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ORIGINAL PAPER

Electrochemical behavior of catechol in the presence of 2-methyl-1,3-cyclopentanedione: application to electrosynthesis

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Abstract Electro-oxidation of catechol in the presence of 2-methyl-1,3-cyclopentanedione as a nucleophile was investigated in water–acetonitrile (90:10 *v*/*v*) solution. The results indicate that the *o*-benzoquinone electrogenerated participates in a Michael addition reaction with this nucleophile. The electrosynthesis of 2-(3,4-dihydroxyphenyl)-2-methylcyclopentane-1,3-dione was carried out. The product was characterized by NMR, MS, FT-IR, and elemental analysis. An EC mechanism was deduced from voltammetric and spectroscopic data. Also, the Michael addition reaction rate constant (k_m) was estimated using digital simulation of voltammograms.

Keywords Electrochemistry · Catechol · Cyclic voltammetry · Michael addition · 2-Methyl-1,3-cyclopentanedione

Introduction

Because of the increasing importance of green chemistry in organic synthesis, development of more efficient and environmentally friendly processes for chemical transformations is desired [1, 2]. One methodology is the development of organic reactions using electrolytic methods in aqueous media or in organic–water mixed solvent (with the minimum ratio of organic solvent to water). Electroanalytical methods offer several advantages over classical organic synthesis: simpler synthesis, waste reduction owing to the fact that the electron is provided directly by the electric current without a reagent and mild conditions (temperature, pH, etc.) [3–5].

In recent years, there has been a growing interest in the study of reactions between electrogenerated benzoquinones from oxidation of polyphenols and some nucleophiles [6]. Among these, interest in catechol has increased, not only because it is a model molecule for compounds bearing catechol as part of their structure, for example dopamine and L-dopa, but also because it has important physiological functions and some pharmacological activity. An important pathway in the metabolism of catechol estrogens and catecholamines is oxidation to their respective semibenzoquinones and benzoquinones [7]. The basic biological activity of catechol-derived benzoquinones is related to their ability to act both as oxidants and electrophiles. As oxidants, benzoquinones form a redox cycle with their semibenzoquinones, producing an elevated level of reactive oxygen species, a condition known as oxidative stress [7]. As electrophiles, benzoquinones that are produced can form stable covalent adducts with cellular macromolecules, including DNA [8]. Thus, DNA can be damaged by reaction with itself and by reaction with oxygen species (hydroxyl radicals) [7, 8]. The formation of depurinating adducts by catechol estrogen quinine reacting with DNA may be a major event in the initiation of breast and other human cancers [8].

It has been shown that *o* and *p*-benzenediols can be oxidized electrochemically to *o* and *p*-benzoquinones. The benzoquinones formed are quite reactive and are attacked by a variety of nucleophiles through a Michael addition reaction [9]. This reaction has been utilized for spectrophotometric determination of some *o*-benzoquinones [10, 11].

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Currently, our interest has focused on electrochemical behavior of polyphenols, including catechols, in the presence of nucleophiles. As a part of our recent research we have reported the Michael addition reaction of diethylamine and dibutylamine with electrogenerated *o*-benzoquinone [12–14]. Michael addition reactions are among the most important carbon–carbon bond-forming reactions in modern synthetic organic chemistry [15]. Thus, in the literature, there are reports on the carbon–carbon bond-forming reaction arising from addition of carbon nucleophiles to electrogenerated *o*-benzoquinone [16–21].

Extending our interest in the research on electrochemical oxidation of catechols in the presence of nitrogen nucleophiles, we became interested in understanding and exploiting the oxidative carbon–carbon bond-forming reaction of electrogenerated *o*-benzoquinone with 2-methyl-1,3-cyclopentanedione (MCPD). Choosing MCPD as nucleophile was on the basis of controlling the reaction conditions. Replacing one of the acidic hydrogens by a methyl group removes, to some extent, the complexity of reactions and eliminates significant by-product formation.

Results and discussion

Electrochemical study

The electrochemical behavior of catechol in the presence of MCPD was studied by cyclic voltammetry. The influence of pH on the behavior of catechol in the presence of 2-methyl-1,3-cyclopentanedione (MCPD) was investigated by examining the electrode response in aqueous solution with different buffered pHs between 2 and 10. Cyclic voltammograms detailing the oxidation of 1.0 mM catechol in the presence of 1.0 mM MCPD at pH 2, 5, 7, and 10 are compared in Fig. 1.

As can be seen, at acidic pH (e.g. 2), the cyclic voltammogram of catechol shows one anodic peak and the corresponding cathodic peak with a peak-current ratio $[I_p(C^1)/I_p(A^1)]$ of nearly unity. Consequently, this shows there is no reaction between electrogenerated *o*-benzoquinone and MCPD, which can be attributed to the fact that at pH 2, MCPD exists totally as the protonated form and has no nucleophilic characteristics. However, with increasing pH, the cathodic peak C^1 diminishes until it disappears at approximately pH 7. The decreasing height of the cathodic peak C^1 (or its disappearance) can be attributed to the occurrence of a reaction between the electrogenerated *o*-benzoquinone and MCPD. In more basic solution (e.g. pH 10), the behavior of catechol in the presence of MCPD is similar to that in the absence of nucleophile and becomes irreversible. This suggests that the oxidation of catechol is followed by an irreversible chemical reaction with hydroxyl ion. Thus, the pH range 7–8 is the optimum range for

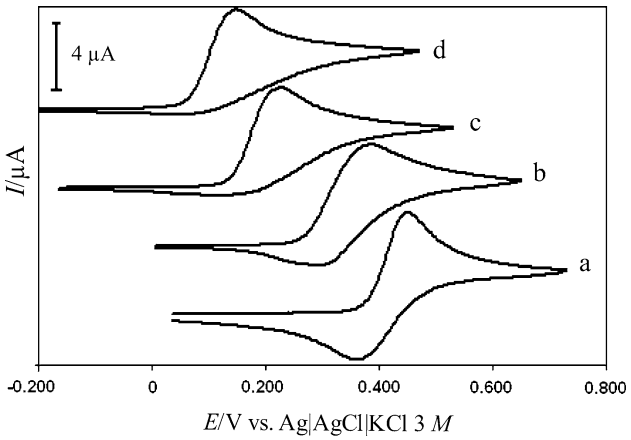


Fig. 1 Cyclic voltammograms of 1.0 mM catechol in the presence of 1.0 mM MCPD at a glassy-carbon electrode in the solvent-supporting electrolyte (SSE) with various pH values. pH for *a–d* are: 2, 5, 7, and 10, respectively. Scan rate is 10 mV s^{-1} and the SSE is water–acetonitrile (90:10 *v/v*) solution containing 0.15 M phosphate buffer

study of the reaction between *o*-benzoquinone and MCPD. The cyclic voltammograms of catechol in the absence and presence of MCPD at a scan rate of 10 mV s^{-1} at pH 7 are shown in Fig. 2.

The cyclic voltammogram of 1.0 mM catechol (Fig. 2a) in water–acetonitrile (90:10 *v/v*) solution containing 0.15 M phosphate buffer (pH 7) showed one anodic peak (A^1) at +0.205 V and a corresponding cathodic peak (C^1) at +0.136 V, which corresponds to the transformation of catechol to *o*-benzoquinone and vice versa (Scheme 1) within a quasi-reversible two-electron process. A peak current ratio $[I_p(C^1)/I_p(A^1)]$ of nearly unity, particularly during repeated recycling of the potential, is considered to

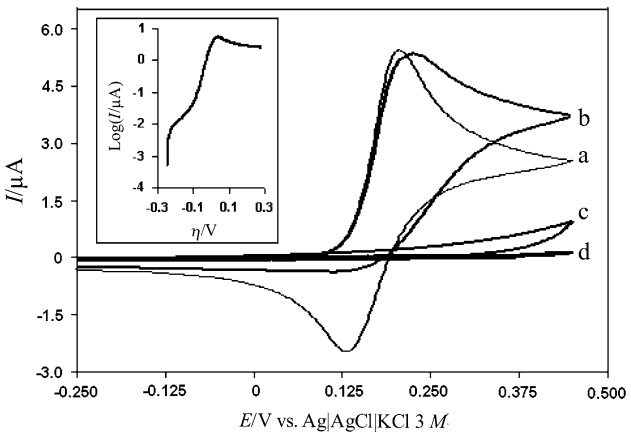
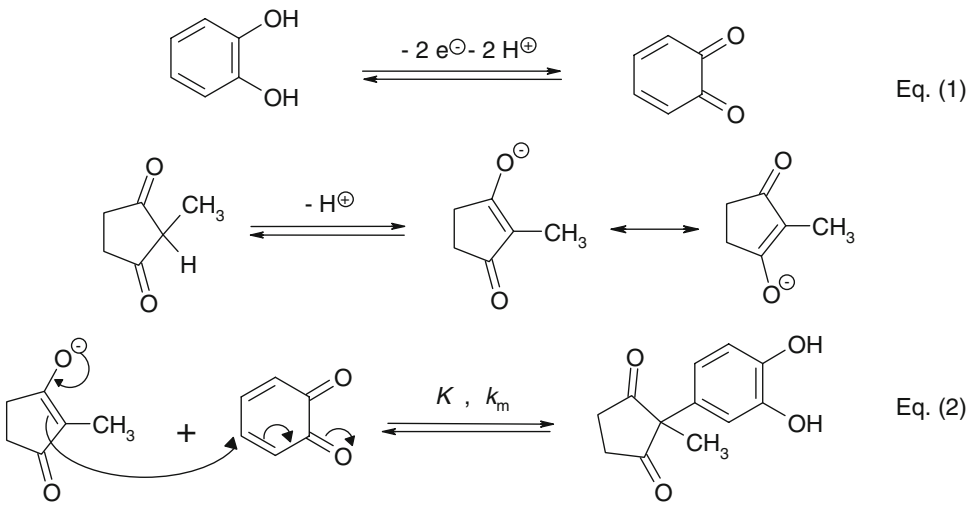


Fig. 2 Cyclic voltammograms of 1.0 mM catechol in the absence (*a*) and presence (*b*) of 1.0 mM MCPD at a scan rate of 10 mV s^{-1} in an SSE of pH 7 at the surface of a GC electrode. Voltammograms (*c*) and (*d*) represent the electrochemical behavior of 1.0 mM MCPD in the SSE and of the pure SSE (pH 7), respectively. *Inset*, the Tafel plot for catechol obtained from the data in Fig. 2a

Scheme 1



be the criterion for production of *o*-benzoquinone at the surface of the electrode under these experimental conditions. This result shows that hydroxylation or dimerization is too slow to be observed on the time scale of experiment [22–25]. The oxidation of catechol in the presence of MCPD as nucleophile was studied in some detail. Figure 2b shows the cyclic voltammogram obtained for a 1.0 mM solution of catechol in the presence of 1.0 mM MCPD. The voltammogram showed only one anodic (A^1) at +0.226 V, and the corresponding cathodic peak was not observed. The anodic shift in A^1 in the presence of MCPD is probably because of the formation of a thin film of product on the surface of the electrode, inhibiting to some extent the performance of the electrode process [26, 27]. Figure 2, curves c and d, are the cyclic voltammograms of MCPD and pure buffer solution in this range of potential, respectively. As can be seen (Fig. 2c), MCPD is not electroactive at the oxidation potential of catechol, consequently it can show its nucleophilic property. The multi-cyclic voltammograms of catechol in the presence of MCPD are shown in Fig. 3.

The voltammograms exhibit a relatively intense decrease in anodic peak current of A^1 together with some potential shift in a positive direction. The positive shift of A^1 peak in the presence of MCPD is probably because of the formation of a thin film of product on the surface of the electrode inhibiting to some extent the performance of electrode process [10]. This problem was circumvented by regular cleaning of the electrode surface.

The effect of MCPD concentration on the cyclic voltammograms of catechol was studied (figure not shown). Cyclic voltammograms of a 1.0 mM solution of catechol in the presence of different concentrations of MCPD showed that at a low concentration ratio of MCPD to catechol (such as 1:4), nucleophilic attack of MCPD on electrogenerated *o*-benzoquinone does not occur to a great extent and,

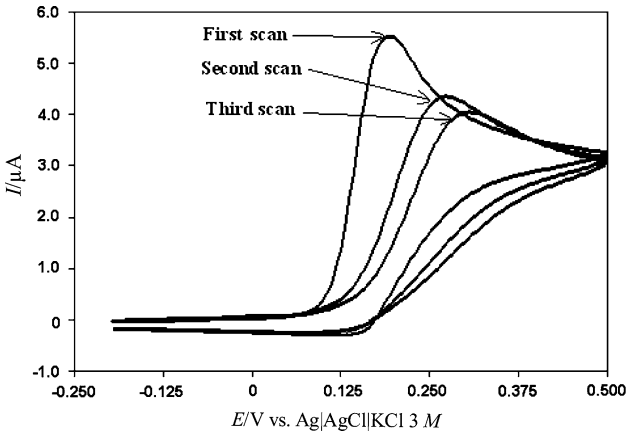


Fig. 3 Multi-cyclic voltammograms of 1.0 mM catechol in the presence of 1.0 mM MCPD at a glassy-carbon electrode at a scan rate of 10 mV s^{-1} in the SSE (pH 7)

consequently, the cathodic peak C^1 does not disappear. The C^1 current decreased with an increase in the concentration of MCPD from 0.25 to 1 mM. Using the obtained voltammograms, $I_p(C^1)/I_p(A^1)$ was extracted and plotted versus the MCPD concentration. These results indicate that nucleophilic attack of MCPD on *o*-benzoquinone increases with an increase in the concentration of MCPD. The dependence of $I_p(C^1)/I_p(A^1)$ on the MCPD concentration shows the dependence of the chemical reaction rate on the MCPD concentration. The absence of an oxidation peak of the Michael adduct can probably be attributed to its insolubility in the solution.

Furthermore, we examined the effect of potential scan rate on the peak current ratio $[I_p(C^1)/I_p(A^1)]$ in the cyclic voltammograms of catechol in the presence of MCPD. It is seen that, in proportion to the increase of the potential scan rate (Fig. 4), the peak current ratio $[I_p(C^1)/I_p(A^1)]$ increases. Since the time window of voltammetry decreases on increasing the potential scan rate, less electrogenerated

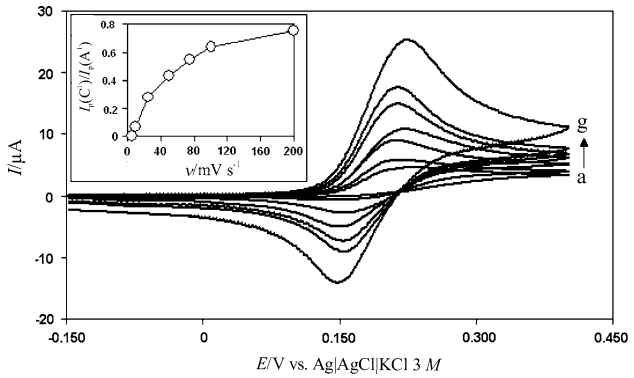


Fig. 4 Cyclic voltammograms of 1.0 mM catechol in the presence of 1.0 mM MCPD in the SSE (pH 7) at a glassy-carbon electrode and various scan rates. Scan rates from *a* to *g* are: 5, 10, 25, 50, 75, 100, and 200 mV s^{-1}. *Inset*, variation of peak current ratio $[I_p(C^1)/I_p(A^1)]$ versus scan rate

o-benzoquinone contributes to the chemical reaction with MCPD. A plot of peak current ratio $[I_p(C^1)/I_p(A^1)]$ versus the scan rate for a mixture of catechol and MCPD confirms the reactivity of *o*-benzoquinone toward MCPD (inset of Fig. 4).

Controlled-potential coulometry was performed in water–acetonitrile (90:10 *v*/*v*) solution containing 0.5 mmol catechol, 0.5 mmol MCPD, and 0.15 M phosphate buffer (pH 7). Monitoring of the electrolysis progress was carried out by cyclic voltammetry (Fig. 5).

It is clearly observed that, in proportion to the advancement of coulometry, the anodic peak A^1 decreases and disappears when the charge consumption becomes about $2e^-$ per molecule of catechol. These coulometry and voltammetry results allow us to propose an EC (electrochemical and chemical) mechanism [28, 29] for the

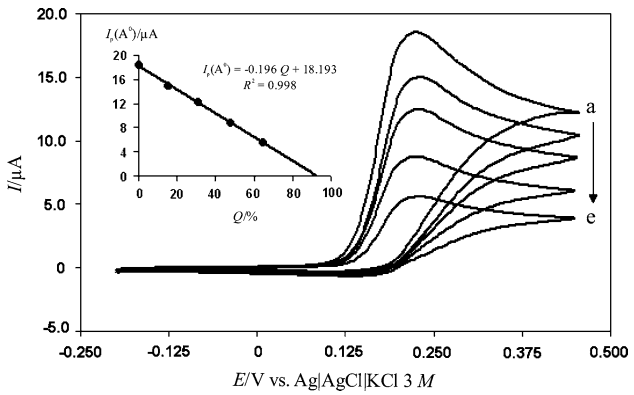


Fig. 5 Cyclic voltammograms of SSE of pH 7 containing 0.5 mmol catechol and 0.5 mmol MCPD at a glassy-carbon electrode during controlled-potential coulometry at 0.35 V versus Ag|AgCl|KCl 3 M after consumption of *a* 0, *b* 15, *c* 31, *d* 48, and *e* 65 C. *Inset*, variation of anodic peak current $[I_p(A^1)]$ versus charge consumption. Scan rate is 10 mV s^{-1}

electrooxidation of catechol in the presence of MCPD (Scheme 1). According to this mechanism, catechol is electrochemically oxidized to *o*-benzoquinone. It is well known that the electrochemical oxidation of catechol to *o*-benzoquinone in water or water–organic mixed solvents (low fraction of organic solvent), is considered as a one step, two-electron, two-proton-transfer process [30–32]. The Michael acceptor of *o*-benzoquinone can then be attacked at position C-4 or C-6 (equivalent positions) by MCPD as a nucleophile to yield the only product.

In order to further confirm the proposed mechanism and synthesis of a new catechol derivative, controlled potential electrolysis of catechol in the presence of MCPD was carried out. The potential of the working electrode (carbon rod) was fixed at +0.35 V versus the reference electrode. As mentioned in previous sections, characterization of the product of electrolysis indicated that it was 2-(3,4-dihydroxyphenyl)-2-methylcyclopentane-1,3-dione (**1**). Electrochemical synthesis of **1** confirms the reactivity of electrogenerated *o*-benzoquinone against MCPD via an EC mechanism.

According to our results, the Michael addition reaction of MCPD to *o*-benzoquinone (Eq. 2) seems to occur much faster than other side reactions, leading to the product **1**. The overoxidation of **1** was circumvented during the preparative reaction because of the insolubility of the product in the phosphate buffer solution medium.

Digital simulation

Digital simulation of cyclic voltammograms provides an opportunity for testing the EC mechanism illustrated in Scheme 1 and, if successful, to estimate the rate of chemical reaction of *o*-benzoquinone with MCPD. To verify the reaction mechanism shown in Scheme 1 for the electrochemical oxidation of catechol in the presence of MCPD, the cyclic voltammograms were analyzed by digital simulation to find the best fit between experimental and simulated cyclic voltammograms.

Digital simulation was carried out using the software DigiElch 4.5 written by Rudolph [33, 34]. The experimental results were simulated according to an EC mechanism. The simulation was carried out assuming semi-infinite diffusion and planar geometry of the electrode and the number of electrons transferred in all steps as two. The formal potential ($E^{0\prime}$) of the catechol/*o*-benzoquinone redox couple was experimentally calculated as $(E_{pc} + E_{pa})/2$ and was assumed to be equal to its standard electrode potential (E^0). The values of α and k^0 were obtained by using the Tafel plot. Tafel plots (inset of Fig. 2) were drawn by using the data driven from the rising part of current-voltage curve at low scan rates, for example 10 and 25 mV s^{-1}. A mean slope of 15.01 (V per decade)$^{-1}$ and intercept (log I^0) of 0.46 were obtained for the Tafel plots. General equations

for the slope value of the anodic branch of the Tafel plot and the exchange current (I^0) are written as below [28]:

$$\text{Slope} = (1-\alpha)n\text{F}/2.3\text{RT} \quad (1)$$

$$I^0 = n\text{FA}k^0c \quad (2)$$

By substituting the slope = 15.01 (V per decade)$^{-1}$, $n = 2$, $F = 96{,}485$ C mol^{-1}, $R = 8.314$ J mol^{-1} K^{-1}, and $T = 298$ K in Eq. 1, the α value was obtained as 0.56. Also, by substituting values of A (electrode surface area) = 3.69×10^{-2} cm^2, c (concentration) = 1×10^{-6} mol cm^{-3}, and $I^0 = 2.88 \times 10^{-6}$ A and other known values in Eq. 2, the value of k^0 was obtained as 4.05×10^{-4} cm s^{-1}. The experimental values entered for digital simulation were: E_{start} −0.15 V, E_{switch} +0.40 V versus Ag|AgCl|KCl 3 M, and the surface area of the electrode was 3.69×10^{-2} cm^2. All these values were kept constant throughout the fitting of the digitally simulated cyclic voltammograms to the experimental data. E^0, k^0, and α were fixed and k_{m} was allowed to change through the fitting process. The estimated value for k_{m} is 13 ± 2 M^{-1} s^{-1} and $k_{\text{f}}/k_{\text{b}}$ is 94 ± 7.

Some cyclic voltammograms of catechol in the presence of MCPD at various scan rates together with their simulated cylic voltammograms were shown in Fig. 6a. By using the data obtained from Fig. 6a, a correlation diagram between oxidation peak current [$I_{\text{p}}(\text{A}^1)$] of experimental and related simulated cyclic voltammograms over various scan rates was drawn (Fig. 6b). According to Fig. 6b, a good correlation of 99.9% between oxidation peak current of experimental and related simulated cyclic voltammograms over various scan rates was found and also close agreement between experimental and the corresponding simulated results was obtained, which confirm the validity of the estimated k_{m}.

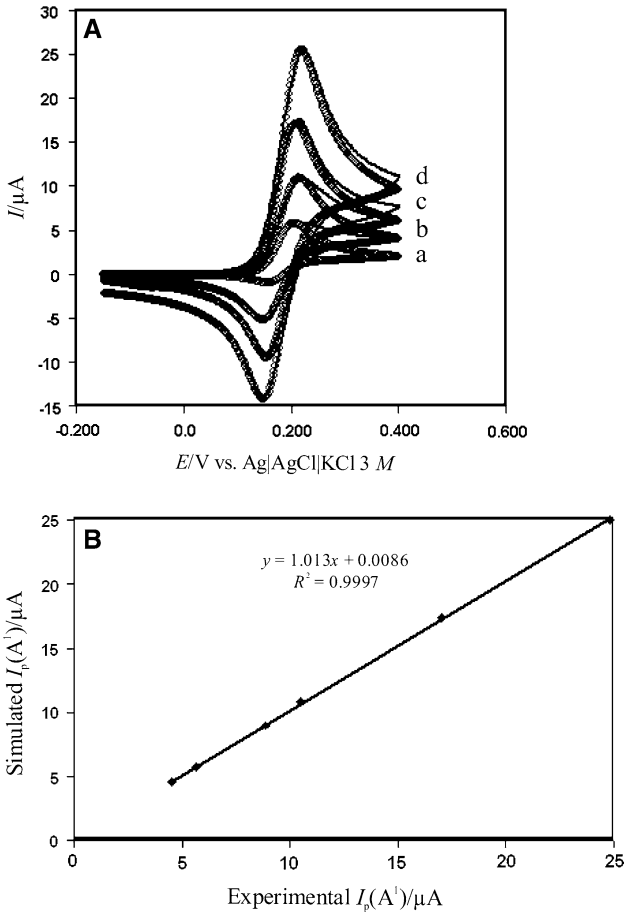


Fig. 6 **a** Experimental cyclic voltammograms of 1.0 mM catechol in the presence of 1.0 mM MCPD in the SSE (pH 7) at various scan rates with corresponding simulated cyclic voltammograms. Scan rates from *a* to *d* are 10, 50, 100, and 200 mV s^{-1}. Experimental: *solid line* and simulated: *dashed line*. **b** The correlation between anodic peak current of simulated and experimental results

Experimental

Apparatus and reagents

Cyclic voltammetry, controlled-potential coulometry, and preparative electrolysis were performed using an Autolab model PGSTAT 30 potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy-carbon disc (Metrohm, 1.8 mm diameter), and a platinum wire was used as the counter electrode. The glassy-carbon electrode was polished between each set of experiments with aluminum oxide powder on a polishing cloth. The working electrode used in the controlled-potential coulometry and macro-scale electrolysis was an assembly of three carbon rods from (6 mm in diameter and 6 cm in length), and a large platinum gauze served as counter electrode. Carbon rods were from Azar electrode (Iran) and the geometrical area of each carbon rod that was inserted in the solution was about 7.8 cm^2. The working electrode potentials were measured versus Ag|AgCl|KCl 3 M (from Metrohm).

The FT-IR spectra (KBr) were determined on a Bruker spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DRX-500 Avance spectrometer at 500.13 and 125.03 MHz, respectively. Mass spectroscopic measurements were acquired on an HP 5973 spectrometer. Elemental analysis (C, H) of the product was performed with a CHNS 932 LECO (USA); its results agreed favorably with calculated values.

All chemicals were reagent-grade materials. Catechol was obtained from Fluka and MCPD was obtained from Merck and used without further purification. All experiments were carried out in 0.15 M phosphate buffer–acetonitrile (90:10 *v*/*v*) solution.

2-(3,4-Dihydroxyphenyl)-2-methylcyclopentane-1,3-dione (1, $C_{12}H_{12}O_4$)

A water–acetonitrile solution (90:10 *v*/*v*, 80 cm^3) containing phosphate buffer (0.15 M, pH 7) was pre-electrolyzed at 0.9 V versus an Ag|AgCl|KCl 3 M reference electrode in an undivided cell, then 0.5 mmol catechol and 0.5 mmol MCPD were added to the cell. Potentiostatic electrolysis was carried out at 0.35 V versus the reference electrode and the current at the beginning of electrolysis was 95 μA. The electrolysis was terminated after about 1.5 h, when the current had decreased by more than 95%. The process was interrupted eight times during the electrolysis and the graphite anode was washed in acetone in order to reactivate it. It can be said that this method can be scaled up to 100 mmol catechol. To decrease the electrolysis time, increasing the anode area (by increasing the number of carbon rods) is necessary. At the end of electrolysis a few drops of acetic acid were added to the solution and the cell was placed in the refrigerator over night. The precipitated solid was collected by filtration and washed thoroughly with cold water. The precipitate was purified by column chromatography using ethyl acetate–*n*-hexane (50:50) as mobile phase. Yield: 79%, m.p.: 162–164 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): $\delta = 1.24$ (s, CH_3), 2.82–2.67 (m, $2CH_2$), 6.37 (dd, $J = 8.3$ Hz, $J = 2.3$ Hz, 1H, arom.), 6.57 (d, $J = 2.3$ Hz, 1H, arom.), 6.69 (d, $J = 8.3$ Hz, 1H, arom.), 8.98 (s, OH), 9.05 (s, OH) ppm; ^{13}C NMR (125.03 MHz, DMSO-d_6): $\delta = 20.25$, 35.93, 61.15, 114.57, 116.77, 118.09, 129.01, 145.85, 146.51, and 214.71 ppm; FT-IR (KBr): = 3,409, 1,705, 1,606, 1,528, 1,458, 1,423, 1,378, 1,296, 1,200, 1,049, 805, 604 cm^{-1}; MS: *m*/*z* = 220 (M^+), 164, 150, 136, and 89.

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