have been carried out on different derivatives of anthraquinone and dihydroxy-9, 10-anthraquinones to see whether they mimic basic electrochemical properties of anthracycline drugs. As the solubility of anthraquinone or dihydroxy-9,10-anthraquinones is small therefore in most cases their soluble derivatives were used. Gill and Stonehill [86] and Furman and Stone [87] studied the electrochemical properties of anthraquinone-2-sulphonate at limited pH range in detail. They showed that it produced a well-defined polarographic wave in basic media. Their results were concordant with two-electron one-proton reduction to produce singly deprotonated dihydroxy-anthracene (Scheme 5). The unusual wave slope in polarography indicates adsorption process at the electrode. Guin et al. [88] carried out a chronocoulometry experiment on sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate at acidic, neutral, and alkaline pH and reported that the quinone molecule undergoes two-electron reduction at any pH. Anson and Epstein [89] noticed that cyclic voltammetry of anthraquinone-2-sulphonate showed a sharp reduction peak which was due to adsorption of the molecule at the mercury electrode. Chronocoulometry was used to determine number of electrons involved in such reduction. The authors showed that in alkaline media the anthraquinone is reduced by two electrons. For other anthraquinone sulphonate molecules like anthraquinone-1-sulphonate, anthraquinone-1,5-disulphonate, anthraquinone-2,6-disulphonate, and so forth, (Scheme 4) adsorption at different working electrodes were seen by different workers [64, 90–106]. He et al. [100] had shown that along with a reversible adsorption peak at 0.0 V there was a quasireversible diffusion peak at -0.2 V in cyclic voltammetry experiment of anthraquinone-2-

sulphonate. Another analogue anthraquinone-2-carboxylic acid was seen to adsorb at a gold electrode surface via self-assembly process [107, 108]. Anthraquinone-2-sulphonate, anthraquinone-1,5-disulphonate, and anthraquinone-2,6-disulphonate can be reduced by two electrons and two protons at acidic pH. The two electrons and two protons reduction at acidic pH was also found for quinizarin [76] and sodium quinizarin-2-sulphonate [77]. In almost all the experiments two electrons two-proton reduction at acidic pH for anthracyclines and other anthraquinone molecules was confirmed by linear relationship of cathodic peak potential, E_{pc} versus pH with a slope of ~ 60.00 mV/pH. Controlled potential coulometry experiments were done to determine the number of electrons involved in the reduction of quinone to dihydroxy anthraquinone or semiquinone or the quinone dianion [77, 88, 100]. In controlled-potential coulometry the total number of coulombs consumed in electrolysis is used to determine the amount of substance electrolyzed. In aqueous buffer, the formal reduction potential of quinizarin-2-sulphonate varies with pH with values of -420 mV, -470 mV, and -485 mV at pH 5.0, 7.0, and 9.0 respectively. At all these three pH that is acidic, neutral and alkaline 10^{-6} (M) quinizarin-2-sulphonate solutions were electrolyzed against constant potential of -400 mV for a long time and the number of coulombs was plotted against time. It was observed whatever is the pH of the solution, two electrons reduce quinizarin-2-sulphonate [88]. For anthraquinone-1,5-disulphonate, anthraquinone-2,6-disulphonate and anthraquinone-2-sulphonate the number of electrons involved in the reduction was observed to be 1.79 ± 0.01 , 1.93 ± 0.02 and 1.91 ± 0.01 [100]. The authors suggested that an early cut off of the chronocoulometry experiment or inaccurate background correction were the possible reasons for lowering of the number of electrons from the expected value of 2.

For an ideal reversible adsorption peak the number of electrons involved in the reduction was also evaluated from the following relation [100, 109]:

$$\left| E_{pc} - \frac{E_{pc}}{2} \right| = \frac{90.6}{n} \quad (2)$$

E_{pc} is the cathodic peak potential while $E_{pc}/2$ is potential at half width of the cathodic peak. n is the number of electrons involved in the process. Anthraquinone-2,6-disulphonate undergoes adsorption controlled reversible reduction and the width ($|E_{pc} - E_{pc}/2|$) was observed to be 48 for reduction peak and 45.6 for the oxidation peak. Considering these values the authors suggested that two electrons are involved in the redox couple for the adsorbates, just as for the dissolved species [100].

The electrochemical reduction of sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate at glassy carbon electrode surface in both aqueous and dimethylformamide media was found to be diffusion controlled [77]. Like anthracyclines, sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate was seen to generate two reduction peaks in which the first reduction is that of the reduction of the quinone while the second reduction peak is the hydrogen evolution peak at acidic pH. The first peak current (I_{pc})

has linear relationship with square root of scan rate and it passes through the origin suggesting a diffusion controlled electrochemical reaction with no adsorption on the electrode surface.

Koyama et al. [138] studied the electrochemical behavior of ten azo-naphthoquinone compounds to correlate their redox behavior on inhibitory effects on Epstein-Bar virus activation. They showed that at pH 7.2 the naphthoquinones were reduced reversibly by two electrons and that the electrode process was mainly diffusion-controlled with minor contributions due to adsorption at the electrode surface.

Studies on the reduction of anthraquinone sulphonates were extended from acidic to alkaline pH by Guin et al. [77] and He et al. [100]. pK_1 and pK_2 of the newly formed phenolic $-OH$ groups at the 9 and 10 positions of the anthraquinone are expected to be approximately 7.35 and 10.3, respectively [100]. Therefore, reduced forms of anthraquinone sulphonate molecules near pH 7.0 exist as a monoanion and so anthraquinone at pH close to 7.0 can be reduced by two electrons and one proton [100]. At high pH the reduced form exists as a quinone dianion specie and anthraquinones are reduced by two electrons only [77, 133]. In case of dihydroxy-9,10-anthraquinone like sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate, [77] for $pH > pK_a$ the newly formed phenolic $-OH$ groups at 9 and 10 positions of the molecule experience strong hydrogen bond between anionic quinone oxygens and phenolic $-OH$ of 1- and 4-positions, respectively, resulting in an almost steady value of reduction potential. After pH 9.0, the reduction potential further drops with pH and is due to deprotonation of phenolic $-OH$ at position 1 ($pK = 9.2$ [77]) which disrupts the stabilizing influence of hydrogen bonding with a simultaneous onset of ionic repulsion between two negatively charged oxygen atoms at 1 and 9, respectively. Thus the product is less stable and results in a decrease in formal potential.

2.2.2. Electrochemical Reduction in Unbuffered Aqueous Media. There are few reports on the electrochemical behavior of quinones in unbuffered aqueous media [2, 3, 139–148]. When the proton concentration nearly equals concentration of the quinone results are consistent with that observed in aqueous buffered media but sometimes explanations are different. In most cases the reduction is two protons two electrons or two electrons only. Shim et al. [139, 140] interpreted this as a case of one-electron reduction that was ruled out by other workers [141–143]. Depending upon the pK_a of hydroquinone the species QH_2 , QH^- , and Q^{2-} are formed. The mono- and dianions are stabilized by hydrogen bonding involving solvent water molecules. Hence, depending upon the pH of the media the nature of reduction varies.

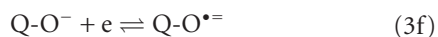
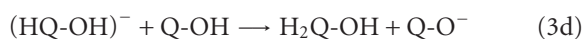
March et al. have extended their study [149] by using 5-hydroxy-3-hexanedithiol-1,4-naphthoquinone which was self-assembled on gold electrode to obtain an electroactive monolayer. This was subjected to cyclic voltammetry experiments in phosphate buffer-saline medium at pH 7.4. A quasi-reversible signal was observed with cathodic and anodic peaks at -0.45 V and -0.36 V, respectively. A kinetic analysis of the redox reactions involving both electron and

proton transfer has revealed an unusual behavior of this molecule due to the presence of the hydroxyl function in the vicinity of the quinone group. The apparent kinetic rate constant and the anodic electron transfer coefficient of this reaction is seen to depend on pH. In acid medium, a classical $2e^-/2H^+$ mechanism was obtained. In basic medium ($pH > 7$), strong intramolecular hydrogen-bonding interactions between the quinone and the hydroxyl function have a strong influence on redox kinetics. By studying the factors influencing the kinetics of the redox reactions, it has been found that hydrogen-bonding interactions have a critical role in the rate limiting step.

2.3. Electrochemical Reduction in Nonaqueous Media. In non-aqueous media, the reductions of quinones (Q) take place by two successive one-electron reduction steps generating two separate cathodic waves in which the first step is completely reversible and the second step is quasi-reversible at customary scan rates [110–122]. The peak currents of first and second reduction waves are proportional to square root of the scan rate, indicating a diffusion controlled process [77, 122, 133, 150–153]. The first step corresponds to the formation of a semiquinone radical $Q^{\cdot-}$ while the second step corresponds to the formation of quinone dianion, Q^{2-} . Semiquinone radicals are short lived and readily undergo disproportionation [2, 3, 154] generating a quinone and its corresponding dianion. Polarity of solvents, ion-pair formation, nature of supporting electrolyte, protonation-deprotonation equilibrium, intra- and intermolecular hydrogen bonding and addition of different acidic species or addition of water play important roles in determining the two formal reduction potentials.

2.3.1. Influence of Hydrogen Bonding, Acidic, and Basic Additives on Reduction. The semiquinone radical and quinone dianion formed are sometimes stabilized by strong hydrogen bonding between the anionic quinone oxygen and the phenolic $-OH$ protons present at β -positions with respect to quinone oxygen. Ashnagar et al. [151] carried out the electrochemical reduction of 9,10-anthraquinone, 1,4-naphthoquinone, and their analogues. It was established that introduction of hydroxy groups at 5- and 8-positions of the 1,4-naphthoquinone nucleus and 1-, 4-, 5- and 8-positions of the 9,10-anthraquinone nucleus increases their reduction potentials. Presence of 1-hydroxy and 1,4-dihydroxy substituents raises the first formal reduction potential relative to 9,10-anthraquinone by 199 mV and 273 mV, respectively. In case of naphthoquinones similar increments of the two potentials were observed. Insertion of methoxy groups at the positions mentioned above for both types of quinones do not show any change as observed in case of the hydroxy substituents. When only one $-OH$ group is present at any of the positions mentioned above then only the semiquinone radical is stabilized leading to an increase in the first reduction potential. However, when two $-OH$ groups are present adjacent to quinone oxygens then both the semiquinone radical as well as the quinone dianion gets stabilized through hydrogen bond formation leading to an increase in both reduction potentials [77, 110].

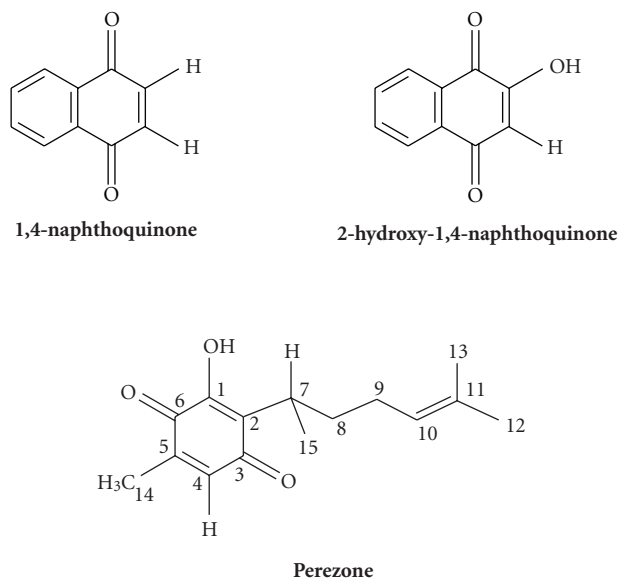
Electrochemical reduction of 2-hydroxy-1,4-naphthoquinone and perezone (2-(1,5-dimethyl-4-hexenyl)-3-hydroxy-5-methyl-1,4-benzoquinone) (Scheme 6) in acetonitrile was studied using cyclic voltammetry and chronoamperometry and the mechanism of such reduction was proposed [131, 155]. For these molecules there is an initial electron transfer step followed by self-protonation (shown below). The products of reduction are the protonated semiquinone and a deprotonated original quinone. Both interact with an electron forming species shown as products in (3c) and (3f), respectively. Product of (3c) later interacts with another quinone molecule resulting in H₂Q-OH and forming another deprotonated original quinone:



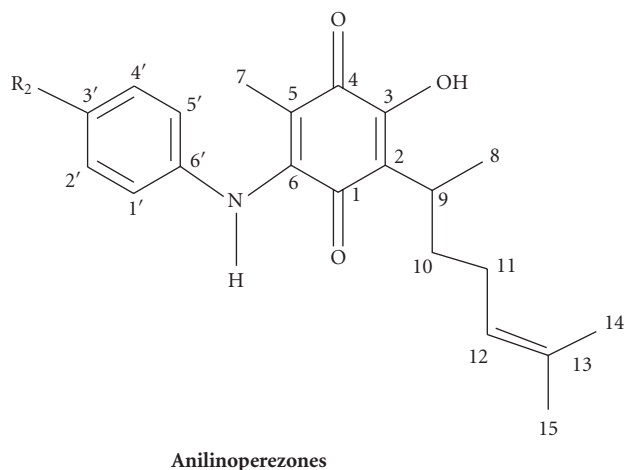
In an actual experiment reactions (3a) to (3d) summarized as (3e) takes place in a single-step two-electron reduction while the reaction shown by (3f) is a separate case of reduction that occurs on the *in situ* formed anion of the original quinone following cases of deprotonation (steps (3b) and (3d) as shown above. It could therefore be concluded from the above study that the first reduction wave corresponds to the overall reaction (3e) where two electrons reduce one of every three molecules of QOH producing the corresponding hydroquinone (H₂Q-OH) while the other two quinones two conjugated base species (2Q-O^{•-}). The second reduction wave corresponds to the one electron reduction of Q-O^{•-} to Q-O^{•=}. However, there is some controversy with regard to the electrochemical reduction of the conjugate base formed from such hydroxy quinones [156–161].

The set of reactions (3a)–(3f) was assumed in some other study using compounds having such type of hydroxy groups [158, 162–168]. The radical dianions formed were detected by Electrochemical-Electron Spin Resonance coupled experiments (EV-ESR). Addition of tetrabutylammonium hydroxide increases ESR signal intensity and proves the radical nature of the species. In acetonitrile along with two reversible reduction waves like other quinones the compounds showed a third irreversible oxidation peak at positive potential. Frontana and coworkers suggested this third oxidation peak to be the oxidation of an intermediate formed during self-protonation pathway [163].

González and coauthors [130] have worked with perezone in acetonitrile using linear sweep voltammetry and single potential step chronoamperometry. The reduction of perezone involves a mono-electronic charge-transfer step, followed by a protonation step and homogeneous charge transfer due to disproportionation of the protonated intermediate. The mechanism for the homogeneous charge-transfer



SCHEME 6: Structures of naphthoquinones and perezone.



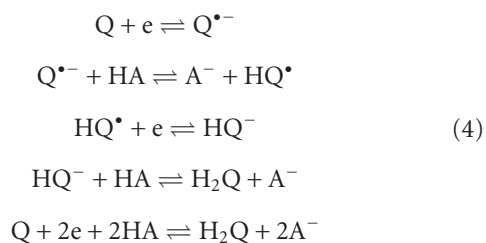
SCHEME 7: Structure of anilinoperezones, R₂ = –OH, –OMe, –Me, –Br, and –CN.

step was found to be first order disproportionation from results of double potential step chronoamperometry experiments that were carried out in mildly acidic medium [130].

Electrochemical behavior of some C₆ *para*-substituted anilinebenzoquinones (APZs) (Scheme 7) derived from perezone (Scheme 6) were analyzed in acetonitrile using cyclic voltammetry to find out the effect of substituents on quinone electronic properties by Aguilar-Martínez et al. [131]. The effect of hydrogen bonding between α -hydroxy and quinone oxygen was determined in perezone derivatives by different substituting electron-donor and electron-acceptor groups like –OMe, –Me, –Br, and –CN and comparing the –OH (APZs) and –OMe (APZms) derivatives. The typical behavior of quinones with α -phenolic protons, in an aprotic medium was not observed for APZs due to

the presence of coupled, self-protonation reactions. The self-protonation process gives rise to an initial wave, corresponding to the irreversible reduction of substituted quinone (HQ) to hydroquinone (HQH₂), and to a second electron transfer that is attributed to the reversible reduction of perezonate (Q^{•-}) formed during the self-protonation process (discussed earlier) [155]. This reaction is favored by the acidity of the α -OH located on the quinone ring. To control the coupled chemical reaction in one case methylation of the -OH group (APZms) was done while in another addition of a strong base, tetramethylammonium phenolate (Me₄N⁺C₆H₅O⁻) completely deprotonated the APZs. In both cases there was a recovery of the reversible character of Q/Q^{•-} and Q^{•-}/Q²⁻.

Electrochemical property of anilinoperezones (2-(1,5-dimethyl-4-hexenyl)-3-hydroxy-5-methyl-6-[4'-(R2-phenyl)amine]-1,4-benzoquinones, PQOHs) (Scheme 7), in acetonitrile and in presence of different proton sources like benzoic acid, perchloric acid was studied and compared with its methylated derivatives (2-(1,5-dimethyl-4-hexenyl)-3-methoxy-5-methyl-6-[4'-(R2-phenyl)amine]-1,4-benzoquinones, PQOMes) by Bautista-Martínez et al. [161]. To control self-protonation reactions mentioned above from occurring during electrochemical reduction of PQOH, weak acids such as benzoic acid and a strong acid such as perchloric acid were used as acid additives while a weak base sodium benzoate and a strong base tetraethylammonium phenolate were used as basic additives. In aprotic medium, the PQOMe family exhibits electrochemical behavior typical of quinones in systems giving two reversible diffusion controlled waves with fast electron transfer characteristics in the absence of external and internal proton donors. This behavior indicated that the -NH group present in the structure of PQOMe does not show appreciable acidic properties in aprotic media. To verify the role of external acidic additives the reduction of PQOMe was carried out in the presence of buffer system benzoic acid-sodium benzoate. It was found that in presence of an acidic additive only one reduction wave appeared in more positive direction and the peak current was greater indicating a two-electron two-proton reduction corresponding to the reduction of quinone to dihydroquinone. This indicates that the semiquinone formed is stabilized by protonation. The mechanism was suggested as follows:

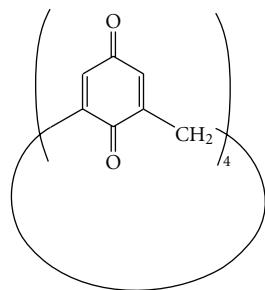


In case of PQOHs the first reduction peak is irreversible along with ill-defined shoulders in between the first and second reduction waves. Since the molecule contains internal proton donor centers therefore it undergoes reduction through self protonation reactions as reported in case of 2-hydroxy-1,4-naphthoquinone and perezone molecules

[155]. The ill-defined shoulders are associated with the reduction of quinone homoconjugated species (hydrogen-bonded complexes) [156, 158, 169]. Like PQOMe in presence of acidic additives PQOHs also undergo two-electron two-proton reduction. In another work by Bautista-Martínez et al. [170] on electrochemical behavior of anilinoperezones and their methylated derivatives in acetonitrile in presence of proton donor and withdrawing agent substituent effect in methylated compounds were correlated quantitatively.

Eggs and Chambers [171] also reported the effect of proton donors on the reduction of 1,4-benzoquinone in aprotic media. According to this report, when a weak acid such as benzoic acid was added, 1,4-benzoquinone undergoes an ECE process in which the first electron transfer follows a proton transfer while the second electron transfer happens apparently at the same potential. The cathodic peak potential (E_p) depends on the concentration of the acid. In presence of a strong proton donor such as perchloric acid electrochemical behavior of 1,4-benzoquinone was altered significantly. The first reduction of 1,4-benzoquinone takes place at several tenths of a volt more positive than the original wave, and its peak current increased as the amount of acid increased. This new peak has been attributed to the prior protonation of quinone. However, the extent of peak shift (ΔE_p) depends not only on acidity of added proton sources but also on the basicity and structure of the quinones. It has been seen that in case of 1,4-benzoquinone (BQ) when the added acid source is stronger than corresponding dihydroquinone then prior protonation of the quinone (BQH⁺) causes a new reduction peak at more positive potential than that of the first reduction wave of free quinone. When the added proton source is weaker than the dihydroquinone such as aliphatic alcohol then no proton transfer was found. The quinone dianion formed in the second reduction step is stabilized by hydrogen bond with such proton sources and change in the second reduction potential was significant while change in first reduction potential was very small. Organic Brønsted acids with medium strength act as proton sources on both steps of electron transfer. Therefore, both redox waves were significantly modified in presence of such acids. As most carboxylic acids, protonated alkylamines and phenol derivatives are regarded as Brønsted acids with medium strength, the redox behaviors of quinones in this study are understood on the basis of an ECE mechanism [172, 173]. A new peak that appears at a more positive potential than the reduction peak due to reduction of free benzoquinone is clear and well developed. Stronger acids cause the potential of the new peak to be more positive. Thus, the difference between the potentials of the new and original reduction peaks, ΔE_p , is sensitive to strength of the acid used. It has been seen that ΔE_p is maximum for tetramethyl benzoquinone and it was used to determine the concentration of various biologically active acids like pyruvic acid, maleic acid, and histamine quantitatively. From these it is clear that depending upon the concentration of proton in reaction media the conventional two-step one-electron reduction is significantly altered.

Gómez et al. [174] have studied the electrochemical behavior of 1,4-benzoquinone in presence of benzoic acid



SCHEME 8: Structure of calix-[4]-quinone.

and tetrabutylammonium hexafluorophosphate as supporting electrolyte in dimethylsulphoxide. They have observed that in absence of benzoic acid 1,4-benzoquinone generates two reversible reduction peaks Ic and IIc with their oxidation peaks Ia and IIa, respectively, corresponding to the formation of semiquinone $Q^{\bullet-}$ and the dianion Q^{2-} (Figure 1). However, in presence of benzoic acid the waves IIc, IIa, and Ia disappear and a new cathodic wave IIIc and anodic wave IIIa develop at more positive potential (Figure 1). They have suggested this modification as a consequence of the protonation of the semiquinone $Q^{\bullet-}$ and the rapid reduction of the protonated semiquinone QH^{\bullet} [110, 131, 159]. Therefore, the signal IIIc represents an overall two-electron reduction mechanism, which can be considered as an ECE or a disproportionation process [176], and the wave IIIa corresponds to the oxidation of the protonated dianion QH^- (Figure 1).

Calix-[4]-quinone (Scheme 8) consists of four *para*-benzoquinone units connected in parallel by four $-CH_2-$ groups present in between. Each *para*-benzoquinone unit undergoes reversible two one-electron reductions to form semiquinone and quinone dianion in rigorously dried acetonitrile solvent [175] like a simple *para*-benzoquinone molecule [2, 3]. The authors [175] have shown that the four *para*-benzoquinone units are reduced consecutively in which the first two quinone units are reduced at less negative potentials while the reduction of other two units occur at more negative potentials (Figure 2). The difference in peak potentials between the second and third waves were significantly larger than those between the first and second as well as the third and fourth waves, indicating that the first two-electron transfers take place at the first and third *para*-benzoquinone units (Figure 2). The third electron transfer, however, occurs at the second *para*-benzoquinone unit, which is located between the two *para*-benzoquinone anion radicals, resulting in a large resistance to the incoming electron. This explains why the potential differences between the first and second waves, as well as the third and fourth waves, are smaller than that between the second and third waves. These quinone radical anions are reduced to quinone dianions and as dianions are more reactive, the reversibility of the last two waves is significantly reduced compared to that of first two waves. In presence of a strong acid like $HClO_4$ the calix-[4]-quinone undergoes eight-proton eight-electron reduction. The electrochemical reduction of calix-[4]-quinone was also studied by other

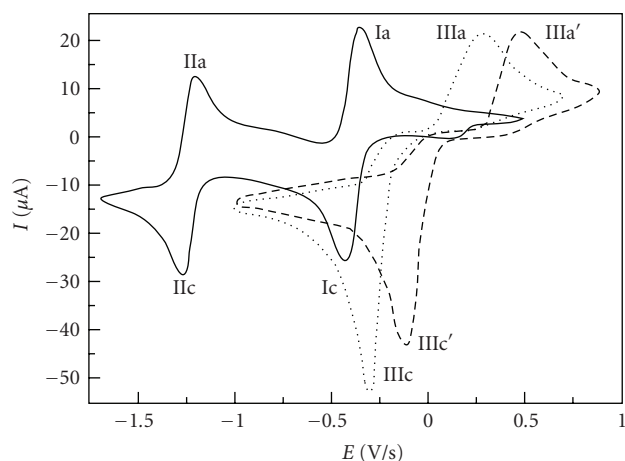


FIGURE 1: Typical cyclic voltammetry of 2.0 mM 1,4-benzoquinone, in DMSO +0.2 M Bu_4NPF_6 , on glassy carbon electrodes ($\phi 3$ mm) at 0.1 V s^{-1} . Several concentrations of benzoic acid were used: (solid line) 0.0 M; (dotted line) 0.03 M and (dashed line) 1.00 M. [174].

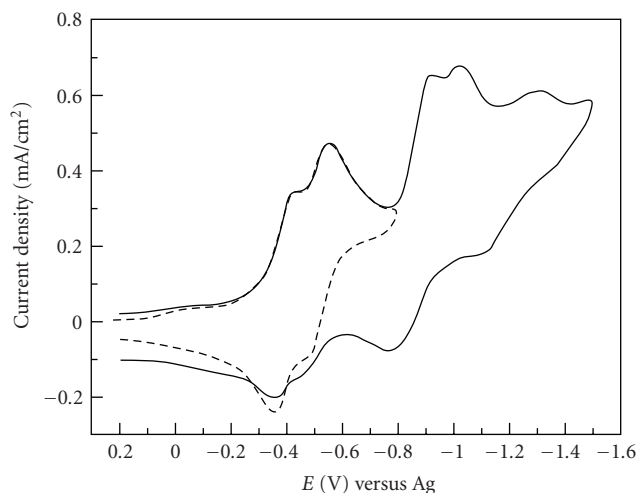


FIGURE 2: CVs for reduction of 1 mM CQ at a GC electrode in rigorously dried CH_3CN containing 0.10 M $TBAPF_6$ as a supporting electrolyte. The scan rate was 100 mV/s. [175].

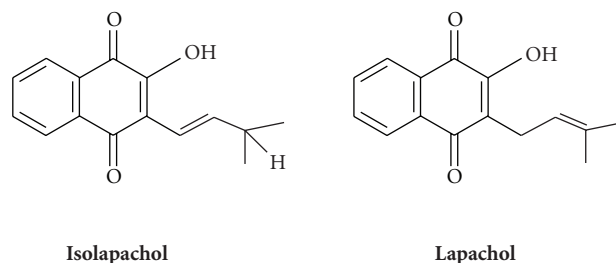
groups in different nonaqueous solvent-like acetonitrile [177], dimethylformamide [178] and dichloromethane [179] and it was observed the mode of reduction in different studies are almost the same.

Like 1,4-benzoquinone the 3,5-di-*tert*-butyl-1,2-benzoquinone (Q) undergoes conventional two-proton two-electron reduction in acetonitrile [180] However, it was seen that in case of long-term experiments such as controlled potential electrolysis, the semiquinone ($Q^{\bullet-}$) formed disappears slowly. The rate of disappearance was seen to increase with addition of water. The water molecule promotes disproportionation of the semiquinone to neutral quinone (Q) and protonated dianion (HQ^-) and hydroxide. In presence of water 1 : 1 hydrogen bonded complex formation between semiquinone and water molecule [$(Q^{\bullet-})(H_2O)$] was proposed to form after semiquinone formation. Due to

such complex formation addition of water changes the standard potential for the first step. The 1:1 complex, $[(Q^{\bullet-})(H_2O)]$, is proposed to be the reactant in the second step of the reduction and it was suggested that the reaction is an electron and proton transfer reaction in which insertion of the electron into the complex is associated with transfer of a proton from water to the developing quinone dianion.

Role of intramolecular hydrogen bonding in reduction has been extensively studied on naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) and quinizarin (1,4-dihydroxy-9,10-anthraquinone) [181–184]. Additionally, intramolecular hydrogen bonding in the one- and two-electron reduction states of hydroxy-naphthoquinones has been studied by electrochemistry and electron spin resonance [185, 186]. Intramolecular hydrogen bonding in β -phenolic quinones cause its electrochemical behavior to be different from α -phenolic quinones and intramolecular hydrogen bonding in β -phenolic quinones stabilize semiquinone and quinone dianion formed by the reduction. Owing to this stabilization the successive reduction potentials will be shifted to more positive potentials [72, 164, 167, 173]. By taking different β -hydroxy naphthoquinones and anthraquinones Gendell et al. [186] have proved that β -hydroxy quinones produce stable semiquinones. The stabilization arises due to strong hydrogen bonding. It has been found that peak potentials shift towards less negative direction for α - and β -isomers compared to naphthoquinone except the second reduction peak for α -isomer which is shifted towards more negative direction. This indicates that the semiquinone and quinone dianion formed on reduction are stabilized by intramolecular hydrogen bonding. The exceptional behavior of α -isomer has been assumed to be due to a self-protonation pathway. To explain the role of hydrogen bonding, intramolecular hydrogen bonding energy of β -isomers was considered [187] and the same for α -isomer was determined and compared. Intramolecular hydrogen bonding increases along the order: 2-hydroxy-1,4-naphthoquinone < 5-hydroxy-1,4-naphthoquinone < 2,5-dihydroxy-1,4-naphthoquinone. The intramolecular hydrogen bonding diminishes the chemical resistance to the formed semiquinone and influences the disproportionation reaction of semiquinone to quinone and quinone dianion. The disproportionation constant decreases as 2,5-dihydroxy-1,4-naphthoquinone > 5-hydroxy-1,4-naphthoquinone > 1,4-naphthoquinone.

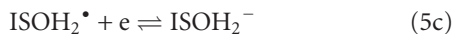
In dimethylsulphoxide and acetonitrile media the electrochemical reduction of 1,4-naphthoquinone, 5-hydroxy-1,4-naphthoquinone, and 5,8-dihydroxy-1,4-naphthoquinone and the effect of acidic additives like benzoic acid and methanol have been studied by Gómez et al. [165]. In both dimethylsulphoxide and acetonitrile it has been seen that as the number of α -phenolic groups increase the stabilization of the quinone anions and the reduction potentials shift to more positive values. This means that the energy required to reduce the neutral quinones and the radical anions follows the order: $H_2NQ < HNQ < NQ$, which accounts for the greater stability of the electrochemically generated semiquinone radical: $H_2NQ^{\bullet-} > HNQ^{\bullet-} > NQ^{\bullet-}$ and quinone dianion: $H_2NQ^{2-} > HNQ^{2-} > NQ^{2-}$.



SCHEME 9: Structures of isolapachol and lapachol.

The cyclic voltammogram of isolapachol (ISOH) (2-hydroxy-3-(3-methyl-1-butenyl)-1,4-naphthoquinone) (Scheme 9) [159] in DMF shows two main pairs of peaks, the first cathodic one, designated as Ic at -0.635 V, with a related anodic peak (Ia) at -0.103 V and the second pair, named IIIc at -1.434 V and IIIa at -1.305 V. The first step is irreversible while the second step is quasi-reversible (Figures 3 and 4). An intermediate shoulder (IIc) at -1.228 V and a prominent anodic wave (Va) at $+0.900$ V were observed. When the run is in the negative direction and was reversed from -1.50 V, then an additional anodic wave (IVa) at $+0.488$ V was observed suggesting it (IVa) is related to the oxidation of the product generated at IIIc (Figure 3). When the run is in the positive direction, one additional reduction peak at -0.358 V was observed and the anodic peak Va shifts to $+0.931$ V (Figure 4). Then the wave IVa vanishes since suggesting that it is related to oxidation of a modified product generated at IIIc. The first reduction peak is due to the generation of the semiquinone ($ISOH_2^{\bullet-}$). The shoulders are related to the reduction of hydrogen-bonded intermediates and the last quasi-reversible reduction is due to the reduction of the semiquinone. After the generation of semiquinone ($ISOH^{\bullet-}$) (5a), self-protonation occurs generating $ISOH_2^{\bullet}$ and $ISO^-(5b)$. $ISOH_2^{\bullet}$ receives a second electron forming the related anion ($ISOH_2^-$), which suffers a second self-protonation leading to the electroinactive specie $ISOH_3$ (toward reduction), together with $ISO^-(5d)$. Thus, the oxidation of the species electrogenerated at Ic occurs at a more positive potential (Ia) due to a lesser electronic density caused by the protonation. That is the reason for the significant separation of waves Ic and Ia ($\Delta E_p = +0.532$ V). Alternatively, the generated radical ($ISOH_2^{\bullet}$) undergoes disproportionation to produce original quinone (ISOH) and the anion (ISO^-), that forms an acid–base homoconjugated dimer. The hydrogen-bonded complex is then reduced in the region of the shoulders. The electrochemical behavior of isolapachol, lapachol (2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone), and other analogues of 2-hydroxy-3-alkylnaphthoquinones are almost similar. A series of natural and synthetic 2-hydroxy-3-alkylnaphthoquinones in DMF have been studied by Ferraz et al. [188]. It was observed that the first cathodic reduction for isolapachol is more positive compared to lapachol. This positive shift in the potential of the first wave of isolapachol, in comparison to lapachol, is related to the higher acidity of the phenolic group in isolapachol. Isolapachol has a conjugated double

bond, which allows a better stabilization of the conjugated base, through resonance. Itoh et al. [156] have seen similar behaviour observed for pyrroloquinolinequinone. The anodic peak Va is related to the irreversible oxidation of the enolic function, leading probably to an extra quinone group, releasing protons



The electrochemical reduction of β -lapachone and its 3-sulphonate salt was studied by cyclic, square wave, and differential pulse voltammetry in aqueous and water-ethanol mixtures using a glassy carbon electrode [189, 190]. Cyclic voltammograms of β -lapachones at a glassy carbon electrode show a reversible process involving the same number of electrons and protons, and the reduction potential of β -lapachone is dependent on pH (slope 59 mV per pH unit). The study was extended to see whether the molecules interact with DNA or L-cysteine and 2-mercaptoethanol. It was found that β -Lapachones do not interact directly with single or double strand DNA. When L-cysteine was added to the medium, the cathodic peak decreased significantly in size. The anodic peak was also affected and new cathodic peaks appeared. Such modifications of electrochemical reduction were seen to be concentration dependent. At high concentration the color of the reaction solution changed immediately from bright yellow to pale yellow. These effects were attributed to the reaction of β -lapachone and L-cysteine. A similar behaviour was observed with 2-mercaptoethanol. The electrochemical observation of the reaction of β -lapachone with L-cysteine and 2-mercaptoethanol corroborates results obtained and constitute additional evidence for the anticancer activity of β -lapachones [191, 192].

The electrochemical behavior of a few 9,10-anthraquinone derivatives was studied in acetonitrile solution using cyclic voltammetry by Shamsipur et al. [121]. The results are similar to the behavior of other anthraquinones as reported earlier. They have correlated the experimental data with theoretical data obtained by quantum theoretical calculations. A linear relationship was observed between the theoretically predicted values and experimentally determined half-wave reduction potentials of the 9,10-anthraquinone derivatives. From this study the authors made two conclusions.

Substitution of the hydrogen on C_1 position of 9,10-anthraquinone by a hydroxy group results in a significant positive shift of peak potential of both the first and second reductions.

Substitution at the C_2 position revealed some shift in peak potentials, either positive or negative, depending on the nature of the substituted group. However, the extent of shift in potential is not as significant as that observed in case of substitution on C_1 .

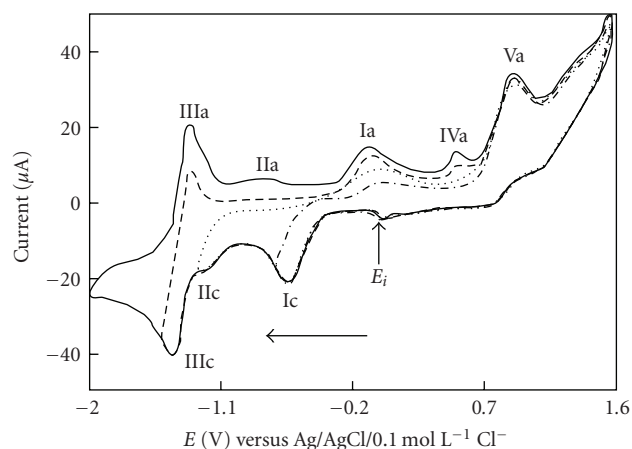


FIGURE 3: Cyclic voltammograms of isolapachol, DMF + 0.1 mol L⁻¹ TBAP, GCE versus Ag/AgCl /0.1 mol L⁻¹ NaCl, $c = 2$ mmol L⁻¹. (solid line), Initial potential = 0 V, $\nu = 0 : 100$ Vs⁻¹. Negative scan. different E_i : (dashed dotted line) -0.739 V; (dotted line) -1.249 V; (dashed line) -1.519 V [159].

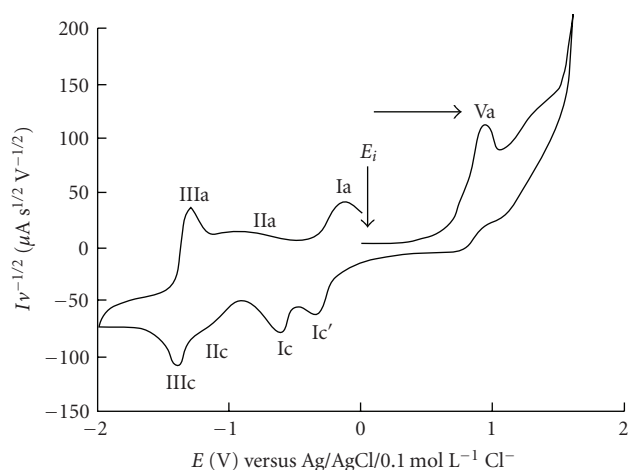
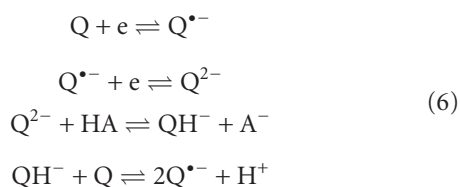


FIGURE 4: Cyclic voltammogram of isolapachol, DMF + 0.1 mol L⁻¹ TBAP, GCE versus Ag/AgCl/0.1 mol L⁻¹ NaCl, $c = 2$ mmol L⁻¹. Initial potential = 0 V, $\nu = 0 : 100$ Vs⁻¹. Positive Scan [159].

In nonaqueous solvents addition of weak hydrogen bonding agents like methanol, ethanol, 2-propanol, *tert*-butanol, and so forth, or strong hydrogen bonding agents like trifluoroethanol can also stabilize the semiquinone radical and the quinone dianion by forming intermolecular hydrogen bonds. Therefore, in presence of such hydrogen bonding agents the two reduction potentials shift towards more positive potential [110, 193–195]. Effect of weak acid like hexafluoro-2-propanol or strong acid like trifluoroacetic acid is almost similar to hydrogen bonding agents. In organic solvents such as DMF, DMSO, and acetonitrile the dissociation of acids is not facile and this is why in such solvents different acids usually cannot protonate the dianion, rather they form hydrogen bonding with the dianion and stabilizes it. Addition of another hydrogen bonding agent water to nonaqueous solvents also changed the reduction potentials and peak current considerably [195]. Gradual addition of

water to dimethylformamide (DMF) or dimethylsulphoxide (DMSO) solution leads to positive displacement of the second reduction potential until the second wave merges with the first owing to stabilization of the dianion by hydrogen bonding with water molecule [193–198]. It was found that in aqueous dimethylformamide solvent, pH determines nature of reduction, that is, whether reduction is single step two-electron or two-step one-electron [77]. For sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate at neutral pH in 95% DMF the two successive reduction waves (observed in pure DMF) did not appear and a single step two-electron wave was observed. It was found that at pH 9.0 two successive one-electron reduction waves were observed in solution having 40% DMF [77]. Similar nature of reduction was observed by Masson et al. [199]. They observed that in anhydrous hydrofluoric acid media quinones are reducible in two mono-electronic reversible steps. However, in hydrogen fluoride-water mixtures, the classical one-step two-electron reduction was found [199].

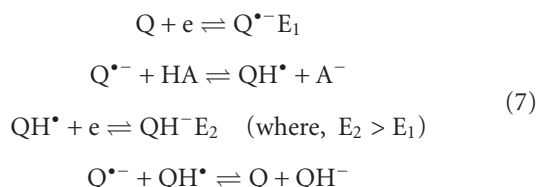
In acetonitrile media, electrochemical behavior of 2,3,5-trimethyl-6-(3'-methyl-3'-hydroxybutyl) quinone was changed significantly by the addition of a weak acid like ethyl malonate [150]. Though the first reduction was unaltered, the second reduction peak broadened, shifted anodically and became irreversible. The corresponding oxidation peak therefore disappeared. In order to explain this result the following mechanism was proposed:



where HA is a proton donor. The protonation of the dianion Q^{2-} is fast relative to potential sweep and the protonated specie (QH^-) readily undergoes comproportionation reaction with (Q) to produce a semiquinone ($Q^{\bullet-}$). Therefore, the oxidation peak corresponding to quinone dianion to quinone disappears.

In presence of stronger proton donors like benzenethiol, the cathodic process is an overall two-electron process and protonation of semiquinone is an important part of the mechanism [150]. The reduction of quinone to semiquinone shifts anodically and doubles in height, while the cathodic wave for the reduction of semiquinone to quinone dianion disappears.

To explain the phenomena the following scheme was proposed:



Quinones having phenolic hydroxy group at α -position, that is quinones capable of forming intramolecular hydro-

gen bonding in the neutral molecule or in the anionic form, show different electrochemical behaviors in non-aqueous solvent on addition of acetic acid. Gómez et al. [165] compared the electrochemical behavior of 1,4-naphthoquinone (NQ), 5-hydroxy-1,4-naphthoquinone (HNQ), and 5,8-dihydroxy-1,4-naphthoquinone (H_2NQ). In 1,4-naphthoquinone intramolecular hydrogen bonding is absent and cyclic voltammetry experiment showed a transition from one-electron to two-electron reduction of the molecule with increase in acetic acid. In presence of acid, the semiquinone formed ($NQ^{\bullet-}$) was converted to the protonated radical anion (NQH^{\bullet}) that was more easily reduced than the neutral quinone NQ. As a result the first and second reductions occur at almost same potential and the overall reduction was observed to be by one step two electrons. A similar behavior of quinones was also described by Gupta and Linschitz [110] and Chambers [2, 3]. Cyclic voltammetry experiments of H_2NQ in presence of different concentrations of acetic acid showed that the chemical reversibility of the two one-electron waves are not lost suggesting typical protonation reactions are inhibited, even at an HAc/H_2NQ concentration ratio close to 200. This effect was explained by considering that the radical anion $H_2NQ^{\bullet-}$ and dianion H_2N formed in the first and second electron transfer steps are highly stabilized by the presence of two intramolecular hydrogen bonds and that it did not undergo any form of external protonation. This observed voltammetric behavior of H_2NQ was supported by other workers [169, 200]. On the other hand, HNQ is an intermediary structure between NQ and H_2NQ . The cyclic voltammetry experiments on HNQ showed a small concentration of acetic acid is required to obtain a reduction wave where apparently first and second reduction waves merged.

The electrochemical properties of quinone-hydroquinone (Q/QH₂) systems in acetonitrile and nitromethane media were studied by rotating-disk electrode voltammetry, cyclic voltammetry, controlled potential coulometry and absorption and ESR spectroscopy [201]. Cyclic voltammetry indicated that the reversibility of the redox system Q/QH₂ was dependent on the nature of the substituents and the acidity of the medium.

At mercury electrode electroreduction of camphorquinone in DMF was investigated by Ouziel and Yarnitzky [202]. In DMF and in absence of proton donor, the molecule showed two one-electron waves. In the second step the monoanion radical, produced in the first step, was reduced to dianion irreversibly. The irreversibility of the second wave was explained by assuming a fast irreversible protonation of the dianion.

2.3.2. Effects of Homogeneous Chemical Reactions in Reduction Process. Besides electrochemical reactions there are other reactions like disproportionation, comproportionation, or dimerization that affect an overall electrochemical reaction. In nonaqueous solvent it has been found that peak current of second reduction was significantly smaller than those of the first and that the second reduction peak deviates considerably than those expected for simple two-electron reductions [4, 77, 110, 114, 150, 203–206]. One of the largest

deviation from ideality was seen in *ortho*-benzoquinone, 3,5-di-*tert*-butyl-1,2-benzoquinone. In such compounds, it was found that the second reduction peak is almost one fourth of that expected [121]. It hints at the fact that the concentration of quinone dianion decreases by some other homogeneous chemical process [77, 122, 133, 207, 208]. In some works, it was explained assuming a comproportionation reaction between the quinone dianion and the quinone to form the semiquinone radical. The comproportionation was further established by Guin et al. [77] who found that in pure DMF, when the scan is reversed after sufficient time elapsed following the second reduction the anodic peak current for the first reduction is markedly increased than when the scan is reversed before the second reduction. This increase in anodic peak current indicates that the semiquinone concentration increases when there is a scope for second reduction. The decrease of the second reduction peak was explained by Lehman and Evans [122] who suggested a fast and irreversible dimerization reaction in between quinone dianion (Q^{2-}) and quinone (Q) to form an electroinactive dimeric species Q_2^{2-} in acetonitrile media. Simulation studies carried out could prove these types of reactions [77, 122]. In different alcohols, Wipf et al. [133] had shown that different anthraquinone compounds would generate two one-step reduction process and difference in the two reduction potentials decreases in the order: 2-propanol > ethanol > methanol > water. In basic methanol and in basic aqueous solution actually only one reduction peak was found and two one-electron peaks merge as their peak potential difference is very small [207, 208]. From pulse radiolysis experiments it has been found that the difference between the reduction potential of quinone and the semiquinone is 9 mV [65]. Wipf et al. [133] showed that at very high pH in protic solvents, protonation is unimportant and the electron-transfer processes would be affected by electron-transfer kinetics and reduction potentials of relevant couples. Under these conditions, the redox chemistry in basic, protic solvents should resemble that found in aprotic solvents [2, 3]. Disproportionation reactions were seen to operate at high pH in these cases.

During the electrochemical reduction of tetramethyl-1,4-benzoquinone (duroquinone), the dimer diduroquinone is produced in high yield. The dimerization is proposed to proceed via a catalytic process as the current passed is much less than one electron per molecule. Diduroquinone is further cleaved to duroquinone anion radical by an electrochemical reduction [203].

Glezer et al. [205] studied electrochemical reduction of intramolecular charge-transfer complexes derived from 1, 4-naphthoquinone in DMF and aqueous DMF solutions. In aprotic media electrochemical reduction of the compounds proceeds via two successive steps; the first leads to the formation of a stable anion radical while the second forms an unstable primary product. The hyperfine structures of the corresponding anion radicals were studied.

2.3.3. Role of Cations and Anions of Supporting Electrolytes. In aprotic media the cation of the supporting electrolyte or any

added cation is known to form ion pairs with semiquinone and quinone dianion produced by the reduction of quinones [123, 206, 209–212]. During the electrochemical reduction of anthraquinones in dimethylformamide the ion pairs of anthraquinone anions were examined where it was found that the ion-pairs were adsorbed on Hg electrodes in the presence of divalent metal ions while the same did not happen at the gold electrode surface. The nature of specific interaction between the semiquinone or quinone dianion and the mercury electrode and possible structure of the ion pairs were also suggested [209].

On addition of metal ions new set of peaks were observed at more positive potential in comparison to the original free ligand wave. This reflects stabilization of the reduced form, radical anion or dianion of diquinone in the presence of metal ions. Such phenomena were seen for quinone-functionalized calix-[4]-arene where the molecule was found applicable to the fabrication of a molecular device that selectively recognize specific cations [213, 214].

Hence, due to ion pair formation reduction potentials were shifted towards positive direction. The extent of such shift depends on the concentration and on ionic potential Φ_{eff} of the cation [214–217]. Φ_{eff} is defined as $z/(r + \delta)$ where, z and r are the charge and Pauling's radius of cation, respectively, and δ is Latimer type correction factor. Hence, the greater charge and smaller size of a metal ion causes larger shift in the reduction potential [153]. Chung et al. [153] have established that the extent of positive shift of reduction potential for few analogues of calix-[4]-arene diquinone after complexation with a series of metal ions follows the order: $\text{La}^{3+} > \text{Mg}^{2+} > \text{Ca}^{2+} > \text{Li}^+ > \text{Na}^+ > \text{K}^+$. Peover and Davies [215] have shown that in dimethylformamide for anthraquinone, *para*-benzoquinone, and chloranil the extent of association of quinone dianion with cation decreases with decreasing positive charge density on the cation and established the decreasing order of association as $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{NEt}_4^+ > \text{NBu}_4^+$. Stoichiometries of such ionic associations are also dependent on the nature of the cation [215]. Metal ion complexes can be considered to undergo a transition of the nature of a host-guest interaction during electrochemical reduction. Ion-dipole interaction is predominant in the neutral ligand complex, but ion-ion interaction or electrostatic interaction becomes an overwhelming factor after electrochemical electron donation. The extent of positive shift of electrode potential is used to determine the association constant, stoichiometry of ion-pair association and thermodynamic parameters [209, 216, 217].

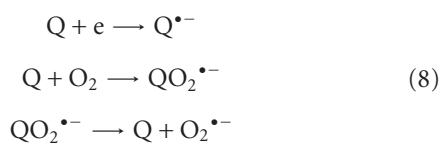
The standard rate constants k_1° and k_2° of the electron transfer between *para*-benzoquinone and its radical and of the radical anion and the hydroquinone dianion have been measured by means of cyclic voltammetry at a plain gold electrode in different aprotic solvents. Four different tetraalkylammonium perchlorates were used as supporting electrolytes. Using standard electrode potentials the association constants of the hydroquinone dianion and the cation of the supporting electrolyte were calculated. The association constants and the observed Gibbs activation energies decrease with increasing size of supporting electrolyte cation [209].

To observe the solvent effect on ion-pair association, Oyama et al. [206] have analyzed the ion-pair formation between 2,3,5,6-tetrachloro-1,4-benzoquinone anion radical and Mg^{2+} in different solvents using pulse electrolysis stopped flow method. It was shown that interaction between semiquinone and Mg^{2+} in acetonitrile was much stronger than in DMF and DMSO which could be explained by the difference in solvating power for the cationic species [4]. The solvation of acetonitrile for Mg^{2+} is assumed to be so weak as to let 2,3,5,6-tetrachloro-1,4-benzoquinone interact with Mg^{2+} . The semiquinone formed by one-electron reduction exists in free state in DMF and DMSO even when a large excess of Mg^{2+} is present. Therefore, the interactions of DMF and DMSO with Mg^{2+} are found to be stronger than that between semiquinone and Mg^{2+} , though the latter is a coulombic interaction. The competing interactions of DMF (or DMSO) and semiquinone for Mg^{2+} could also be observed in the kinetic measurements. Pulse electrolysis stopped flow method also showed that in spite of complex electrochemical responses, the kinetic processes dominate the ion pair formation between 2,3-dichloro-5,6-dicyano-1,4-benzoquinone dianion and Na^+ [206].

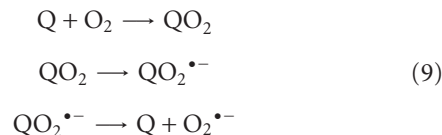
The values of heterogeneous electron transfer rate constants for the reduction of different quinones in nonaqueous solvents at different electrodes have been measured by cyclic voltammetry [217]. Theoretically, the redox potentials have been calculated including solvent effect, for a series of anthraquinone and few other quinone derivatives by Alizadeh and Shamsipur [218] and compared with the available experimental electrode potentials [122] in two consecutive electron transfer steps in acetonitrile solution. The theoretical values of redox potentials in the two successive one-electron steps in most cases show a relatively good agreement with the corresponding experimental electrode potentials [218].

A recent report on electrochemical behavior of a Cu(II) complex of sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate shows that upon complex formation the electrochemical behavior of such molecules is significantly modified. In dimethylformamide solvent the Cu(II) complex of sodium 1,4-dihydroxy-9,10-anthraquinone-2-sulphonate shows only one reversible reduction peak corresponding to one-electron reduction of the complex [219].

2.4. Electrochemical Reduction of Quinones in Oxygenated Nonaqueous Solutions. In oxygenated nonaqueous solvent anthraquinones mediate one-electron reduction of oxygen to superoxide anion radical as follows. At first quinone (Q) is reduced to semiquinone ($Q^{\bullet-}$) by one-electron reduction. In presence of oxygen the semiquinone formed reacts with molecular oxygen to form a complex ($QO_2^{\bullet-}$) which then breaks to anthraquinone (Q) and superoxide anion radical ($O_2^{\bullet-}$) [220–224]



An alternative mechanism was also proposed in which the first step involves the formation of an adduct between singlet oxygen to anthraquinone. In the second step the adduct is reduced by one electron and it then dissociates to anthraquinone and superoxide radical [225–229]



It has been observed that in nonaqueous media hydroxy-anthraquinones catalyze the reduction of molecular oxygen significantly in comparison to that of anthraquinones without hydroxy group. This phenomenon has been explained by the assumption that anthraquinone reduction is accompanied with oxygen addition to form hydroperoxide anion radicals, which can be formed by anthraquinones having proton-donor like hydroxy groups only. This observation has been justified theoretically and experimentally [230].

3. Conclusions

Quinones undergo one-step two-electron reduction in aqueous buffer at acidic, neutral, and alkaline pH generating one reversible reduction wave. However, at acidic pH the reduction involves two protons while at alkaline pH the reduction does not involve any proton. In neutral pH, the reduction may or may not involve proton depending upon the pK value of the phenolic $-OH$ group of the hydroquinone. In acidic and neutral pH, quinizarin (1,4-dihydroxy-9,10-anthraquinone) and some of its analogues such as quinizarin-2-sulphonate, adriamycin, and daunorubicin show another irreversible reduction peak at much more negative potential, but such reduction peak was not observed in case of pure anthraquinone. Thus it was suggested that presence of two adjacent hydroquinone moieties is essential for such a reduction peak and was proposed to be due to hydrogen evolution. In case of adriamycin, in addition to the above two peaks at pH 4.5 a reversible anodic peak at +500 mV was observed which has been assigned as the redox process involving the oxidation of the hydroquinone group of dihydroxy-9,10-anthraquinone moiety. In unbuffered media, when proton concentration is similar to that of the quinone then the reduction is a single-step two-electron two-proton reduction. When the proton concentration is small then depending upon the pKs of hydroquinone neutral, anionic, and dianionic species are generated. In nonaqueous media, the reduction of quinones takes place by two successive one-electron reduction steps in which the first step is completely reversible, while the second step quasi-reversible at customary scan rates. In the first step, the quinone becomes semiquinone and in the second step the semiquinone becomes quinone dianion. The two reduction steps are greatly influenced by nature of the solvents, intramolecular hydrogen bonding, protonation-deprotonation equilibrium, addition of acidic or basic additives or even addition of water, ion-pair formation, nature of supporting electrolyte, polarity of solvents and so forth.

Introduction of hydroxy groups at 5- and 8-positions of the 1,4-naphthoquinone nucleus and 1-, 4-, 5- and 8-positions of the 9,10-anthraquinone nucleus enable the formation of hydrogen bond with semiquinone radical and quinone dianion that increases their reduction potentials. Hydrogen bond was also observed in case of semiquinones, quinone dianions with added proton sources such as acids, alcohols, and water which shift the reduction potential towards positive directions. Besides electrochemical reactions there were other homogeneous chemical reactions like disproportionation, comproportionation, or dimerization that affect the overall electrochemical reaction. In nonaqueous media the cation of the supporting electrolyte or any added cation was known to form ion pairs with semiquinone and quinone dianion. Owing to ion-pair formation reduction potentials were shifted towards positive direction. In oxygenated nonaqueous solvents, quinones mediate one-electron reduction of oxygen to superoxide anion radical by different mechanisms but itself remains unaltered. All such effects in the reduction of quinones in aqueous and nonaqueous solvents have been summarized and correlated with electrode potentials.

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