Electrochemistry of selected quinones at immiscible n-octyl-2-pyrrolidone/aqueous interface using a three-phase electrode system

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Abstract

Both endogenous and synthetic (e.g. drugs) quinones are essential functional moieties in various biological systems and their activity is mainly governed by their electrochemical properties. In recent years they are also more readily applied in novel energy storage devices, such as batteries and solar cells. In this work, the redox behaviour of 1-aminoanthraquinone (AQ), and 2,3-dichloro-1,4-naphthoquinone (NQ) is studied at a three-phase junction formed by n-octyl-2-pyrrolidone and aqueous electrolyte solution on a glassy carbon working electrode. We show that the two quinones behave quite differently when undergoing reduction at the three-phase junction. AQ underwent a 1-step, 2-electron reduction resulting in transfer of cations from the aqueous phase, while reduction of NQ occurred in two steps, the first of which was accompanied by a transfer of the $NQ^{\bullet -}$ radical to the interface with the reduction potential dependent on the anion present in the aqueous phase due to salting out effects. After that, the quinone was able to undergo a second reduction process forming a dianion which similarly to AQ resulted in a transfer of cations from the aqueous phase. Importantly, the cation transfer potential is determined by ion-pair formation with the quinone, rather than the solvation energy of cation in the pure organic solvent.

Keywords: 1-aminoanthraquinone, 2,3-dichloro-1,4-naphthoquinone, three-phase electrode, immiscible liquids, ITIES

1. Introduction

The redox chemistry of quinones is important from both a chemical and biochemical perspective. The chemical aspects are largely related to the industrial production of hydrogen peroxide [1], development of novel energy storage materials for batteries [2,3], dye-sensitized solar cells [4], and other [5]. The redox behaviour of different quinones also plays a significant role in the biochemistry of living systems [6–8]. Some classes of quinones, like anthraquinones and naphthoquinones, are vital building blocks of various molecules of utmost biological importance. Anthracycline drugs (a class of anthraquinones) are used in cancer chemotherapy to treat numerous types of cancer [9,10]. But their effectiveness in cancer

therapy is mainly limited by cardiotoxicity and chromosome damaging properties [9–12]. Numerous studies have revealed that both the healing efficiency and toxicity of anthracyclines have a good correlation with their redox properties [9,13–15]. The toxicity of anthracyclines is often attributed to the one-electron reduced semiquinone form of the quinone moiety [9,16,17].

Another class of quinones, the naphthoquinones (e.g. alkannin and shikonin), is recognized for their anti-inflammatory, antibacterial, topoisomerase inhibition, antitumor and wound healing properties [18–20]. The naphthoquinone moiety is the main component in vitamin K formulations. Additionally, Ubiquinone-10 (coenzyme Q) plays a critical role in the respiratory chain of mitochondria. It acts as both an electron carrier and a redox component for the pairing of electron and proton transfer enabling the generation of pH gradients across the membrane in mitochondria (the Q cycle) [1,21,22].

Considering the above, quinone redox chemistry is essential to understand the factors which control the reaction pathways and the redox behaviour of different quinones in the biological and chemical environment. To study this, electrochemical, electron spin resonance and pulse radiolysis techniques are mainly used [9,23,24]. Generally, the redox chemistry of quinones in different solvent systems and under various conditions is studied using polarography, cyclic voltammetry, and square wave voltammetry [9]. So far, electrochemical studies of quinones were carried out varying pH, type of the supporting electrolyte, a polarity of the solvent, and through adsorption on different electrode surfaces. Additionally, the effect of other additives, intramolecular/intermolecular hydrogen bonding, ion pair formation with supporting electrolytes, stabilization of the semiquinone and quinone dianion are reported [9].

Generally, functionalization of quinones with electron donors lowers their reduction potential [2]. Similarly, in the three-phase electrode (TPE) configuration, it can be observed that quinones bearing any substituents, which enhance their solubility in water, present lower reduction potentials [25]. We performed initial studies with 10 different quinones such as substituted benzophenones, acenaphthenequinone, 1,8-naphthalic anhydrides, substituted acetophenones, and other aromatic quinones (see supplementary material). We observed that compounds bearing two keto groups on the opposite sides of the anthracene and naphthalene structures can be reduced at TPE configuration. In this work, we used quinones having Cl and NH_2 substituents, which can be reduced at the TPE before the water reduction occurs, while still remaining relatively insoluble in water. For the complete study we investigated the redox behaviour of 1-Aminoanthraquinone (AQ), and 2,3-Dichloro-1,4-naphthoquinone (NQ) in a TPE configuration.

In the TPE configuration, a neutral electroactive compound is dissolved in a water-immiscible organic solvent containing no supporting electrolyte. A small droplet of this organic solvent is placed on the working electrode, which is thereafter submerged in an aqueous electrolyte to form the TPE system. A three-phase junction exists where the organic and aqueous phases meet on the working electrode. The reference and counter electrodes are placed in the aqueous phase. Since the organic phase has no supporting electrolyte, the initial reaction can take place only at the three-phase junction. The interface is generally very small, which results in low

capacitive current. Any electron transfer between the electrode and compounds in the organic phase has to be compensated by an ion transfer between the aqueous and the organic phases to maintain the electroneutrality of the organic phase [26–30]. The ion transfer across the organic/aqueous interface is fundamental for a better understanding of the transport through biological membranes, electrochemical sensing and phase transfer catalysis, electro-assisted solvent extraction, and other potential applications [31–35]. TPE systems are one of the most popular experimental setups used to study the ion transfer at the organic/water interface [26,30,36,37].

The three-phase electrode configuration, where the lipophilic/hydrophilic interface can be created is one of the simplest models of the complex biological membrane. Living systems are assembled from adjacent lipophilic/hydrophilic compartments, and compounds are constantly being transported across these interfaces. Factors like lipophilicity, redox activity, and structure of the compound influence its movement, distribution, metabolism, toxicity and the biological activity [9,26,38,39]. Furthermore, this kind of system allows us to assess different redox behaviour of quinones at organic/aqueous interface like precipitation of redox product at the interface, adsorption of the redox complex at the liquid/electrode interface and dissolution of the redox complex in aqueous phase when pH is altered. Examples of some of the above mentioned different redox behaviours are discussed in this article, showing the potential of the TPE setup as means to study reaction mechanisms of quinones, which up till today was scarcely explored using this technique [40].

In aqueous media, quinones undergo a single step two-electron reversible reduction. In acidic pH, a single two-electron two-proton reduction takes place while in alkaline and neutral pH, either a single two-electron or a single two-electron one-proton reduction occurs [3,9]. In neutral aprotic or non-polar solvents, two separate one-electron reductions take place; first to a semiquinone radical anion ($Q^{\bullet-}$) and further to a quinone dianion (Q^{2-}) [9]. In this work, we used the aprotic non-polar solvent n-octyl-2-pyrrolidone (NOP) as the organic phase and various inorganic and organic salts in water as the aqueous phase (W) to create a TPE configuration on glassy carbon (GC) electrode. The electrochemical reduction of neutral lipophilic quinone in NOP disturbs the charge neutrality of the NOP phase. Therefore, this can either promote the transfer of cation ion from W to NOP or the transfer of the reduced quinone from NOP to W phase. The cation transfer happens if the free energy of such transfer is lower than the free energy of transfer of the reduced quinone from NOP to W phase [27,29,30]. When a reducible non-ionic compound is dissolved in a nonpolar organic solvent (like NOP), the transfer of the reduced lipophilic compound from the organic to the aqueous phase is the most probable reaction pathway [30]. However, in this case we have chosen quinones that are sufficiently lipophilic to stay in the organic solution also after reduction. During reduction, AQ stays in the organic phase and a cation is transferred from the aqueous phase to compensate for the charge. The potential at which the reduction happens depends on the transfer potential of the cation in question. However, contrary to previous reports on cation transfer at a TPE the overpotential does not increase with increasing hydrophilicity of the ion [27,29,41,42], but rather varies with ionic potential. We explain this by formation of ion-pairs between the quinone and the cation [43,44]. NQ, on the other hand, shows two

reduction peaks. In the first case, the $NQ^{\bullet -}$ anion is probably transferred to the aqueous phase, but adsorbs on the liquid-liquid interface, while the second reduction product is stable in the organic phase and is again paired with a cation transferred from the aqueous phase. In this report, we investigate the different reactions for these two quinones in detail and discuss the different mechanisms.

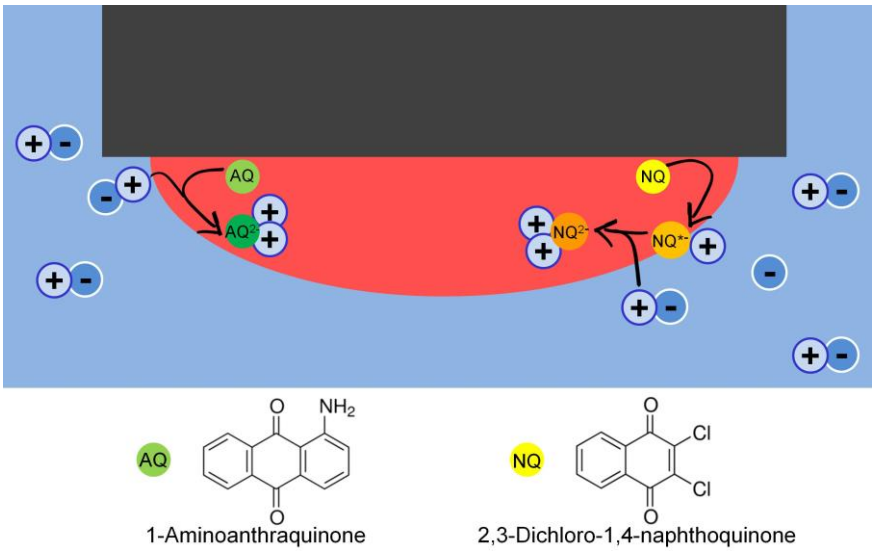

Figure 1. Reaction mechanism of quinones at the three-phase junction, a droplet of organic phase with dissolved quinone is deposited on the glassy carbon electrode, which is submerged in the aqueous phase containing a supporting electrolyte. 1-Aminoantraquinone undergoes a 1-step, 2-electron reduction accompanied by transfer of cations to the organic phase. 2,3-Dichloro-1,4-naphthoquinone is first reduced to an anion radical, which is entrapped at the liquid-liquid interface and later reduced to bivalent anion.

2. Experimental

2.1. *Chemicals and materials*

1-Aminoanthraquinone, 2,3-dichloro-1,4-naphthoquinone (both from Sigma), and n-octyl-2-pyrrolidone (Santa Cruz Biotechnology) were used as received. Inorganic and organic salts of analytical grade: KNO_3 (99%, POCh), KCl (>99.99%, Sigma-Aldrich), NaCl (pure p.a., POCh), $NaNO_3$ (pure p.a., ChemPur), LiCl (99%, Sigma-Aldrich), NH_4NO_3 (pure p.a., Chempur), $MgCl_2$ (99%, Sigma-Aldrich), $CaCl_2$ (99%, POCh), $AlCl_3$ (≥98%, ROTH), Tetramethylammonium chloride (TMA) (≥99%, Fluka), Tetraethylammonium chloride (TEA) (≥99%, Fluka), Tetrapropylammonium chloride (TPA) (≥98%, Sigma-Aldrich) were used as received. All the inorganic and tetraalkylammonium salts were dissolved in ultrapure water to

prepare the aqueous phase. The aqueous phase was not saturated with NOP solvent. Water was filtered and demineralized with ELIX system (Millipore).

2.2. *Electrochemical Measurements*

A conventional three-electrode cell setup was used in which glassy carbon was a working electrode (3 mm radius), Ag/AgCl (3.5 M KCl) was the reference electrode and a Pt wire served as the counter electrode. The GC electrode was polished, rinsed with pure water, acetone, and air dried after which a 2 µL NOP droplet containing dissolved quinone was deposited on its surface with a micropipette. The modified GC electrode was submerged in the aqueous solution. Due to the very small volume of NOP droplet, NOP does not completely cover the surface of GC thus forming a three-phase junction after immersing into the aqueous phase. For each new measurement, the electrode was cleaned and a new droplet was deposited on its surface. Chronoamperometry (CA) measurements were performed using large and equal volumes of NOP and the aqueous phase in the cell having Au wire as working, Ag/AgCl reference and Pt counter electrodes. The wire serving as the working electrode passed through both phases forming the 3-phase junction. The reference and counter electrode were positioned in the aqueous phase. The reduction potentials for CA were selected after performing the CV in the same setup. CVs, SWVs and CA measurements were recorded using the Biologic SP-300 potentiostat. CVs were performed in order to check the reversibility and stability of the quinone redox process at the three-phase junction. SWVs were recorded to analyse the reduction potential of the quinones in contact with different aqueous salt solutions.

3. Results and discussion

3.1. *1-Aminoanthraquinone reduction in the presence of organic and inorganic salts*

Preliminary CV measurements were performed to observe the electrochemical behaviour of AQ in NOP solvent (**Fig. S1)** without the presence of the aqueous phase. AQ shows two reductions with the potential values of -0.77 V and -1.3V, which correspond to the AQ radical anion ($AQ^{\bullet-}$) and AQ dianion (AQ^{2-}) respectively. NOP is a nonpolar aprotic solvent and it is well known that quinones show two cathodic waves corresponding to $Q^{\bullet-}$ and Q^{2-} in neutral aprotic media [9].

Fig. 2 shows multiple CV cycles of 10 mM AQ dissolved in a NOP droplet, deposited on the GC electrode and submerged in 0.1 M tetrabutylammonium chloride (TBACl) aqueous solution. The CVs show a single pair of redox peaks and the signal is quite stable over multiple cycles, with only a very slight decrease in the peak current. This behaviour is typical for quinones in an aqueous environment, where a one-step two-electron reduction takes place directly from Q to Q^{2-} [9,45,46]. Thus, the presence of the aqueous phase changes the reaction route as compared to the case in pure NOP. However, the stability of the CVs show that the AQ does not escape to the aqueous solution, which would be marked by a considerable decrease in current with each subsequent scan. [30,37]. AQ is only sparingly soluble in water, which can account for the slight decrease between scans. Initially, the cathodic peak shifts towards less negative potentials but quickly stabilises. Such an initial shift of the peak in three-phase systems have been observed previously by e.g. Scholz and co-workers but the reason for it is not yet known [37]. As seen in **Fig. S2** the initial shift observed in CV measurements does not influence the SWV peak potential.

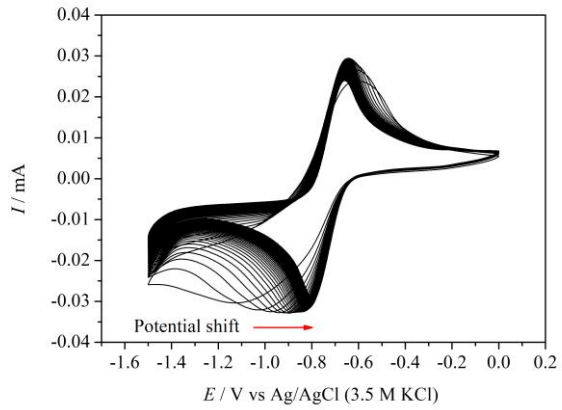

Figure 2. CV (50 cycles at 40 mV s^{-1}) performed at TPE configuration, droplet of NOP (having 10 mM AQ) deposited on GC electrode and immersed in 0.1 M TBACl.

Fig. 3a displays the CVs of various scan rates ranging from 20 to 400 mV s^{-1}. The separation of cathodic and anodic peaks changes from 117 to 242 mV and the ratio between cathodic and anodic peak areas is very close to unity. The peak potential variation with the scan rate most likely due to uncompensated resistance in the system [27]. A plot of the cathodic peak current vs square root of scan rate is presented in **Fig. 3b**.

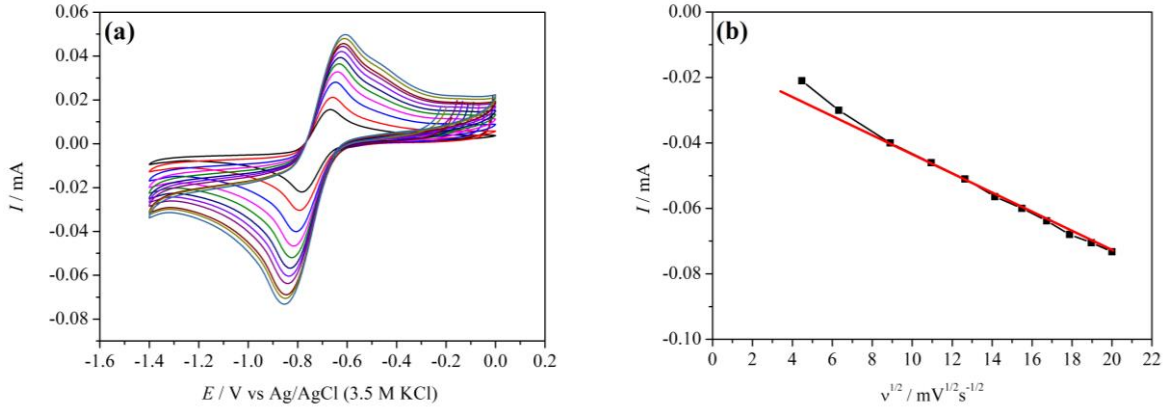

Figure 3. (a) CVs at different scan rates (20, 40, 80, 120, 160, 180, 240, 280, 320, 360, 400 mV/s) performed at TPE configuration, droplet of NOP (having 10 mM AQ) deposited on GC electrode and immersed in 0.1 M TBACl. **(b)** dependence of cathodic peak current on square root of scan rates.

Anthraquinone derivatives are well known to adsorb on different electrode surfaces, especially on the GC [9,47–49]. However, the linear variation of peak current with the square root of the potential sweep rate indicates the reduction of the AQ system is dominated by diffusion of the AQ towards the three-phase junction. The deviation from linearity at low scan rates can be explained by the thinness of the organic phase. With the large diffusion zone observed at low scan rates, the droplet acts like a thin cell thus presenting a linear dependence of the scan rate similar to the case of adsorbed species [50].

Fig. S3 shows an experiment performed using 10 mM of AQ in NOP droplet on GC electrode, which was immersed in 0.1 M KCl to observe the electrochemical behaviour of AQ in an inorganic salt solution. The result is virtually identical to the case with TBACl in **Fig 1**. However, this should be contrasted with the behaviour if HCl is used instead of KCl as supporting electrolyte in the aqueous solution. In this case, (**Fig. S4)** the CV is completely irreversible and the current decreased markedly with each subsequent scan. The reason is the rapid hydrogenisation of the O^- groups on the quinone and transfer to the aqueous phase. AQ is soluble in water under acidic conditions and can be polymerised at positive potentials in highly acidic solutions (2.0 mol/L of H_2SO_4 and above). [51]

3.2. *Influence of different cations and anions on the 1-Aminoanthraquinone reduction*

If, as indicated above, the reduction of AQ in the organic phase results in the transfer of a cation across the liquid|liquid interface to maintain charge neutrality in the droplet, the use of different electrolytes in the aqueous phase should affect the reduction potentials. In the case of ion transfer, the SW potentials are dependent on the lipophilicity of the transferring cation from W to the organic solvent. Lipophilic ions are generally transferring easier than more hydrophilic ions, leading to a larger overpotential needed in the latter case. [26,27,29,36]

A series of SWV measurements executed using AQ dissolved in the NOP droplet immersed in the different inorganic salt solution is presented in **Fig. 4**. The shift of the peak potential in **Fig. 4a**, is quite small for Li^+, Na^+ and K^+ ions, and the potentials vary as $K^+ > Na^+ > Li^+$. As shown in **Fig. 4b**, for the cations with +2 charge potential shifts are distinct and in the order $Ba^{2+} > Ca^{2+} > Mg^{2+}$, with Al^{3+} being still less negative (**Fig 4c**). Here the reduction potentials do not follow the expected order of lipophilicity as described by the so-called Hofmeister series, where, according to the Born rule, the transfer potential, $\Delta_{aq}^{org}\phi_{Cat^+}^{0}$, should scale with the inverse of the ionic radius. [52] Such behaviour was observed earlier by Scholz and co-workers using iron(III) tetraphenyl porphyrine chloride (Fe(III)-TPP-Cl) or iodine as a redox probe [27,41], by Quentel et al. using Lutetium Bis(tetra-tert-butylphthalocyaninato) [29] and by our group using C_{60} [42]. In contrast, the SWV peak potential in this case becomes more negative with increasing ionic radius. Jaworski and collaborators showed in a series of papers that cations and various reduced quinones form ion pairs and that the reduction potential of the quinone in aprotic solvents depends on the supporting electrolyte. [43,44] They show that for the alkali ions the redox potential is dependent on the association constant K_{ass} between the quinone and the cation in the ion pairing

$$Q^{n-} + Cat^+ \overset{K_{ass}}{\rightleftarrows} Q^{n-} \ldots Cat^+,$$

which in turn is a function of the ionic potential [43]. The same trend was later shown also for doubly charged ions [53]. The most likely explanation for the anomalous dependence on the type of cation is that the reduced quinone, AQ^{2-} forms an ion pair with the transferred cation. This is further supported by the good linear relationship between the ion potential — $\Phi_{eff} = Z/(r + \delta)$, where Z is the charge of the cation , r the Pauling radius of cation and δ = the correction factor — and the SWV reduction peak potential. Thus, the greater charge and

smaller size of a metal ion cause the larger positive shift in the reduction potential which is clearly shown in **Fig. 4d**. This would indicate that the pair formation has a more significant influence on the transfer potential than the solvation of the cation in the pure organic solvent.

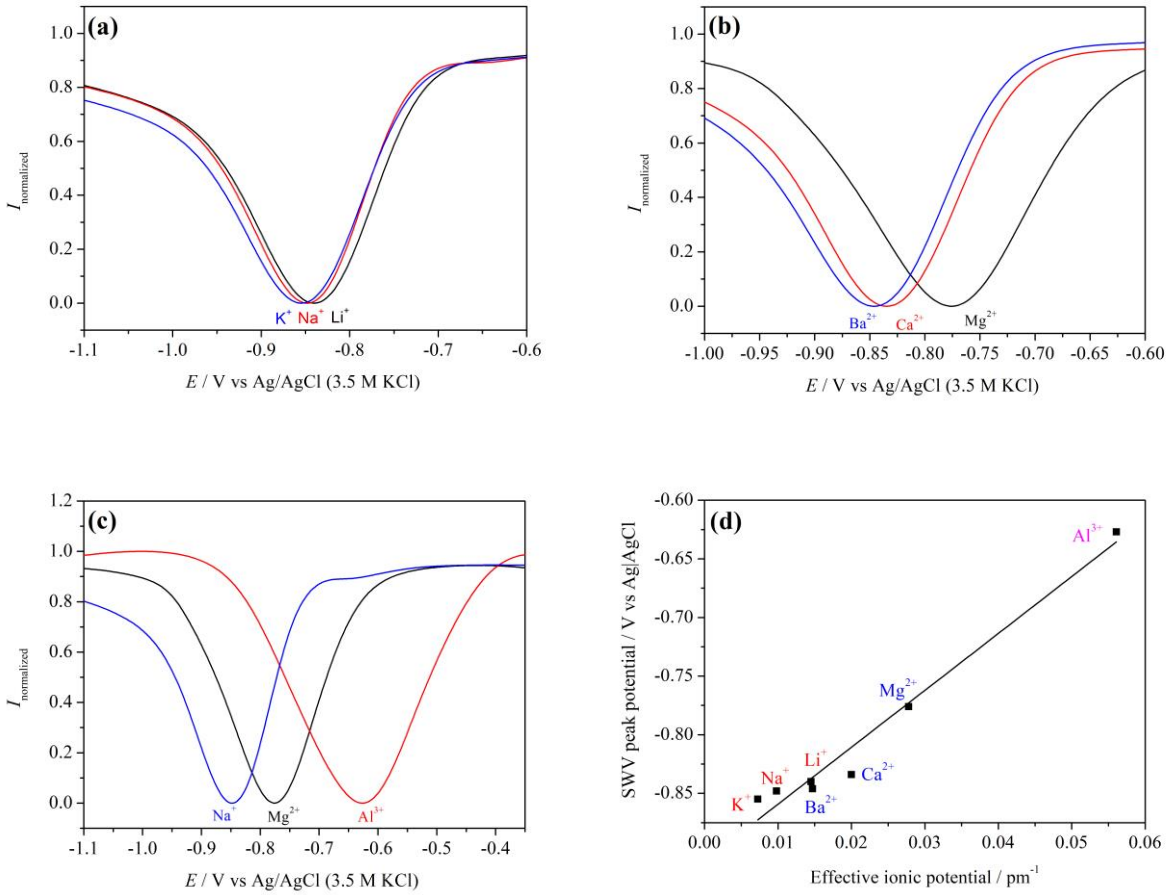

Figure 4. Normalized SWVs of NOP droplets having 10 mM AQ, deposited on GC and immersed in different salt solutions.(a) monovalent cations, (b) bivalent cations, (c) comparison of mono-, bi- and trivalent cations, (d) linear relationship between the peak potential and the effective ionic potential

3.3. *2,3-Dichloro-1,4-naphthoquinone reduction in the presence of organic and inorganic salts*

Preliminary CV measurement (**Fig. S5a**) of NQ in NOP exhibits two major reductions, the first reduction is assigned to NQ radical anion ($NQ^{\bullet-}$) and the second reduction is to NQ dianion (NQ^{2-}). In the presence of even small amounts of protons in the solvent NQ also undergoes a two-electron reduction directly to NQ^{2-}, and in most of the experimental conditions, the two processes coexist. The one-step two-electron reduction dominates only

when the solvent is changed to almost pure methanol (**Fig. S5b)**, and not, as in the case of AQ when only a little MeOH is added to the NOP. NQ undergoes two step reduction when NOP is saturated with distilled water as shown in **Fig. S6.**

In contrast to the measurements with AQ, CV measurements of 10 mM NQ at a TPE configuration (**Fig. 5a**) show two pairs of redox peaks, where the first reduction and oxidation peaks are unstable (-0.5 to -0.2 V) and disappear with continuous cycling, while the second set of redox peaks (around -0.85 V) is quite stable as cycling continues. The first reduction is allocated to $NQ^{\bullet-}$ and the second reduction is assigned to NQ^{2-}. As discussed above, the gradual decrease in the current of first redox peaks, (marked with arrows in **Fig. 5a**) indicates that $NQ^{\bullet-}$ is transferred from the NOP to the W phase, whereas the stability of the second pair of redox peaks, shows that NQ^{2-} stays in the organic phase. However, the escape of $NQ^{\bullet-}$ would also lead to a decrease of the next reduction step $NQ^{\bullet-} \rightarrow NQ^{2-}$. It is instead possible that what we see is a gradual change of mechanism from the one-electron two-step reaction to the two-electron one-step reaction as the NOP increases its water content over time, possibly due to the formation of a micro-emulsion at the three-phase junction [54–56]. To investigate this further a series of SWV studies were carried out in different electrolytes.

3.4. *Influence of different anions and cations on the 2,3-Dichloro-1,4-naphthoquinone reduction*

Fig. 5b displays the SWVs of NQ (first reduction peak only) in aqueous electrolytes with different cations. In contrast to the case above with AQ, here we see no dependence of the peak potential on the different ions, with the exception of Al^{3+}. Instead, we have a clear dependence on the *anion* present in the electrolyte (**Fig 5c**), where the negative potential shift ($SO_4^{2-} < Cl^- < Br^- < NO^-_3 < SCN^- < ClO^-_4$**)** follows the hydrophilicity of the anions, as is seen when in experiments when these are transferred into the organic phase to compensate for the charge of an oxidation process in the droplet. [26,37,57] However, that cannot be the case here as it would further increase the negative charge of the organic phase. Instead, what we see is the "salting out" of the $NQ^{\bullet-}$ as it is transferred to the aqueous phase. This is a well-known phenomenon for many types of molecules, analogous to the more widely recognised salting out of proteins. [58,59] As noted above, the NQ cannot escape to the bulk of the aqueous phase, as this would also decrease the current of the second reduction peak. Instead, the $NQ^{\bullet-}$ is probably trapped within the micro-emulsion, or alternatively, adsorbed on the liquid-liquid interface. [37].

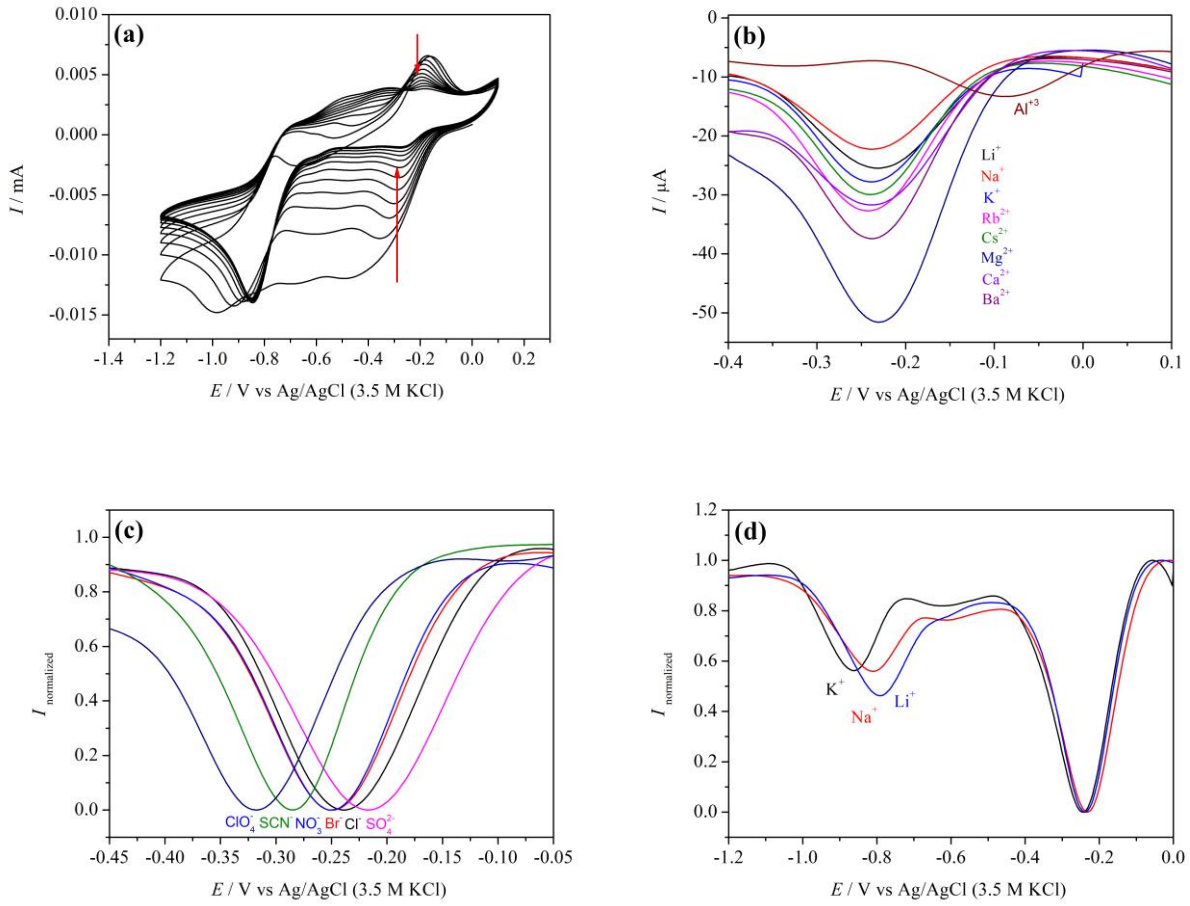

Figure 5. All CV and SW measurements carried out using 10 mM NQ in NOP droplet on GC and submerge in different electrolytes. **(a)** CVs of NQ in 0.1 M TBACl. (b) Normalized SWVs of NQ in electrolytes of different anions. **(c)** SWVs of NQ in electrolytes having different cations. **(d)** SWVs of NQ showing two reduction steps.

To understand further, chronoamperometry was performed at -0.5 V vs Ag (first reduction potential) for 6 hours at TPE configuration using a Au working electrode in equal volumes of both phases. A photograph of the cell after CA (**Fig. S7)** clearly shows the turbid aqueous phase and precipitation at the NOP/W interface. The transferred $NQ^{\bullet-}$ with aqueous cation is only sparingly soluble in water and eventually forms a precipitate at the NOP/W interface.

Fig. 5d show both the reduction processes, for electrolytes having the same anions and different cations (LiCl, NaCl, and KCl) in the aqueous phase. The first reduction is at the same potential (-0.25 V) since the anion in all the cases is the same. The second reduction shows the potential shifts based on the size of the cations, as was also seen in the case of AQ. The order of the reduction potentials is $K^+ > Na^+ > Li^+$. These results indicate that while the

first reduction peak involves the transfer of the NQ to the aqueous phase, the NQ^{2-} forms a pair with a cation in the organic droplet.

4. Conclusions

We have investigated the reduction of two different quinone compounds, 1-Aminoanthraquinone and 2,3-Dichloro-1,4-naphthoquinone, at a liquid|liquid|solid three-phase junction. Both quinones undergo successive one-electron reductions $Q \rightarrow Q^{\bullet -} \rightarrow Q^{2-}$ in single phase aprotic solvents, whereas in contact with the aqueous solvent the reaction process changes to a one-step two-electron reduction. For AQ this change is immediate, and the reduction is coupled to the transfer of cations from the aqueous to the organic phase. Although, instead of the transfer potential becoming more negative with increasing cation hydrophobicity, as expected from earlier experiments [27,29,41,42], the quinone forms an ion pair with the transferred cation. The association constant here is strongly dependent on the ionic potential of the paired cation [43]. For NQ the change of reaction mechanism is gradual, and we can follow the disappearance of the first reduction step $NQ \rightarrow NQ^{\bullet -}$ in successive cyclic voltammograms. The first reduction step is coupled to transfer of the $NQ^{\bullet -}$ radical to the aqueous phase, where it is either trapped in an emulsion or adsorbed on the liquid|liquid interface, while the second step is analogous to the case of AQ.

This knowledge can be useful for prediction of metabolic pathways of new quinone drugs as it can shed light on which reaction (1 or 2-step, involving protons or not) can occur and in which environment (cell membrane, extracellular matrix etc.). Many popular analgesics such as Phenacetin were withdrawn due to the toxicity of quinone metabolites (in this case a quinoneimine dimer). Even popular drugs such as acetaminophen can form toxic by-products like N-acetyl-p-benzoquinoneimine when metabolized by oxidise enzymes and benzoquinone if the product is subsequently hydrolysed. Electrochemistry is an invaluable tool for cytotoxicity studies, as it was long shown that higher redox potential naphthoquinones were much more toxic to hepatocytes than the ones exhibiting lower redox potentials [60]. Of no lesser importance is the question if the quinone will pass through a highly toxic radical stage, in which case it will be able to influence the formation of reactive oxygen species or undergo a direct two-electron reduction. The same is true for energy storage applications, in which the exact mechanism of the reaction, which can be studied in three-phase junction setups, for example help to design more efficient artificial photosynthetic systems, or aqueous flow batteries [2].

Acknowledgments

The authors thank Professor Marcin Opallo and Dr Joanna Niedziółka-Jönsson for valuable discussions.

This work was financed by the National Science Centre Poland under grant no 2015/18/E/ST4/00319.

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