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REVIEW

Redox chemistry of coenzyme Q—a short overview of the voltammetric features

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Abstract Quinones constitute a big family of organic redox active compounds that are overwhelmingly involved in important physiological processes. The most important members in the class of quinones are, indeed, the plastoquinones and the coenzyme Q (CoQ) derivatives. Voltammetry of coenzyme Q family members attracts significant attention since 50 years ago. In this work, we refer to some of the most important voltammetric features of coenzyme Qs studied in aprotic and in aqueous media. While the redox chemistry of coenzyme Q members in non-aqueous aprotic organic solvents can be described by two consecutive one-electron transfer steps, more complex situation exists in the voltammetry of coenzyme Qs performed in aqueous media. Although it has been claimed for a while that the voltammetric processes of coenzyme Qs in aqueous solutions proceed via formation of semiquinone radical intermediate species, it has been recently proven that this can be not completely true. Intensive voltammetric and spectroscopic studies of coenzyme Q systems in buffered and non-buffered aqueous media revealed that hydrogen bonding between electrochemically created CoQ species and the water molecules plays an important role in stabilizing electrochemically generated species of these systems. We also pay attention to the amazing redox chemistry of coenzyme Qs in strong alkaline media, while we refer to the chemical features of novel coenzyme Q derivatives obtained under such conditions. Hints are presented about the antioxidant capacity of some of the novel hydroxylated coenzyme Q systems. Also, the possibility of these systems to bind and transfer earth-alkaline cations across biomimetic membranes is shortly elaborated. In the end, we refer to some relevant theoretical works that describe closely the voltammetric behavior of various coenzyme Q systems. We believe that this short review will contribute towards better understanding of the amazing chemistry of coenzyme Q derivatives.

Keywords Quinones · Voltammetry · Mitochondrial electron transfer chain · Antioxidants · Embelin

Introduction

Quinones are probably the most abandoned class of redox active organic compounds involved in many important chemical and physiological processes [1, 2]. Many quinones are found in plenty of bacteria and various plants, and they are ubiquitous in all living systems [3]. Vitamin E, coenzyme Qs, plastoquinone, naphthoquinones, anthraquinones, and plenty of polyphenols (flavonoids and stilbenes) are just some representatives belonging to the class of quinones. The most important members of the quinone family are, indeed, Coenzyme Q_{10} (CoQ10) and plastoquinone. These two benzoquinones play fundamental roles in vital biological functions such as oxidative phosphorylation and mitochondrial electron transfer processes. Their function as redox mediators in the crucial energetic processes like photosynthesis and respiration is essential to life on Earth. As we know, the major pathway for creating energy in all living systems is via the mitochondrial electron transfer chain (METC) that takes place in the inner membranes of the mitochondria. In the METC, electrons and protons are shuttled between various redox

Dedicated to the 65th birthday of our great friends and collaborators Dr. Milivoj Lovric and Dr. Sebojka Komorsky Lovric

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proteins to reach the final target—the oxygen molecules. The final output of this complex system of redox transformations in METC is reduction of oxygen to water. This reaction is followed by consecutive formation of adenosine triphosphate (ATP), whose one-phosphate group dissociation releases thermal energy that is crucial for supporting of many physiological processes. Embedded in the inner mitochondrial membrane is the compound Coenzyme Q_{10} (or Ubiquinone 50) that mediates the transfer of electrons between complexes I, II, and III in the METC, while also transferring protons across the mitochondrial membrane. During the occurrence of the electron and proton transfer reactions in the METC, Coenzyme Q_{10} turns between fully oxidized form-quinone and fully reduced form-quinol (or ubiquinol). Next to this crucial role in the cell energy creation, there are lots of studies dedicated to many other functions of Coenzyme Q_{10} in the living cells [4, 5]. It is well known that Coenzyme Q_{10} occurs in all subcellular membranes, while having a very important role in functioning of many membrane oxido-reductase systems such as mitochondria, Golgi apparatus, lysosomes, and plasmalemma [1, 5]. In these systems, Coenzyme Q_{10}, via its redox chemistry, influences many pathways in the cells, ranging from pro-oxidant to antioxidant activities (free-radical generation and scavenging of free radicals) and modulating cellular pathology [6–8]. Our focus in this short review is to bring the readers some important insights into the redox features of coenzyme Q family members studied by voltammetric techniques and to emphasize several recent findings in respect to their chemical reactivity. Although the redox chemistry of coenzyme Qs is a subject of interest for over 50 years, many new aspects of their amazing chemistry still emerge. We hope that this work will help readers to understand some of the most important features of CoQs (Scheme 1).

Redox chemistry of coenzyme Qs in non-aqueous media

In the family of quinones, the coenzyme Q compounds (CoQs) are, indeed, the most important biological systems. Although it has been thought for a while that these systems exhibit superficially simple redox behavior, this, in fact, has been proven not so simple. The redox chemistry of coenzyme Qs can be extremely complex, and many aspects of their electrochemical behavior are not well understood even nowadays. The simplest voltammetric scenario of the redox transformations of coenzyme Qs one finds is if these biological systems are studied in organic solvents, but in absence of proton-donating substances. Numerous works focused on the voltammetric features of coenzyme Q family members have revealed that the redox chemistry of these systems depends significantly on the solvent medium and the proton availability in the electrolyte system [see 2 and 9 for more details]. Except the simplest member of the coenzyme Q family, i.e., Coenzyme Q0, which is a nicely water-soluble substance, all the other coenzyme Qs are hardly water-soluble substances. Therefore, in majority of the works found in the literature, the redox chemistry of Coenzyme Q_1 to Coenzyme Q_{10} members has been studied in non-aqueous media. Many studies of coenzyme Q members performed in organic solvents in the absence of protons reveal that a stepwise two-electron reduction of these compounds occurs [9–12]. In the first step, a semi-quinone radical anion of CoQs is formed (CoQ^{-}), while in the second step a dianion is obtained (CoQ^{2-}). Many of these scenarios are thoroughly elaborated in the literature, while various authors agree that the redox chemistry of coenzyme Qs in organic solvents in the absence of protons can be represented by the following redox scheme:

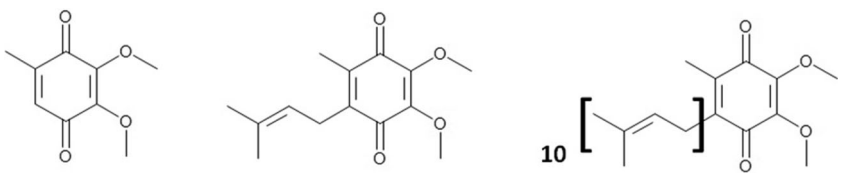
$$CoQ + 1e^{-} \leftrightarrow CoQ^{\cdot -} + 1e^{-} \leftrightarrow CoQ^{2-} \quad (1)$$

The redox chemistry of CoQs dissolved in organic electrolyte solutions in the absence of protons is mainly portrayed via two distinct voltammetric signals controlled by diffusion (see Fig. 1).

Addition of proton-donating compounds in the electrochemical cell containing aprotic organic solvent brings exceptional complexity in the redox features of CoQ systems. As explained in several relevant works [2, 9–14], in such scenario, nine CoQ species can exist (theoretically) in the system, while various equilibriums among them are also possible (see Scheme 2).

Indeed, what is missing in all scenarios similar to those given in Scheme 2 is the possibility of CoQ's radical reaction that commonly leads to dimerization of two CoQ radical species. In a mixture of acetonitrile and acetic acid, for example, it has been found that Coenzyme Q_{10} exhibits two consecutive one-electron-one-proton transfer steps [15]. The author of [15] has also found that the redox process of Coenzyme Q_{10} in such environment proceeds via creation of unstable semiquinone radical. This has also been confirmed when CoQ10 was studied in glacial acetic acid solution [16]. Similar findings about coenzyme Q's redox conversion are also reported elsewhere in many other works performed in

Scheme 1 Structural formulas of Coenzyme Q0 (*left*), Coenzyme Q_1 (*middle*), and Coenzyme Q_{10} (*right*)



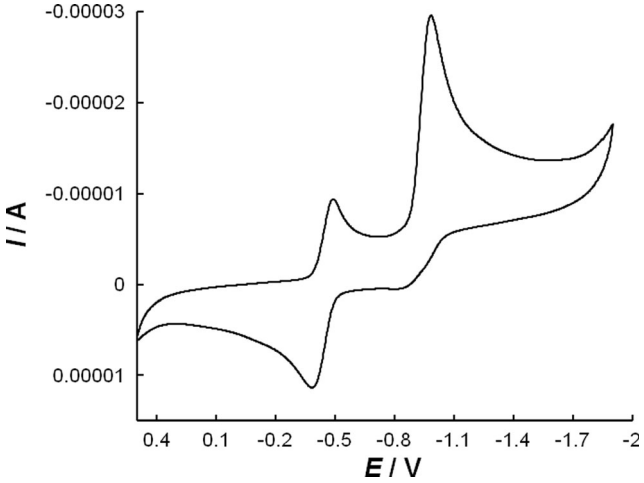
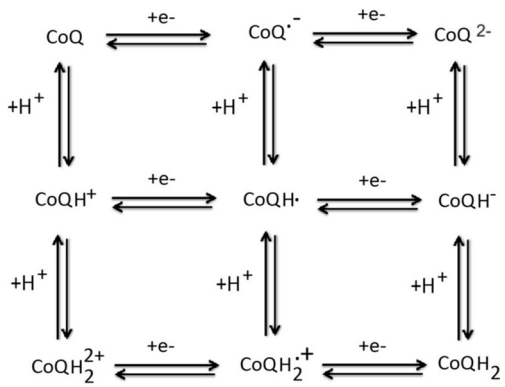


Fig. 1 Cyclic voltammogram of 0.5 mmol/L Coenzyme Q_1 recorded in acetonitrile (0.05 mmol/L tetrabutylammonium perchlorate was used as a supporting electrolyte) at a glassy carbon working electrode. Scan rate was 20 mV/s. The peak at less negative potentials corresponds to the reaction $CoQ + 1e^- \leftrightarrow CoQ^{\bullet -}$, while the voltammetric signal at more negative potentials is due to reaction $CoQ^{\bullet -} + 1e^- \leftrightarrow CoQ^{2-}$

waterless organic solvents, regardless of the nature of the aprotic organic solvent used [2, 9, 10, 12, 13, 17–20]. Itoh et al. [21] reported a rather complex behavior of plastoquinone, observing three reduction and four oxidation peaks in the cyclic voltammograms recorded in aprotic organic solvents. Some of the signals observed are due to the CoQ dimmers formed during the course of the voltammetric experiment. Existence of several semiquinone radicals is reported in this work [21], one of them having potential to bind calcium cations. It is worth mentioning that many of the theoretically predicted CoQ species described in Scheme 2 of this work have never been detected by studying CoQs in organic waterless media. Only some of the species in the two upper lines of Scheme 2 as well as $CoQH_2$ species are experimentally detected and reported.



Scheme 2 Possible redox transformations and equilibria in the coenzyme Q's redox chemistry [2, 13]

Redox chemistry of coenzyme Q in aqueous media

Due to the poor solubility of CoQs in water, more complex scenarios are applied to study these systems in aqueous environment. Except with Coenzyme Q0, and to some extent with Coenzyme Q_1, it is quite difficult to perform common voltammetric experiments with native forms of higher CoQ members in acidic, neutral, or slightly alkaline water solutions at solid working electrodes. Indeed, the reason for this is the poor water solubility of the higher members of the coenzyme Q family. Many of the obstacles met by the voltammetric determination of coenzyme Qs dissolved in aqueous environment are described in the work of Turkowicz et al. [22]. The authors of [22] refer to the adsorption of CoQs and the blocking of the active surface area of the working electrode as major obstacles in the experiments of coenzyme Qs performed from water solutions. Indeed, additional obstacle is seen in chemical features of the long isoprenoid chains. This isoprenoid chain is considered as insulating part of the CoQ's moiety that hinders the electron transfer between the working electrode and the redox active site(s) of the CoQs. However, there are some reports in the literature that refer to achieving a direct determination of Coenzyme Q10 even from pure water buffers in voltammetric experiments by using glassy carbon as a working electrode [23]. In [23], the authors describe a simple and rapid voltammetric method for quantification of coenzyme Q_{10} dissolved in a phosphate buffer solution (pH 6.86). The authors of [23] report to existence of an electrochemically irreversible and diffusionally controlled single process of CoQ10 recorded under such conditions. They claim that they succeeded to quantify CoQ10 in submillimolar concentrations. Yet, it is not clear how the authors achieved to dissolve such a significant concentration of Coenzyme Q10 in pure water buffers. Lemmer et al. [24] describe an elegant strategy of studying lipophilic CoQs by using an Au-working electrode modified with lipophilic thiols in which CoQ was embedded. Under such circumstances, the voltammetric features of Coenzyme Q_2 were studied in pH range from 2.50 to 12.50. Moreover, in that work [24], the authors go one step further and they report to the kinetic parameters of electron transfer steps. In such an arrangement, the authors report that CoQ_2 undergoes common redox transformation as described in Reaction (I) of this work. A bit different scenario for studying the voltammetric features of CoQ10 at solid electrodes in water media is reported in [25]. In that work [25], Coenzyme Q_{10} and plastoquinone were incorporated in a lipid bilayer composed of dimyristoyl phosphatidylcholine that was supported by vesicle fusion. The redox properties of CoQ10 and plastoquinone were studied in a wide pH range. Only above pH of 13 did the authors report a reversible redox behavior of these substrates. Below pH of 12, severe kinetic hindrances are reported that, as the authors claimed, were due to the slow kinetic of electron transfer steps. Similar scenario

for studying the lipophilic coenzyme Qs and CoQ oxidoreductase enzymes is also reported in [26]. One can find in the recent book an important source that reports to different methodologies applied for achieving better strategies for voltammetric study of Coenzyme Q_{10} [27]. Using some of the strategies explained in [27], various authors report on designing voltammetric sensors based on CoQ10 redox features. For example, the redox chemistry of Coenzyme Q_{10} embedded in the lipid membranes has been explored to construct some elegant sensors in the recent years. In the work of Ru et al. [28], a CoQ10-modified electrode was explored for designing a nano-to-micromolar sensor for glutathione detection. The sensor was constructed by using its gel form that was mixed with multi-walled carbon nanotubes/ionic liquid. In another work [29], the authors have used CoQ10 supported in lipid bilayers to construct a sensor for acetylcholine detection. The features of several other CoQ-based voltammetric sensors are reported elsewhere [30].

Getting insight into the redox features of Coenzyme Q_{10} by performing voltammetry on solid electrodes is quite difficult to be achieved. A better option for this purpose is, indeed, the use of the lipophilic mercury as a working electrode. As highly lipophilic compounds, most of the higher members of the CoQ family adsorb significantly at the surface of the working mercury electrode. This phenomenon allows achieving preconcentration of the CoQs on the mercury electrode, while common voltammetric experiments can be performed in such scenario. Many authors report on the mechanistic studies of various coenzyme Qs from an aqueous environment at mercury electrode [2, 9, 31, 32]. In the works [31, 32], authors observed common voltammetric features of the coenzyme Qs as reported elsewhere [2, 9, 33]. In the work of Gordillo and Schiffrin [32], instability of the voltammograms of CoQ10 has been reported in strong alkaline media. However, the authors did not pay more efforts to clarify this phenomenon. More relevant aspects related to the coenzyme Q's redox chemistry in aqueous media can also be found in [34–40].

Voltammetry of coenzyme Qs in buffered and non-buffered aqueous media

Several recent comprehensive studies related to the voltammetric features performed with water-soluble quinones and coenzyme Qs in buffered and non-buffered aqueous media probably gave best explanations about the disputed redox behavior of these systems [41–44]. In fact, many authors claimed that the redox chemistry of coenzyme Qs and quinones from water solutions is always linked to a mechanism in which free radical intermediates are involved [see 2, 9, and 33, for example]. However, with the results published in the last 8 years, the question about the redox chemistry of quinones in aqueous solutions seems to be a step closer to the final solution. The initial study of Smith et al. [41] brought a new light in explaining the complex redox chemistry of coenzyme Qs in water. As explained in [41], and later on in several recent works [42, 43], the two electron-two proton voltammetric behavior of coenzyme Qs ($CoQ + 2e^- + 2H^+ \leftrightarrow CoQH_2$) can only be seen in buffered aqueous systems, in regions of pH between 2.0 and 11.0, or in very strong acidic media. Under such circumstances, a single pair of voltammetric peaks is observed whose mid-peak potential is sensitive to pH, shifting by −60 mV/pH. The entire process exhibits strong kinetic hindrances in the region of pH between 2.5 and 10.5 (see Fig. 2, the cyclic voltammograms of Coenzyme Q0, for example). These are portrayed via a huge peak-to-peak separation that increases from 450 mV (at scan rate of 10 mV/s) to over 650 mV (at scan rate of 200 mV/s). It has been a question for a while to determine whether the observed kinetic hindrances are due to the slow electron transfer or due to the slow proton transfer step. Although many authors claimed that this behavior is due to the slow rate of the heterogeneous electron transfer step [2, 9, 12, 33], it seems that the protonation step is crucial for these features in the CoQ voltammetry. This will be shortly elaborated later on in this chapter.

The voltammetry of water-soluble CoQs and quinones in non-buffered aqueous media is much more complex compared with that in buffered aqueous solutions. Depending on pH and the $c(\text{CoQs})/c(H^+)$ ratio, at least three different scenarios can be observed with coenzyme Q systems dissolved in non-buffered aqueous media in pH region between 1.0 and 11.0. In the cyclo-voltammetric experiments, roughly in the pH region between 1.0 and 2.5, a single pair of peaks exists. The mid-peak potential $E_{\text{mid,p}}$ vs. pH dependence in this region of pH is about −60 mV/pH. However, in the region from pH = 2.50 to pH = 4.00 (assuming a 0.5-mmol/L concentration of coenzyme Qs in the electrochemical cell), there are two distinct processes at the cyclic voltammograms. The mid-peak potential ($E_{\text{mid,p1}}$) of the signal appearing at more positive potentials is a linear function of pH with a slope

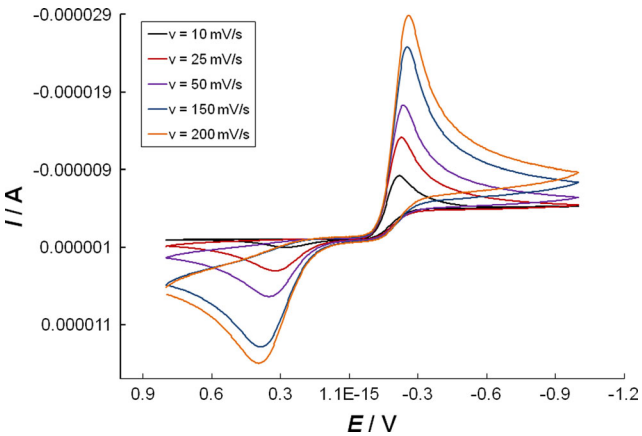


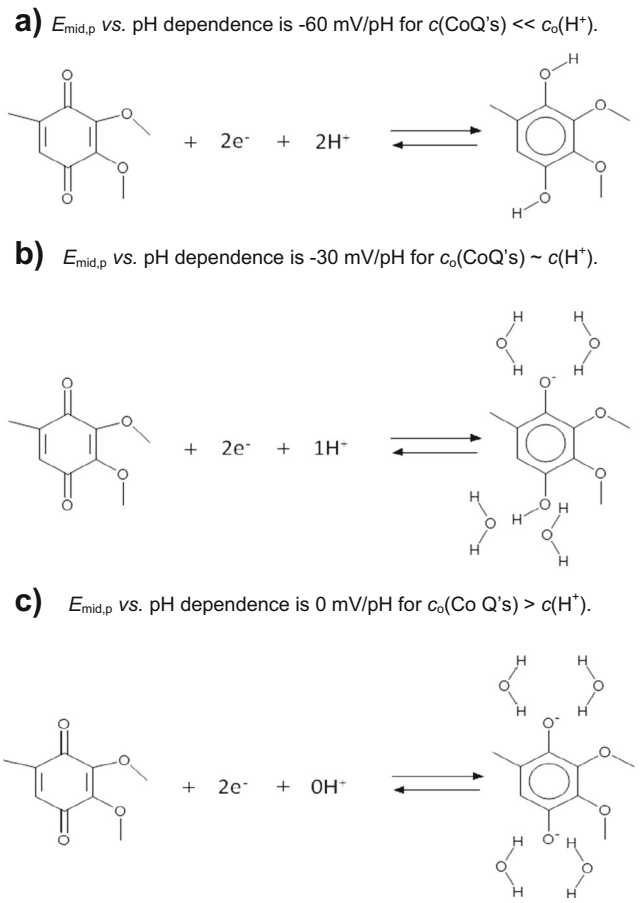
Fig. 2 Cyclic voltammograms of Coenzyme Q0 recorded in ammonia buffer (pH = 7.40) as a function of the applied scan rates. *c*(Coenzyme Q0) was 0.5 mmol/L

of about −60 mV/pH. However, the second signal positioned at more negative potentials shifts linearly in a negative direction for about −30 mV/pH. In non-buffered water solutions having pH in the region between pH = 4.0 and pH = 4.70, the intensity of the second signal (at more negative potentials) decreases in the course of a slight increase of pH. Concomitantly, a new reversible voltammetric signal appears (in the potential region between the first two peaks) that gains in intensity by increasing pH. Above a pH of about 5.0, this new (third) pair of peaks is the only one existing in the voltammetric output. The intensity of this new voltammetric pair of peaks is virtually constant in the pH region from 5.50 to 10.5. However, what is more intriguing is that the mid-peak potential of this third voltammetric peak gets unaffected by pH. By making comprehensive voltammetric, electron paramagnetic resonance (EPR), and UV-Vis studies [42, 43], it has been confirmed that the water-soluble CoQs undergo three different redox transformations in non-buffered aqueous media that can be represented by the following reaction schemes:

As it is presented in Scheme 3, next to the two electron-2 H^+ reduction of coenzyme Qs to a hydroquinone form (situation a), there are two more scenarios in which monoanionic (b) and dianionic (c) forms of coenzyme Qs are created. It has been reported that the stabilization of the monoanionic and dianionic coenzyme Q species was achieved by hydrogen bonding with the water molecules [41–43]. Indeed, as described in [18, 41–43], hydrogen bonding, alongside the protonation steps, is a fundamental factor that controls the potentials and mechanisms in the reduction of coenzyme Qs. All these situations of the voltammetric behavior of Coenzyme Q0 in non-buffered aqueous media (a nicely water-soluble coenzyme Q simplest member) are shown in Scheme 3. Several recent studies [41–43] also revealed that no radical reactions take place in voltammetry of water-soluble quinones in pH regions from 1.0 to 11.0, as it has been thought for a while [2, 33]. Contrary to the situation in buffered aqueous media, where one sees strong kinetic hindrances in the cyclic voltammograms (see Fig. 2 in this work, for example), cyclic voltammograms of Coenzyme Q0 at pH of 7.00 show almost no kinetic obstacles (see Fig. 3). Recall that the voltammograms in Fig. 3 depict the following situation:

$$CoQ + 2e^- + 0H^+ \leftrightarrow CoQ^{2-} \quad (2)$$

Therefore, since no protons are involved in the entire redox process (II), it is reasonable to assume that the kinetic constraints seen in the cyclic voltammograms of CoQs met in buffered media (Fig. 2) are mainly due to the slow proton transfer step. This is another point to be emphasized in the redox chemistry of CoQs, which differs from what is given in the literature [2, 9, 31–33]. Various authors claim that the protonation is a fast process in the quinone redox chemistry, and the kinetic constraints met in the voltammetric behavior of quinones are due to the slow heterogeneous electron transfer step [2, 9, 10, 13]. Features of the voltammograms given in Fig. 3 throw a new light to resolve the question about the rate



Scheme 3 Redox transformation of Coenzyme Q0 in non-buffered aqueous media. **a** $E_{mid,p}$ vs. pH dependence is −60 mV/pH for c(CoQ) << $c_o(H^+)$. **b** $E_{mid,p}$ vs. pH dependence is −30 mV/pH for c_o(CoQ)~$c(H^+)$. **c** $E_{mid,p}$ vs. pH dependence is 0 mV/pH for c_o(CoQ) > $c(H^+)$

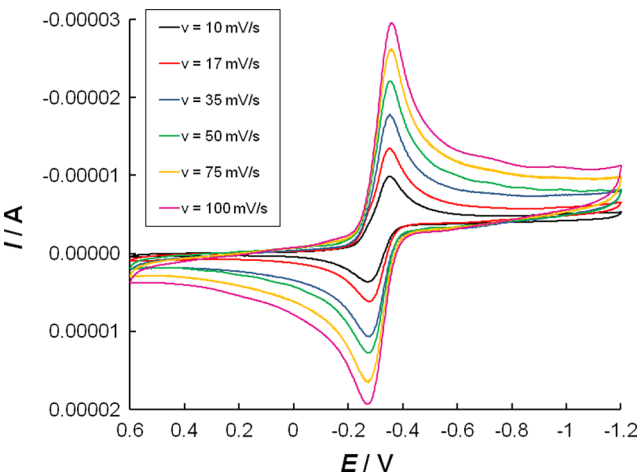


Fig. 3 Effect of the scan rate to the features of the cyclic voltammograms of 0.1 mmol/L Coenzyme Q0 recorded at pH of 7.00 in non-buffered aqueous media

of the protonation steps by the redox chemistry of CoQ systems. Quite different phenomena are observed when coenzyme Qs are observed in strong alkaline solutions (in aqueous solutions with pH above 11.50).

Recent findings on coenzyme Q's reactivity in alkaline media

As shortly mentioned in the work of Gordillo and Schiffrin published more than 20 years ago [32], a sort of chemical instability of CoQ10 has been observed, when it was studied at mercury electrode at pH above 12.50. However, in their work [32], the authors did not pay too much attention to this phenomenon. Even recently, the authors of [42, 43] have studied extensively the chemistry of several coenzyme Qs in a strong alkaline environment. By exploring HPLC MS, EPR, voltammetric, NMR, and UV-Vis experiments, it has been confirmed that many hydrophilic as well as the highly lipophilic coenzyme Qs undergo significant structural changes in a strong alkaline environment. Via a complex radical reaction pathway (see schemes in 42 and 43), one or both of the methoxy groups ($-O-CH_3$) from the CoQ structures are cleaved under the attack of the OH^- anions. This happens in all coenzyme Qs having no single unsubstituted place at the quinonic ring. As a consequence, monosubstituted or disubstituted hydroxyl derivatives of coenzyme Qs are obtained. The newly obtained hydroxyl CoQ derivatives show relatively higher hydrophilicity than their parent compounds. Since the radical reactions are quite fast in pH above 12.50, formation of CoQ dimmers also happens [42, 43]. The complex radical reaction can be quenched by making re-titration (with some strong inorganic acid) to neutral, acidic, or slightly alkaline pHs. However, if there is at least one unsubstituted place in the structure of the quinone ring of CoQs, then only one methoxy group can be cleaved and it can be replaced by one OH group [43]. In addition, one or two of the unsubstituted sites of the quinone ring of such CoQ derivatives can be substituted by OH group(s). The hydroxyl derivatives of coenzyme Qs obtained under such circumstances show strong affinity to bind (and some derivatives even to transfer) earth-alkaline cations. Moreover, they show much higher antioxidative potential than the reduced forms of their parent compounds. The reactions of CoQs in alkaline media are seen as a simple method for synthesizing hydroxy CoQ derivatives (OH-CoQ) with significantly improved water solubility. These new OH-CoQs can be used as systems for metal binding and efficient scavengers of free radicals [42, 43].

Metal-binding properties of coenzyme Qs

Various authors have attempted to find out whether native coenzyme Qs have a potential to bind metal cations [see for example 2, 9, 18, 24, 33]. However, most of their efforts were without success. Recently, it has been shown that the hydroxyl derivatives of CoQs obtained via reaction in alkaline media posses a pronounced affinity to bind earth-alkaline cations [42, 43, 45]. Indeed, the presence of proton-donating OH groups in their structure opens up a way to existence of anionic forms of these hydroxylated CoQ forms in neutral media. Upon the electrochemical reduction, a huge electronic density exists in the structures of the hydroxyl CoQs. Existence of such negatively charged patterns in CoQ structures is quite a suitable platform for interacting with highly positive cations. It has been reported that moderate-to-strong complexes are created between hydroxyl derivatives of CoQ1, CoQ0, and CoQ10 and the cationic forms of Ca, Sr, Mg, and Ba [42, 43]. Moreover, the hydroxylated form of CoQ10 was able even to transfer Ca^{2+} cations across lipid biomimetic membranes [42]. A similar feature has also been observed by another artificial lipophilic coenzyme Q-like derivative named 2-palmitoylhydroquinone [45]. It is worth mentioning that all efforts aiming to show whether hydroxylated forms of CoQs are able to bind monocharged cations failed. A set of representative cyclic voltammograms showing the potential of the dihydroxyl CoQ0 to make complexes with Ca^{2+} cations is given in Fig. 4.

Antioxidant properties of coenzyme Qs

The reduced forms of native coenzyme Q family members are known as good antioxidants since long ago [1–3, 9, 46, 47]. As we know, CoQs are able to protect the cell membranes of the destructive lipid peroxidation processes. Due to their role in reducing the damaging effects of the highly reactive free radicals, coenzyme Q-based antioxidants are seen as

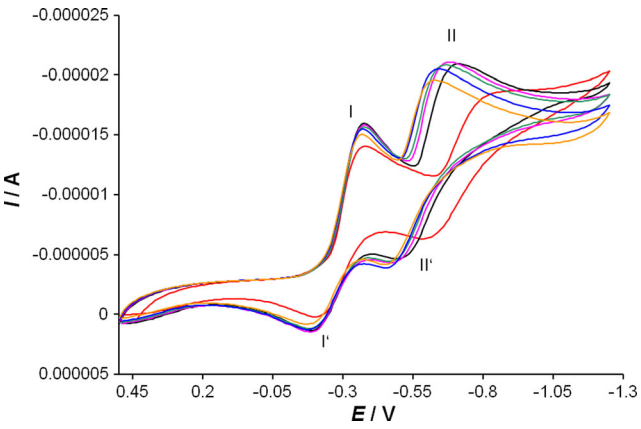


Fig. 4 Cyclic voltammograms of 0.1 mmol/L Coenzyme Q0 recorded at pH of 7.00. Effect of the Ca^{2+} concentration: $c(Ca^{2+})$/mmol/L = 0 (*red curve*), 1, 3, 5, 20, and 50 (*orange curve*). Coenzyme Q0 was initially in contact with 0.1 mol/L NaOH for 45 and afterwards re-titrated to pH of 7.00 with 5 mol/L HCl. Peak I-I' is from the native form of Coenzyme Q0 (insensitive to Ca^{2+} concentration), while peak II-II' originates from the dihydroxy form of Coenzyme Q0 (sensitive to Ca^{2+} concentration). Scan rate was 50 mV/s

indispensible systems that protect the occurrence of many physiological processes in all living organisms. The potential of acting of various coenzyme Q antioxidants toward different targets (reactive oxygen species ROS) is described in several review works and books [20, 47–53]. Indeed, the antioxidant potential of all coenzyme Qs depends significantly on the nature of the substituents existing in their structural pattern [2, 9, 33]. In general, the presence of groups with electron withdrawing abilities (OH, Cl, I, F, NO_2) in the structure of CoQ derivatives increases significantly their potential as antioxidants. In recent experiments with hydroxyl derivatives of coenzyme Qs [42, 43], it has been shown that these substances have much higher potential as antioxidants than the reduced forms of their parent compounds. Moreover, in experiments with macrophage cells, it has been shown that the hydroxyl coenzyme Q derivatives have antioxidant potentials similar to that of vitamin C. Indeed, the unique amphiphilic structures of the hydroxyl coenzyme Qs make them very suitable to act as antioxidants on both sides of the biological membranes. In our recent works [42, 43], new voltammetric methods have been developed to assess the antioxidant potential of CoQs. In addition, in our recent theoretical work related to the new features of electrochemical catalytic reactions [54], we described a new simple voltammetric and time-independent methodology to determine the rate constant of heterogeneous electron transfer step from the features of the electrochemical-catalytic (EC) mechanism studied in square-wave voltammetry. The synthesis of novel CoQ-based antioxidants will certainly be one of the future challenging tasks in the further experiments with these physiologically important compounds.

Theoretical studies relevant to the coenzyme Q's redox chemistry

As it has been mentioned at several spots in this review, the redox chemistry of coenzyme Qs proceeds mainly via two electron transfer steps, which can be additionally coupled to one or two protonation steps. Keeping in mind all the possible redox transformations in which CoQs are undergoing in both aprotic or aqueous media [2, 9, 31–47], several relevant theoretical models can be applied to describe their voltammetric behavior. In the last few years, several groups worked on the development of mathematical models of coupled redox reactions under conditions of cyclic and square-wave voltammetry. The theoretical results relevant to the voltammetric behavior of the so-called EE (electrochemical-electrochemical), ECE (electrochemical-chemical-electrochemical), and EECat (electrochemical-electrochemical-catalytic) redox mechanisms under conditions of cyclic staircase voltammetry are comprehensively elaborated in the recent work of Gulaboski et al. [55]. Moreover, the voltammetric features of EEcat [56], CE (chemical-electrochemical) [57], ECE [58], and EC [54] redox mechanisms have also been studied under conditions of square-wave voltammetry by Gulaboski et al. Mirceski et al. [59–61], Lovric and Komorsky-Lovric et al. [62–71], and Molina et al. [72–76] also made several great contributions towards theoretical understanding of the complex voltammetric behavior of coenzyme Qs under various conditions. Several recent review works report on the major achievements in the theory of square-wave and cyclic voltammetry [77–81]. Many of the theoretical features described in [45–66] fit to the experimental voltammetric behavior of the coenzyme Qs. The results of all considered theoretical models provide valuable information about making diagnostic criteria for recognizing particular redox transformation of the CoQs. Additionally, valuable and simple methods are proposed about assessing the kinetic and thermodynamic parameters relevant to each step of CoQ redox transformation [55–81].

Future perspectives

The number of natural members belonging to the family of coenzyme Q-related compounds is quite impressive [47]. Various important benzoquinones (fumigatin, spinulosin, embelin, rapanone, mesaquinone, rhodoquinone, thymoquinone, mitomycin) naphthoquinones (lawsone, juglone, ramentone, menadion, phthiocol, dunnione, alkanin), and anthraquinones (rhein, emodin, physcion, alizarin, rubiadin, lucidin, purpurin, kermeseic acid) are commonly seen as close relatives to coenzyme Qs. Many of these natural CoQ-like compounds have immense importance in pharmaceutical and chemical industry [47, 82]. Although there are numerous voltammetric studies already reported on some of these naturally occurring quinones [83], there is still much work to be done in order to recognize much closer the chemical features and the mechanisms of redox transformation of these compounds. For example, even recently it has been recognized that Coenzyme Q10 can undergo structural changes in the presence of the membrane-bound Cytochrome P450 enzyme [42]. That reaction is quite important, since it can lead to modification of the pathway of mitochondrial electron transport chain. It is well known that many of the CoQ relatives mentioned above are seen as potent antioxidants having amphiphilic properties [84]. However, the role of these CoQ-like compounds in the transfer of ions across biological membranes is not well elucidated. Recently, in our laboratory, we performed voltammetric experiments with the compound Embelin (2,5-dihydroxy-3-undecyl p-benzoquinone) and we showed that this compound can bind and transfer Ca^{2+} cations across the liquid-liquid interface between phospholipid-modified 1,2-dichlor ethane and water (see Fig. 5). We already reported similar findings with the hydroxyl derivatives of Coenzyme Q_{10} [42, 45]. Indeed, these findings are quite relevant, since it can throw a new light towards understanding of novel physiological functions of these compounds. Voltammetry can be a

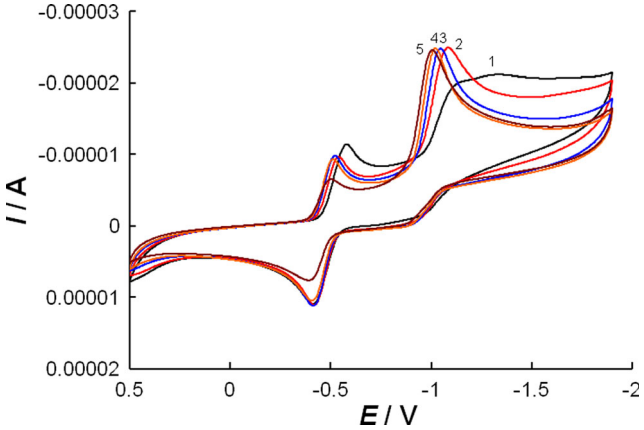


Fig. 5 Three-phase electrode cyclo-voltammetric experiments with Embelin dissolved in 1,2-dichlor ethane (DCE). A droplet of Embelin solution in DCE was attached to the surface of a glassy carbon electrode and immersed in water solutions containing 0 mmol/L Ca^{2+} (1), 1 mmol/L Ca^{2+} (2), 3 mmol/L Ca^{2+} (3), 5 mmol/L Ca^{2+} (4), and 10 mmol/L Ca^{2+} (5). Shifting of the peak potentials of both peaks by increasing Ca^{2+} concentration implies complexation reaction between reduced Embelin molecules and the Ca^{2+} ions. Scan rate was 50 mV/s. Concentration of Embelin dissolved in DCE was 10 mmol/L. (For more details of these experiments, see [85].)

valuable tool to study the interactions of the CoQ-like systems with relevant physiological targets [59, 84, 85]. Not only can it help in revealing their mechanism of actions, but also it can be seen as a tool to measure important kinetic and thermodynamic parameters of those interactions. Indeed, such voltammetric studies will lead to better understanding of the drug-target interactions, and it will be of immense help in the field of drug design. Sabuzi et al. [86] recently reported about a new class of quinoid compounds named KuQuinones. These have a very low reduction potential, and they are characterized by a broad absorption spectrum in the visible region, mainly due to their pentacyclic, highly conjugated structure. The unique properties of these compounds make them promising candidates as sensitive material in constructing photoelectrochemical devices.

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