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ORIGINAL PAPER

Electrochemical synthesis of coenzymes Q_n by oxidation of tetramethoxy precursors

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Abstract The electrochemical oxidation of tetramethoxy precursors (**2**) to coenzymes Q_n (**1**) at a carbon anode was investigated both in a bench-scale batch electrochemical reactor and in a continuous recirculation reaction system equipped with a parallel-plate electrochemical divided cell. High faradic efficiency (>60%) and excellent selectivity (>90%) in coenzymes Q_n were obtained in CH_3CN or CH_3CN/CH_2Cl_2 + 0.15 M Bu_4NBF_4 under potentiostatic or amperostatic alimentation.

Keywords Electrosynthesis · Coenzymes Q_n · Anodic oxidation · Ubiquinones

1 Introduction

Industrial chemistry in the twenty-first century must offer more sustainable processes characterized by high energy and material yields. At the same time specific processes characterized by high selectivity should be designed for the syntheses of fine and specialty chemicals where the overall cost of the process is often mainly determined by separation and purification steps rather than by chemical conversion. In this context the electrochemical route offers an additional parameter with respect to conventional processes because the modulation of the applied electric potential allows one to have an accurate dosage of the driving force of the process. Moreover, chemical redox reagents commonly adopted in chemical syntheses quite often have high toxicity and impose several waste stream treatments. Although the electrochemical reaction usually is only one step in a complex sequence, it has often the key-role of generating the activated intermediate. Hence, in the last years industrial and academic groups were involved several times in the investigation of new electrosynthetic routes for the preparation of fine and specialty chemicals [1–4]. Interestingly, many of these researches are not known because of secrecy requirements [1].

In particular, we have recently reported a very efficient electrochemical route for the synthesis of the coenzyme Q_{10} (compound **1c** in Scheme 1) [5, 6]. Coenzyme Q_{10}, also known as ubiquinone, plays a vital role in maintaining human health and vigor. The strong demand for coenzyme Q_{10} as a dietary supplement and as a drug [7] has led to an extensive research effort aimed at finding efficient synthetic routes [8–16] for this compound and for lower homologues which present astonishingly high costs (e.g., >10.000 €/g for coenzymes Q_7 and Q_9 for research purposes [17]). In particular very promising approaches for the synthesis of the tetramethoxy precursors (compounds **2** in Scheme 1) have been developed, in most cases relying on C–C bond formation between a benzylic center and an E-vinylic organometallic [11–16], where the methoxyls serve as protecting groups. Unfortunately, these routes have been frustrated since the chemical oxidation of precursors **2** to coenzyme Q_n occurs with quite low selectivity (about 50–60%) and requires expensive separation and purification procedures. On the other hand, we have recently shown that the electrochemical oxidation of the methoxy precursor (**2c** in Scheme 1) performed under potentiostatic alimentation in bench scale cell gives the coenzyme Q_{10} with very high selectivity (>90%) and high faradic efficiencies [5, 6]. On the bases of these excellent results, we have carried out a study aimed to verify if this approach can be used also for the synthesis of the other coenzymes Q_n. The synthesis of

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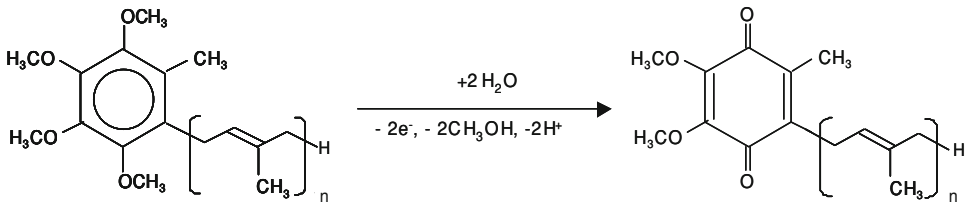
Scheme 1



2

2a n = 0
2b n = 1
2c n = 10

1

1a n = 0
1b n = 1
1c n = 10

Q_0, Q_1 and Q_{10} was investigated with the aim to evaluate the possible effect of the presence and of the length of the isoprenoid chain on the performances of the oxidation process. Electrolyses were performed both in a bench-scale batch electrochemical reactor and in a continuous recirculation reaction system equipped with a parallel-plate electrochemical divided cell, with the additional aim to evaluate the effect of the experimental system on the performances of the process.

2 Experimental

The electroanalytical experiments were carried out in CH_3CN or CH_3CN/CH_2Cl_2 mixed solvent using 0.15 M Bu_4NBF_4 as the supporting electrolyte at glassy carbon or platinum. The counter-electrode and the reference electrode were a platinum spiral and a SCE, respectively. Potential scans were performed by Ecochemie BV Autolab PGSTAT12.

Electrosyntheses were performed in two different systems: system **I** was constituted of a bench-scale two-compartment glass cell equipped with a cation-exchange membrane (Nafion 324). The volume of the anode and cathode solutions was 25 mL. Anodic solution was stirred by magnetic stir bar. The anode zone was equipped with gas inlet and outlet, reference electrode (SCE) and working electrode (compact graphite cylinder of about 5–6 cm^2) with a distance between the cathode and anode of 7.5 cm. Platinum was used as cathode. System **II** was constituted of a continuous batch recirculation reaction system equipped with a filter press two-compartment microflow cell ElectroCell AB. The cell was equipped with compact graphite as anode (apparent surface about 9 cm^2), a nickel cathode (inter electrode gap 1.4 cm) and a cation-exchange membrane Nafion 324. The overall arrangement of the batch pilot reactor is shown in Fig. 1. The electrolytic circulating solutions (250 mL volume) were saturated with a continuous stream of nitrogen fed by two diffusers in the two jacketed solution reservoirs of 250 mL. The circulation of the solutions was provided by two centrifugal pumps. An Amel 2055 potentiostat and 3300 current integrator were used in all experiments. The graphite electrodes were mechanically polished. The electrolyses were generally performed in solutions of ca. 10 mM of **2** in CH_3CN or CH_3CN/CH_2Cl_2 + 0.15 M Bu_4NBF_4 and in the presence of a large excess of H_2O (ca. 1 M). The potentiostatic experiments were generally stopped when the charge passed was that theoretically required for the total conversion of the substrate with a two electron process. Amperostatic electrolyses were generally stopped when a conversion of about 90–95% of the initial substrate was achieved. Different values of the current intensity were tested. The eluent was a mixture of methanol and ethanol. CH_2Cl_2 from Fluka and CH_3CN from Aldrich both HPLC grade and Bu_4NBF_4 analytical grade from Fluka were used as received for the solvent-supporting electrolyte system. The concentrations of **2a**, **2b**, **2c**, **1a**, **1b** and **1c** were evaluated by calibration curves with an HPLC instrument (HP 1100 Agilent) equipped with a UV detector and Alltima C8 (Alltech) column. Standard samples of Coenzymes **1** were obtained from Aldrich. Tetramethoxy precursor **2c** was kindly supplied by Industrie Caffaro. Precursors **2a** and **2b** were synthesized by using the coenzyme Q_0 as substrate according to the literature [14–16]. In particular, $NaBH_4$ [18] and ICH_3 were used as co-reagents in the hydrogenation and methylation steps, respectively, for the synthesis of **2a**. Precursor **2b** was prepared by Friedel-Crafts allylation of **2a** with 3,3-dimethylallyl alcohol in the presence of $SnCl_4$ [18].

3 Results and discussion

3.1 Electroanalytical data

The electrochemical oxidation of the tetramethoxy precursors **2** were preliminary investigated by cyclic voltammetry at Pt and glassy carbon anodes. Figure 2 shows cyclic voltammogram (CV) recorded in CH_3CN at Pt for

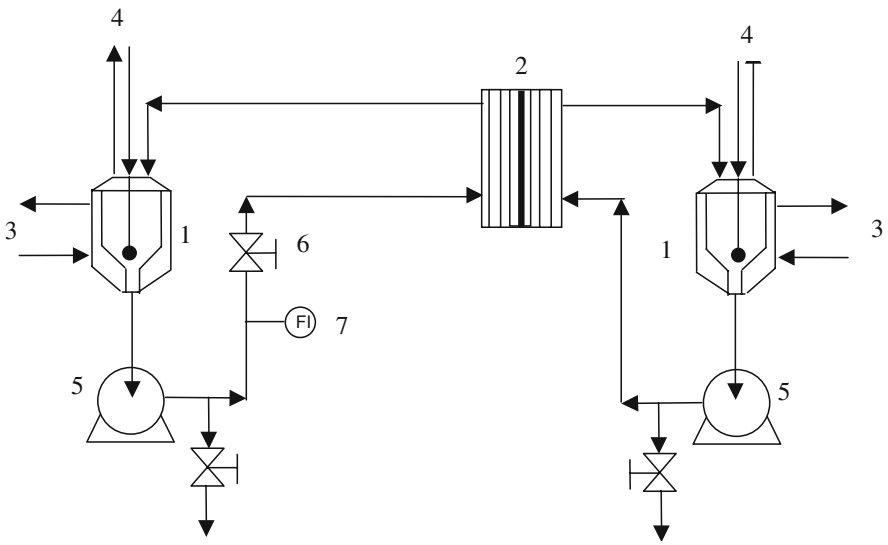


Fig. 1 Simplified flow-sheet of reaction system II: *1* Saturation jacketed tanks, *2* electrochemical cell, *3* thermal exchange fluid, *4* nitrogen gas inlet and outlet, *5* centrifugal pumps, *6* flow valve regulation, *7* flow indicator

precursors **2a** and **2b**. A partially reversible electronic oxidation peak at 1.28 V vs. SCE is seen followed by an irreversible peak at 1.63 V for **2a** (Fig. 2a). When cyclic voltammograms of **2a** were stopped at about 1.4 V, a reversible oxidation peak was observed at any adopted scan rate (from 50 to 10 V s^{-1}) for a large range of the substrate concentration (2–8 mM). For **2b** a partially reversible and

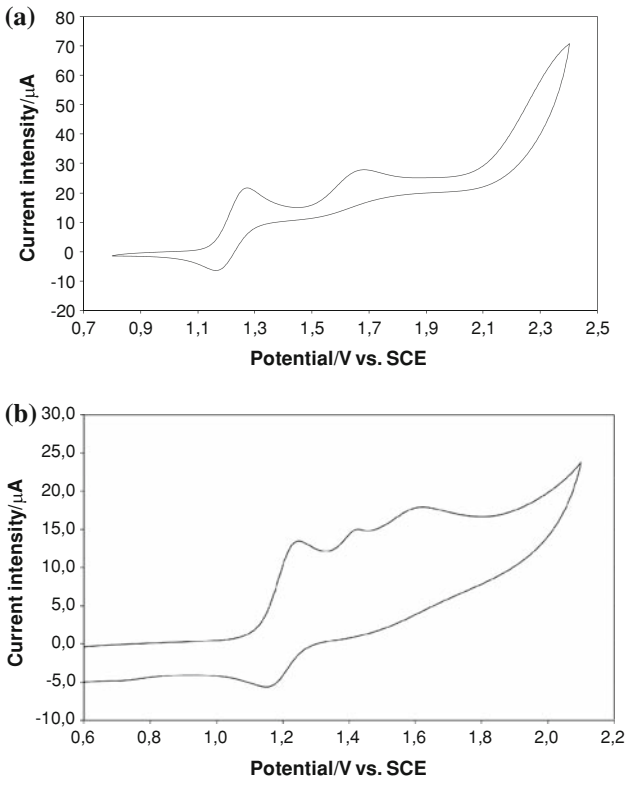


Fig. 2 Cyclic voltammogram of **2a** (**a**) (4 mM) and **2b** (**b**) (2 mM) recorded at 0.1 V s^{-1} in $CH_3CN + 0.15$ M Bu_4NBF_4 at a Pt electrode

an irreversible peak were observed at 1.25 and 1.43 V, respectively, followed by a third peak at about 1.61 V (Fig. 2b), that probably corresponds to the oxidation of the lateral isoprenoic chain. As previously reported [5], the cyclic voltammogram of **2c** at CH_3CN/CH_2Cl_2 gives rise to a partially reversible electronic oxidation peak at 1.39 V followed by a shoulder and by a multi-electronic wave starting at about 1.65 V that probably results from the oxidation of the isoprenoid chain. Similar cyclic voltammograms were obtained at glassy carbon anode for the investigated precursors and in CH_3CN/CH_2Cl_2 for **2a** and **2b**. It was observed that electrode fouling occurred both at Pt and glassy carbon for **2c**. Hence, for the CV recorded in the presence of this compound it was necessary to polish the electrode after each voltammogram to obtain reproducible results.

3.2 Electrosyntheses

3.2.1 Effect of the nature of the substrate

As reported in literature [5], the potentiostatic electrolysis of **2c** gives rise at proper operative conditions to the formation of coenzyme Q_{10} with high faradic efficiency and excellent selectivity. In order to evaluate the possibility to extend the electrochemical approach previously developed for the synthesis of the coenzyme Q_{10} to the class of ubiquinones, some potentiostatic electrolyses were performed in the presence of **2a**, **2b** and **2c** at carbon anodes. CH_3CN was used as solvent for **2a** and **2b** while a mixture of CH_3CN and CH_2Cl_2 was employed for **2c**. Electrolyses were performed at compact graphite at a potential corresponding to the first oxidation potential peak. Indeed, according to the previous studies above mentioned, this choice was made to have high selectivity in the coenzyme

Q_{10}, because concomitant oxidation of isoprenoid chain occurs at high values of the anodic potential, thus leading to the formation of other products. Compact graphite was selected as anode since it gave rise to higher selectivity in the target **1c** with respect to platinum and diamond anodes while glassy carbon presents a rapid decrease of the current density which prevented to perform the experiments up to the total conversion of the substrate [5].

The experiments, carried out with an initial concentration of the tetramethoxy precursor of 10 mM, were generally stopped when the charge passed was that theoretically required for the total conversion of the substrate with a two electron process. As shown in Table 1, for both **2a** and **2c**, a selectivity higher than 90% for the formation of the corresponding coenzymes Q_n, in spite of the fact that these precursors are characterized by a quite different structure. Indeed, **2c** has a very long isoprenoid chain that is not present at all in **2a**. In the case of **2b**, a slight lower selectivity in **1b** was obtained. Otherwise the value of the selectivity of **1b** is probably underestimated since the methoxy reagent was difficult to purify. Interestingly, a quite high current efficiency was also obtained for all the substrates. The experiments were performed in the presence of purposely added water because the formation of quinone type derivatives is likely to involve addition of water molecules to the substituted methoxy carbonium ion generated by oxidation of the substrate. Indeed, when the electrolyses were carried out with no water added a drastic decrease of both faradic efficiency and selectivity of **1** occurred.

Hence, it is possible to conclude that potentiostatic electrolyses can offer an interesting tool for the synthesis of all the coenzymes Q_n.

3.2.2 *Amperostatic electrolyses*

In our previous work it was reported that the selectivity of the process, in the case of the synthesis of **1c**, dramatically depends on the adopted working potential [5]. Hence, potentiostatic electrolyses seem intuitively more appealing than galvanostatic ones, which, however, are generally preferred in industrial applications. Therefore, in the following we wish to study the possibility of synthesizing coenzymes Q_n by galvanostatic electrolyses. In particular, precursors **2a** and **2c** were oxidized under amperostatic alimentation at different values of the current intensity. The experiments were carried out first with a current intensity slightly lower than 30 mA corresponding to the initial value of the current intensities recorded in potentiostatic electrolyses and stopped when a conversion of about 95% of the initial substrate was achieved. As shown in Table 2 (entries 2 and 4), when experiments were carried out under amperostatic alimentation quite high selectivities and faradic efficiencies were still obtained for the electrosynthesis of **1a**. Selectivities and faradic efficiencies were significantly lower with respect to that obtained under potentiostatic electrolyses for the synthesis of **1c** (see Tables 1 and 2, entry 4). When experiments were repeated with lower current densities, both higher selectivities and current efficiencies were otherwise obtained (entries 1 and 3).

These results are quite interestingly, since they demonstrate that the electrosynthesis of coenzymes Q_n can be performed also under amperostatic alimentation if quite low values of the current density are imposed. It is interesting to observe that the low current density imposed should involve, on an applicative scale, very large electrodic surfaces. On the other hand, an applicative scale should require quite higher concentrations of the substrate so that higher current intensity could be successfully applied. Indeed, when the anodic oxidation of **2a** was repeated with an initial concentration of the substrate of about 50 mM and a current intensity of 150 mA, good selectivities and current efficiencies were obtained (entry 5).

Attempts to scale up electrochemical organic syntheses resulted in some cases in drastic decreases of both yields and faradic efficiencies as compared to experiments performed in bench-scale systems under similar operative conditions [4, 19]. Hence, in order to test the role of the experimental system on the electrosyntheses of coenzymes Q_0 and Q_{10}, some amperostatic electrolyses were performed in a continuous batch re-circulation cell (system **II**) with an initial substrate concentration of 10 mM. As shown

Table 1 Potentiostatic electrooxidation of **2** (10 mM) at compact graphite in CH_3CN or CH_3CN/CH_2Cl_2 + 0.15 M Bu_4NBF_4 + 1 M of H_2O

Substrate	E_{app}[a]	Initial and final current intensity (mA)	Solvent	Faradic efficiency (%)	Selectivity (%)[b]
2a	1.28	28-5	CH_3CN	87	93
2b	1.25	28-5	CH_3CN	57	83
2c	1.40	26-4	CH_3CN–CH_2Cl_2	76	97

[a] Applied potential (V vs. SCE)

[b] 100 × (moles of product **1**/moles reacted of **2**)

Table 2 Amperostatic electrooxidation of **2a** and **2c** (10 mM) at compact graphite in CH_3CN or CH_3CN/CH_2Cl_2 + 0.15 M Bu_4NBF_4 + 1 M of H_2O

Entry	Electrolytic system	Substrate	Current intensity (mA)	Initial and final E_{app}[a]	Solvent	Faradic efficiency (%)	Selectivity (%)[b]
1	I	**2a**	14	1.28–1.50	CH_3CN	65	96
2	I	**2a**	28	1.32–1.62	CH_3CN	63	91
3	I	**2c**	13	1.38–1.60	CH_3CN–CH_2Cl_2	44	95
4	I	**2c**	26	1.42–1.74	CH_3CN–CH_2Cl_2	29	81
5[c]	I	**2a**	150	ND	CH_3CN	76	85
6	II	**2a**	33		CH_3CN	56	89
7	II	**2a**	33		CH_3CN	60	93
8	II	**2c**	30		CH_3CN–CH_2Cl_2	60	91

ND not determined

[a] Potential difference between anode and reference electrode (V vs. SCE)

[b] 100 × (moles of product **1**/moles reacted of **2**)

[c] Substrate concentration: 50 mM

in Table 2, for the synthesis of **1a**, similar performances were obtained when the experiments were performed either in system **I** (entry 2) or in system **II** (entries 6 and 7), using compact graphite as anode at a constant current intensity of about 30 mA. Quite interestingly, in the case of the synthesis of **1c**, higher current efficiencies were obtained in the system **II** (see entries 4 and 8) as a probable result of the fact that a better mixing of the electrolytic solution is obtained in this system, thus giving rise to an higher mass transport rate of the high molecular weight reagent towards the anodic surface.

4 Conclusions

The electrochemical oxidation of tetramethoxy precursors **2** is proposed as a key step for the synthesis of coenzymes Q_n and homologues. We have shown that electrosynthesis of very different coenzymes Q_n can be achieved with high selectivity and current efficiencies both under potentiostatic and amperostatic alimentation if suitable working potential or current densities are, respectively, used. When the process was scaled up in a continuous batch recirculation reaction system equipped with a parallel-plate electrochemical cell under amperostatic conditions, similar or better results in terms of selectivity and faradic efficiency were, furthermore, obtained.

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