Mechanistic Study of Electrochemical Oxidation of 2,5-Dihydroxybenzoic Acid and 3,4-Dihydroxybenzaldehyde in the Presence of 3-Hydroxy-1*H*-phenalene-1-one

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The mechanism of the electrochemical oxidation of 2,5-dihydroxybenzoic acid and 3,4-dihydroxybenzaldehyde in the presence of 3-hydroxy-1*H*-phenalene-1-one as a nucleophile has been studied in water/acetonitrile (80/20 v/v) solution using cyclic voltammetry and controlled-potential coulometry methods. The results indicate that the quinones derived from oxidation of 2,5-dihydroxybenzoic acid and 3,4-dihydroxybenzaldehyde participate in Michael addition reactions with 3-hydroxy-1*H*-phenalene-1-one and *via* ECE and ECEC mechanisms convert to the different products, with good yield under controlled potential conditions, at carbon electrode.

Key words cyclic voltammetry; 3-hydroxy-1*H*-phenalene-1-one; 2,5-dihydroxybenzoic acid; 3,4-dihydroxybenzaldehyde

Quinones are of considerable interest because many drugs such as doxorubicin, daunurobicin and mitomycin C in cancer chemotherapy contain quinones,[1] whereas various other quinones have found use in industry.[2] Some of them also exhibit antitumor and antimalarial activities[3] and many of them are also involved in enzyme inhibition and DNA cross-linking.[4] On the other hand, in recent years, medicinal properties of benzofuran derivatives have been investigated widely and were shown to be effective as antitumor,[5] anti-depressant,[6] antifungal,[7] anti-hypertensive, and cytotoxic.[8] They are also potent and selective oxytocin antagonists,[9] PDE5 inhibitor for treatment of erectile dysfunction,[10] and H_3 receptor antagonists.[11] In order to synthesise new quinone derivatives we studied the electrochemical oxidation of benzenediols in the presence of a variety of nucleophiles.[12,13] Also, in order to synthesise benzofuran derivatives we investigated the electrochemical oxidation of catechols in the presence of β-diketones such as acetylacetone,[14] dimedone,[15] and dibenzoylmethane.[16] In this connection, the electrochemical oxidation of hydroquinones and catechols in the presence of 3-hydroxy-1*H*-phenalene-1-one (**3**) as a nucleophile has been recently reported by us (Chart 1).[17]

In the present paper, we describe the preparation of the new polycyclic quinone derivative **6a** and the new polycyclic benzofuran derivative **8b** using electrooxidation of 2,5-dihydroxybenzoic acid (**1a**) and 3,4-dihydroxybenzaldehyde (**1b**) in the presence of 3-hydroxy-1*H*-phenalene-1-one (**3**) as a nucleophile *via* ECE and ECEC electrochemical mechanisms respectively.

Results and Discussion

Electrochemical Study of 2,5 Dihydroxybenzoic Acid Cyclic voltammogram of a 0.5 mM of 2,5-dihydroxybenzoic acid (**1a**) in water/acetonitrile (80/20) solution containing 0.1 M acetate buffer (pH=5.5) is shown in Fig. 1 curve a. As can be seen, one anodic (A_1) and its corresponding cathodic peak (C_1) was obtained, which correspond to the transformation of 2,5-dihydroxybenzoic acid (**1a**) to the related *p*-benzoquinone **2a** and *vice versa* within a quasi-reversible two-electron process. A peak current ratio (I_{pA1}/I_{pC1}) of nearly unity in the cyclic voltammogram can be considered as a criterion for a stable benzoquinone produced at the surface of electrode under the experimental conditions. In other words, any side reactions such as hydroxylation and/or dimerization reactions are too slow to be observed at the time scale of cyclic voltammetry.[17] The oxidation of 2,5-dihydroxybenzoic acid (**1a**) in the presence of **3** as a nucleophile was studied in some detail. Figure 1 (curve b) shows the cyclic voltammogram obtained for a 0.5 mM solution of **1a** in the presence of 0.5 mM **3**. The voltammogram exhibits one anodic peak A_1 and two cathodic peaks (C_1 and C_0). The second cycle in the cyclic voltammogram (Fig. 1, curve c) shows that, parallel to the decrease in current of A_1 and the shift of its potential in a positive direction, a new anodic peak

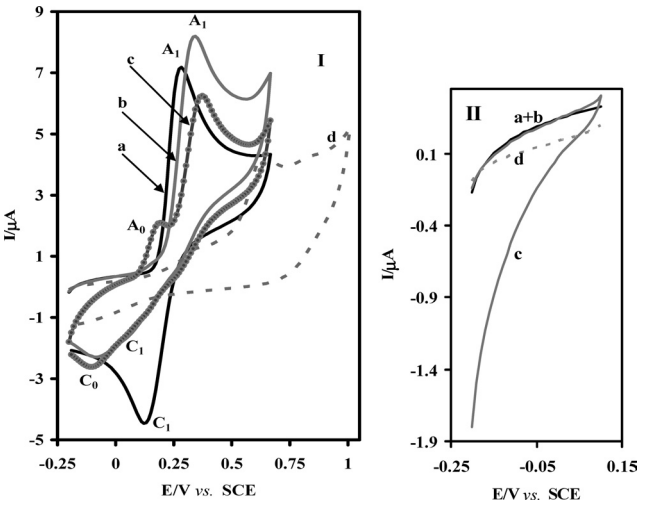

Fig. 1. Cyclic Voltammograms of (a) 0.50 mM 2,5-Dihydroxybenzoic Acid (**1a**), (b) 0.5 mM 2,5-Dihydroxybenzoic Acid, (**1a**) in the Presence of 0.5 mM 3-Hydroxy-1*H*-phenalene-1-one (**3**), the First Cycle, (c) 0.5 mM 2,5-Dihydroxybenzoic Acid in the Presence of 0.5 mM **3**, the Second Cycle and (d) 0.5 mM 3-Hydroxy-1*H*-phenalene-1-one (**3**) at a Glassy Carbon Electrode in Water/Acetonitrile (80/20) Solution Containing 0.1 M Acetate Buffer (pH=5.5). Scan rate: 100 mV s^{-1}; t=25±1 °C

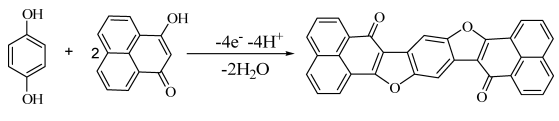

Chart 1

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(A_0) appears at less positive potential. The positive shift of the A_1 peak in the presence of **3** is probably due to the formation of a thin film of product at the surface of the electrode, inhibiting to a certain extent the performance of the electrode process. On the other hand, another important difference between these voltammograms, is related to the amounts of their currents at starting potential (−0.20 V *versus* SCE). The results show that the amount of current for curves a and b at starting potential is nearly zero, but curve c shows cathodic current at starting potential. This cathodic current is related to reduction of **6a**. In this Figure, curve d is the voltammogram of **3** in the same condition and in the absence of **1a**.

Also, it is seen that proportional to the augmentation of the potential sweep rate, parallel to the increase in the height of the C_1, the height of C_0 decreases. A similar situation is observed when the **3** to **1a** concentration ratio is decreased. A plot of peak current ratio (I_{pA1}/I_{pC1}) *versus* scan rate for a mixture of **1a** and **3**, appearing as an increase in the height of the cathodic peak C_1 at higher scan rates confirms the reactivity of **2a** towards **3**. On the other hand, the current function for the A_1 peak ($I_{pA1}/v^{1/2}$) decreases on increasing the scan rate. In addition, electrochemical oxidation of **1a** in the presence of **3** was studied at various pHs. The results indicate that, the peak current ratio (I_{pC1}/I_{pA1}) increases with decreasing pH. This can be related to protonation of **3** and inactivation of it towards Michael addition reaction with *p*-benzoquinone **2a**. This indicates that, the rate of coupling reaction is pH dependent and enhanced by increasing pH. On the other hand, in basic solutions and in the absence of **3**, the peak current ratio (I_{pC1}/I_{pA1}) is less than unity and decreases with increasing pH. This is related to the coupling of the anionic or dianionic forms of **1a** with *p*-benzoquinone **2a** (dimerization reaction). Therefore, in this study, solution containing 0.1 M acetate buffer (pH=5.5) has been selected for electrochemical study and synthesis of **1a** in the presence of **3**.

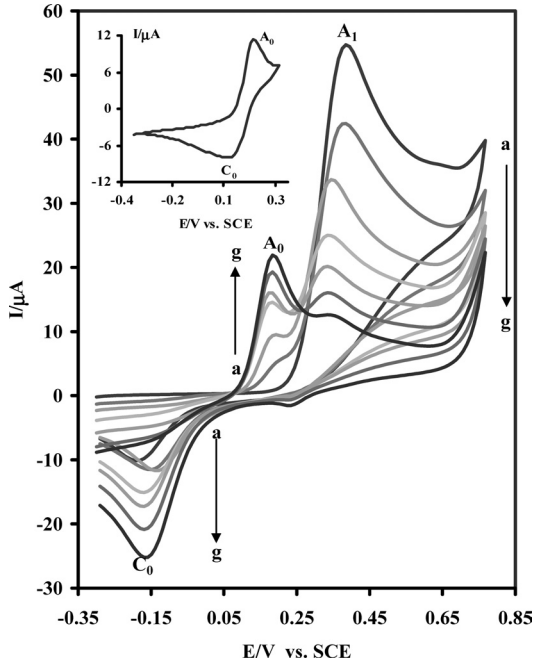

Fig. 2. Cyclic Voltammograms of 0.2 mmol 2,5-Dihydroxybenzoic Acid (**1a**) in the Presence of 0.2 mmol 3-Hydroxy-1*H*-phenalene-1-one (**3**) at a Glassy Carbon Electrode during Controlled Potential Coulometry at 0.35 V *versus* SCE. After consumption of (a) 0, (b) 10, (c) 20, (d) 32, (e) 42, (f) 52, and (g) 62 C. Scan rate: 100 mV s^{-1}

Controlled-potential coulometry was performed in water/acetonitrile (80/20) solution (60 ml) containing 0.2 M acetate buffer (pH=5.5), 0.2 mmol of **1a** and 0.2 mmol of **3** at 0.35 V *versus* SCE. The electrolysis progress was monitored using cyclic voltammetry (Fig. 2). It is shown that, proportional to the advancement of coulometry, the anodic peak A_1 decreases and A_0 increases. Anodic peak A_1 disappears when the charge consumption becomes about $4e^-$ per molecule of **1a**. These observations and the mass spectra of isolated product (*m*/*z*, 346), allow us to propose an ECE pathway in Chart 2 for the electrooxidation of **1a** in the presence of **3**. The existence of carboxylic group probably causes the Michael acceptor **2a** to be attacked by **3** at the A (C-6), B (C-4) or C (C-3) positions to yield three types of products in each case (Fig. 3) (Chart 2).

In this connection, the ^{1}H-NMR of product **6a** indicates that the coupling constants, *J*, for the two quinoneic peaks (7.05, 7.70 ppm) are 14 and 13 Hz respectively, which are in

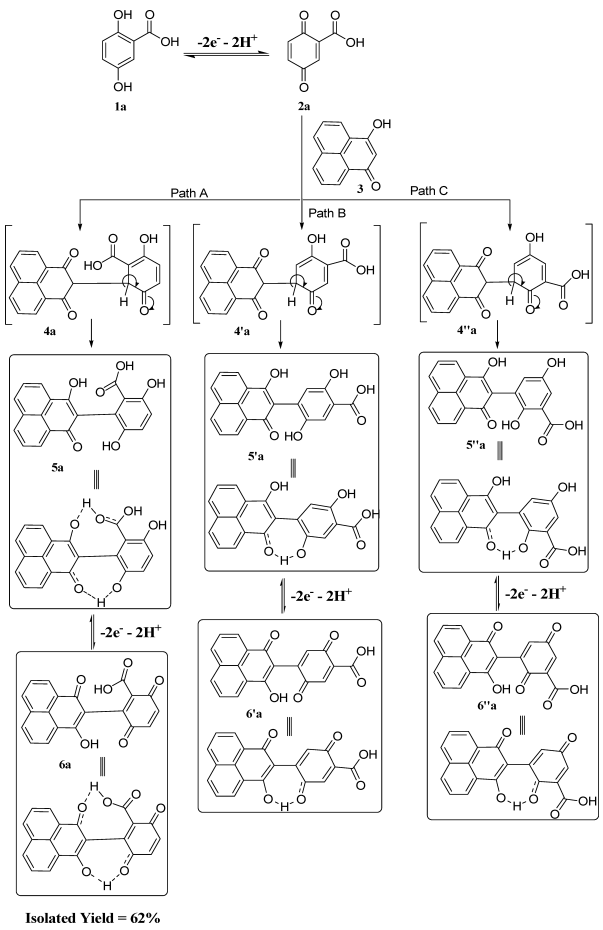

Chart 2

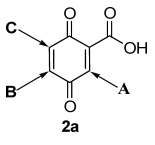

Fig. 3. The Structure of *o*-Benzoquinone **2a**

agreement with the existence of two protons in the quinone ring in the *ortho* position.[18] Therefore, according to the ^{1}H-NMR results we suggest that *p*-benzoquinone **2a** is attacked in the A (C-6) position by **3** leading to the formation of **6a** (path A).

According to our results, the anodic peaks of the voltammograms presented in Fig. 1 (A_1 and A_0) pertain to the oxidation of 2,5-dihydroxybenzoic acid (**1a**) and intermediate **5a** to the *p*-benzoquinones **2a** and **6a**, respectively. Obviously, the cathodic peak C_1 and C_0 are corresponding to the reduction of *o*-benzoquinone **2a** and **6a**, respectively.

In the present paper, we describe the preparation of a highly conjugated quinone derivative **6a** using electrooxidation of 2,5-dihydroxybenzoic acid (**1a**) in the presence of 3-hydroxy-1*H*-phenalene-1-one (**3**) as a nucleophile *via* an ECE electrochemical mechanism. We think that, electron-withdrawing effect of carboxyl group in one hand and formation of two intramolecular hydrogen bonding in intermediate **5a** and final product **6a**, on the other hand, causes *p*-benzoquinone **2a**, which is attacked in the A (C-6) position by **3** (path A). Also, contrary to previous cases (Chart 1),[17] *p*-benzoquinone **6a** (final product) is highly stabilized by two intramolecular hydrogen bonding, and remained in quinone form. The synthesis of **6a** has been performed using electrochemical oxidation of 2,5-dihydroxybenzoic acid in the presence of **3** in water/acetonitrile (80/20) solution (pH 5.5, 0.2 M acetate buffer) in a divided cell at a potential 0.35 V.

Electrochemical Study of 3,4-Dihydroxybenzaldehyde Electrochemical oxidation of dihydroxybenzaldehydes has been investigated in various solvents previously.[19—21] The electrochemical oxidation of 3,4-dihydroxybenzaldehyde (**1b**) in the presence of **3**, has been studied in water/acetonitrile (80/20) solution containing 0.10 M acetate buffer (pH 5.5). Figure 4 shows the voltammograms of 3,4-dihydroxybenzaldehyde (**1b**) in the presence of **3**. The anodic (A_1) and its cathodic counterpart (C_1) are corresponding to the transformation of 3,4-dihydroxybenzaldehyde (**1b**) to the related *o*-benzoquinone (**2b**) and *vice versa* within a *quasi*-reversible two-electron process.[19—21] Under these conditions, the cathodic counterpart of A_1 peak decreases. Anodic peak (A_0) which predominates at low scan rates could be indicative of the oxidation of a new compound produced from the consumption of **2b** in the course of following chemical reaction on the time scale of the experiment. This idea is supported by the fact that the peak current ratio, (I_{pA1}/I_{pC1}) decreases with increasing scan rate (Fig. 5) and the anodic current function, ($I_{pA1}/v^{1/2}$), decreases with increasing sweep rate. The multicyclic voltammetry of **1b** in the presence of **3** shows that parallel to the shift of the A_1 peak in a positive direction a new peak (A_0) appears at less positive potential in the second cycle (Fig. 4, 2nd. scan). Since the existence of a β-diketon type group, as an electrodonating group, on the catechol ring makes its oxidation easier, this new peak (A_0) is related to electrooxidation of intermediate **5b**. In this case, each molecule of **1b** in the presence of **3** converts to **8b**, *via* inter and intramolecular Michael addition reactions.

Controlled-potential coulometry was performed in water/acetonitrile (80/20) solution containing 0.2 M acetate buffer (pH=5.5), 0.1 mmol of **1b** and 0.1 mmol of **3** at 0.45 V *versus* SCE. The electrolysis progress was monitored using cyclic voltammetry (Fig. 6). It is shown that, proportional to the advancement of coulometry, the A_1 anodic peak decreases. All anodic and cathodic peaks disappear when the charge consumption becomes about 4e$^-$ per molecule of **1b**. Our experiences on electrochemical oxidation of catechols in the presence of nucleophiles,[12—17,19—21] diagnostic criteria of cyclic voltammetry, consumption of four electrons per molecule of **1b** and the mass spectra of isolated product (*m*/*z*, 330), indicate that the reaction mechanism of electrooxidation of **1b** in the presence of **3** is ECEC (Chart 3).

According to our results, it seems that the Michael addition reaction of **3** to *p*-benzoquinone **1b** (Chart 3, Eq. 2) is faster than other secondary reactions, leading to the intermediate **5b**. The oxidation of this compound (**5b**) is easier than

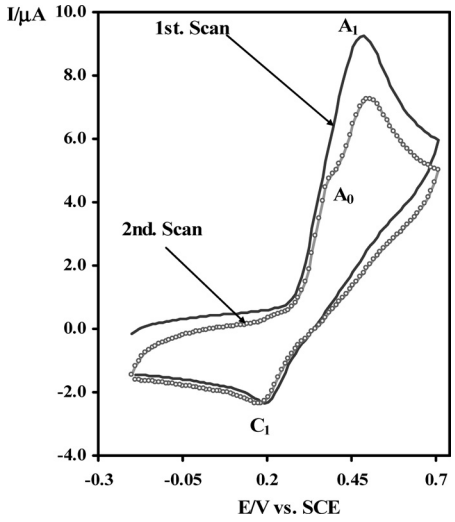

Fig. 4. First and Second Cyclic Voltammograms of 0.5 mM 3,4-Dihydroxybenzaldehyde (**1b**) in the Presence of 0.5 mM 3-Hydroxy-1*H*-phenalene-1-one (**3**) at a Glassy Carbon Electrode in Water/Acetonitrile (80/20) Solution Containing 0.1 M Acetate Buffer (pH=5.5). Scan rate: 100 mV s^{-1}; t=25±1 °C

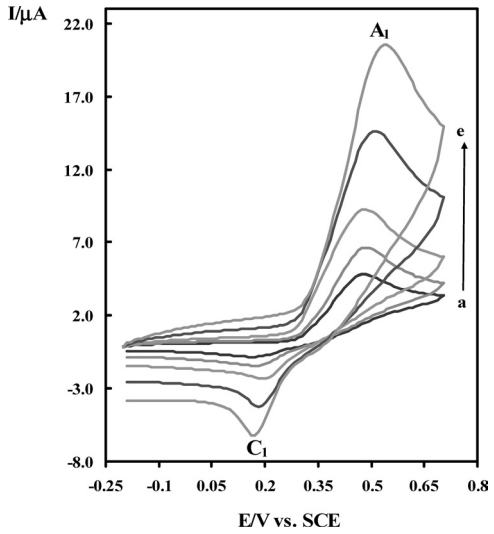

Fig. 5. Typical Voltammograms of 0.5 mM 3,4-Dihydroxybenzaldehyde (**1b**) in the Presence of 0.5 mM 3-Hydroxy-1*H*-phenalene-1-one (**3**) at a Glassy Carbon Electrode (1.8 mm Diameter), in Water/Acetonitrile (80/20) Solution Containing 0.1 M Acetate Buffer (pH=5.5) and at Various Scan Rates. Scan rates from (a) to (e) are 25, 50, 100, 250 and 500 mV s^{-1}, respectively

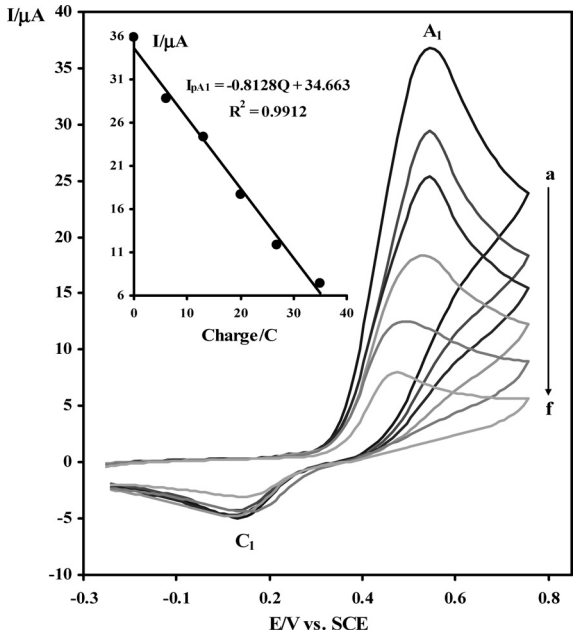

Fig. 6. Cyclic Voltammograms of 0.1 mmol 3,4-Dihydroxybenzaldehyde (**1b**) in the Presence of 0.1 mmol 3-Hydroxy-1*H*-phenalene-1-one (**3**) at a Glassy Carbon Electrode during Controlled Potential Coulometry at 0.45 V *versus* SCE. After consumption of (a) 0, (b) 6, (c) 13, (d), 20 (e) 27, and (f) 35 C. Scan rate 100 mV s^{-1}. Inset: variation of peak current (I_{pA1}) *versus* charge consumed. $t = 25 \pm 1$ °C

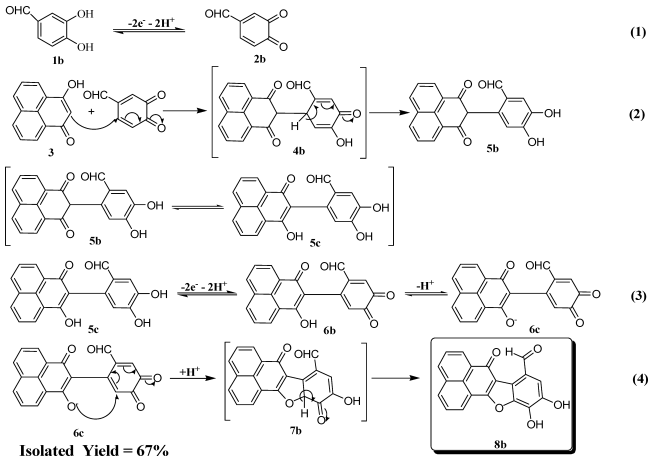

Chart 3

the oxidation of the parent-starting molecule (**1b**). The intramolecular reaction (Chart 3, Eq. 4), performed *via* a 1,6-addition reaction, leads to the formation of the final product **8b**. The reaction product **8b** can also be oxidized at a lower potential than the starting 3,4-dihydroxybenzaldehyde (**1b**). However, overoxidation of **8b** was circumvented during the preparative reaction because of the insolubility of product in the electrolysis media. The synthesis of **8b** has been performed using electrochemical oxidation of 3,4-dihydroxybenzaldehyde (**1b**) in the presence of **3** in water/acetonitrile (80/20) solution (pH 5.5, 0.2 M acetate buffer) in a undivided cell at a potential less than the 0.45 V.

Conclusions

The present results complete the previous reports on the anodic oxidation of some catechols and hydroquinones in the presence of 3-hydroxy-1*H*-phenalene-1-one (**3**).[17] We observed an interesting diversity in the mechanism (ECE, ECEC) of electrochemical oxidation of **1a** and **1b** in the presence of **3**. In the case of 2,5-dihydroxybenzoic acid (**1a**), the final product is a quinone derivative, whereas in the case of 3,4-dihydroxybenzaldehyde (**1b**), the final product (**8b**) is a dihydroxybenzofuran derivative that was obtained after intramolecular Michael addition reaction. Nature stability of *p*-quinone in comparison with *o*-quinone in one hand and stability of final product arising from two intramolecular hydrogen bonding, on the other hand, are responsible for remaining the final product in a quinone form. And finally, although the experiments were conducted on a relatively small scale, there is little difficulty in producing larger quantities either by using larger cells or by running several cells in series.

Experimental

Apparatus Cyclic voltammetry, controlled-potential coulometry and preparative electrolysis were performed using an Autolab model PGSTAT 20 potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disc (1.8 mm^2 area) and a platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and macroscale electrolysis was an assembly of four carbon rods (31 cm^2) and a large platinum gauze constituted the counter electrode. The working electrode potentials were measured *versus* SCE (all electrodes from AZAR Electrodes).

Reagents All chemicals (2,5-dihydroxybenzoic acid, 3,4-dihhydroxybenzaldehyde and 3-hydroxy-1*H*-phenalene-1-one) were reagent-grade materials. Sodium acetate, solvents and reagents were of pro-analysis. These chemicals were used without further purification.

Electro-Organic Synthesis of 6a and 8b In a typical procedure, 60 ml of acetate buffer solution (0.2 M, pH = 5.5) in water/acetonitrile (80/20) was pre-electrolyzed at 0.45 V *versus* SCE, then 0.20 mmol of **1a** or **1b** and 0.20 mmol of **3** were added to the cell. The electrolysis was terminated when the current decayed to 5% of its original value. The process was interrupted during the electrolysis and the carbon anode was washed in tetrahydrofuran (THF) in order to reactivate it. At the end of the electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in refrigerator overnight. The precipitated solid was collected by filtration and washed several times with water. After washing, products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and MS. The Faraday yields of **6a** and **8a** are more than 95% and the isolated yields of **6a** and **8a** after washing (in the case of **6a**) and recrystallization (in the case of **8a**, the crude product was purified by recrystallization from a mixture of THF/acetonitrile in room temperature) are 62 and 67%, respectively.

Characterization of Products 6a and 8b. (**6a**) ($C_{20}H_{10}O_6$): mp 125—127 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.05 (d, J = 14 Hz, 1H, quinone) and 7.70 (d, J = 13 Hz, 1H, quinone), 7.80—8.00 (m, 2H, aromatic), 8.30—8.60 (m, 4H, aromatic), 9.8 (broad, 1H, –COOH), 12.85 (broad, 1H, enol-OH). ^{13}C-NMR, (125 MHz, DMSO-d_6) δ: 112.6, 115.1, 115.7, 116.3, 119.6, 120.7, 125.4, 125.5, 127.0, 127.4, 129.1, 130.1, 132.0, 132.9, 135.3, 148.3, 151.3, 161.3, 167.5, 178.5. IR (KBr) cm^{-1}: 3408, 3062, 1690, 1630, 1608, 1550, 1460, 1418, 1379, 1226, 1105, 978, 903, 824, 779. MS (EI): *m*/*z* (relative intensity): 346 ($M^{+\cdot}$, 2.1), 330 (100), 313 (26.8), 286 (41.5).

(**8b**) ($C_{20}H_{10}O_5$): mp >230 °C (dec). IR (KBr) cm^{-1}: 3484, 3421, 1710, 1627, 1587, 1525, 1451, 1426, 1368, 1343, 1255, 1195, 1076, 893, 785. ^{1}H-NMR, δ ppm (300 MHz, DMSO-d_6) δ: 6.90 (s, 1H, aromatic), 7.87—8.78 (m, 6H aromatic), 9.56 (broad 1H, OH), 10.26 (broad 1H, OH), 11.33 (broad, 1H, aldehyde). MS (EI): *m*/*z* (relative intensity): 330 ($M^{+\cdot}$, 2.08), 302 (1.48), 196 (33.3), 163 (11.9), 126 (33.3), 87 (14.3), 63 (26.19), 44 (100).

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