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# Anodic Oxidation of Catechols in the Presence of 1,3-Indandione. A Green Electrosynthetic Approach to New Catechol Derivatives

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Efficient carbon–carbon bond-forming reaction at the 5- and 6-positions of catechol skeleton was achieved through anodic oxidation of catechol, 3-methylcatechol, and 4-methylcatechol in the presence of 1,3-indandione as a nucleophile. The electrochemical synthesis was carried out in aqueous solution, which is a green solvent, using cyclic voltammetry and controlled-current coulometry techniques. The results indicate that the electrogenerated benzoquinone from the electrooxidation of the corresponding catechol participates in a Michael addition reaction with 1,3-indandione. The mechanism of anodic oxidation was deduced from voltammetric and spectroscopic data. The galavanostatic electrochemical synthesis of compounds **2a**, **2b**, and **2c** was successfully performed in an undivided cell in good yield. The products were characterized by $^{1}$H NMR, $^{13}$C NMR, DEPT, FT-IR, and mass spectrometry.

Due to 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 ideal methodology is the development of organic reactions using electrolytic methods in aqueous media. Electrolytic 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 polyhydroxyphenols and some nucleophiles.[6] Among them, the interest in catechol has increased, not only because it is a model molecule for benzenediols compounds, such as dopamine and l-dopa, but also because it has important physiological functions and some pharmacological activities. An important pathway in the metabolism of catechol estrogens and catecholamines is the oxidation to their respective semibenzoquinones and benzoquinones.[7] The basic biological activity of catechol benzoquinones is related to their ability to act both as oxidants and electrophiles. As oxidants, catechol benzoquinones redox cycle with their semibenzoquinones, producing an elevated level of reactive oxygen species, a condition known as oxidative stress.[7] As electrophiles, benzoquinone that are produced can form covalent adducts with cellular macromolecules, including DNA.[8] These are stable adducts that remain in DNA unless removed by repair and depurinating ones, which are released from DNA by destabilization of the glycosyl bond. Thus, DNA can be damaged by reacting with themselves and by reacting with oxygen species (hydroxyl radicals).[7,8] The formation of depurinating adducts by catechol estrogens quinines reacting with DNA may be a major event in the initiation of breast and other human cancers.[8] The depurinating adducts are released from DNA, leaving purinic sites in the DNA that can generate mutations leading to cancer.[9,10]

It has been shown that *o*- and *p*-benzenediols can be oxidized electrochemically to *o*- and *p*-benzoquinones, respectively. The benzoquinones formed are quite reactive and are attacked by a variety of nucleophiles through a Michael addition reaction.[11] This reaction has been utilized for spectrophotometric determination of some *o*-benzoquinones.[12,13]

As part of our recent research, we have reported the Michael addition reaction of diethylamine and dibutylamine with electrogenerated *o*-benzoquinone.[14–16] Michael addition reactions represent one of the most important carbon–carbon bond-forming reactions in modern synthetic organic chemistry.[17]

To the best of our knowledge, less common is carbon–carbon bond-forming reaction arising from addition of carbon nucleophiles to oxidized catechol, although such reactions have great synthetic potential. Extending our interest in research on electrochemical oxidation of catechols in the presence of nitrogen nucleophiles, we became interested in understanding and exploiting oxidative carbon–carbon bond-forming reaction of catechols with 1,3-indandione.

We describe, herein, a new facile method for carbon–carbon bond formation between a catechol skeleton and 1,3-indandione as a diketone. In this present study, the anodic oxidation of catechol (CAT), 3-methylcatechol (3MCAT), and 4-methylcatechol (4MCAT) in the presence of 1,3-indandione in aqueous solution using cyclic voltammetry was demonstrated. Consequently, the electrochemical synthesis of catechols derivatives was performed in an undivided cell in good yield and purity and was characterized by $^{1}$H NMR, $^{13}$C NMR, DEPT, FT-IR, and mass spectrometry.

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## Experimental

**Chemicals and Apparatus.** All chemicals were reagent grade material. CAT was obtained from Fluka, and 4MCAT and 3MCAT were obtained from TCI (Japan) and were used without further purification. All solutions and subsequent dilutions were prepared using double-distilled water. All experiments were carried out in 0.15 M ($1\,M = 1\,mol\,dm^{-3}$) sodium acetate.

The voltammetric experiments were performed using an Autolab potentiostat & galvanostat (Eco Chemie, Netherlands) coupled with a Pentium IV personal computer with a standard three-electrode configuration. A glassy carbon disk (Metrohm, diameter 1.8 mm) served as working electrode; a platinum wire electrode was used as counter electrode with an Ag|AgCl|$KCl_{3M}$ reference electrode completing the cell assembly. The glassy carbon electrode was polished between each set of experiments with aluminum oxide powder on a polishing cloth. The working electrodes used in electro-organic synthesis was an assembly of three carbon rods (6 mm in diameter and 6 cm in length) and large platinum gauze served as counter electrode. All experiments were carried out at room temperature.

The FT-IR spectra (KBr) were determined on a Bruker spectrometer. $^1$H and $^{13}$C NMR spectra were measured on a Bruker DRX-300 Advance spectrometer at 300 and 75 MHz, respectively, using TMS as internal standard. Mass spectroscopic measurements were carried out on a Thermo Fingan spectrometer.

**Electrosynthesis of 2a, 2b, and 2c.** In a typical procedure, 100 mL of an aqueous solution containing 0.15 M sodium acetate as supporting electrolyte was pre-electrolyzed at 1.0 V vs. Ag|AgCl|$KCl_{3M}$ reference electrode in an undivided cell, then 1 mmol of **1a**, **1b**, or **1c** and 1 mmol of 1,3-indandione were added to the cell. Galvanostatic electrolysis was carried by applying a current density of $2\,mA\,cm^{-2}$, and the electrolysis was terminated after passing $2\,F\,mol^{-1}$ electricity. The electrodes were washed with the acetone several times during the electrolysis in order to remove any byproducts and to reactivate them. At the end of electrolysis, a few drops of acetic acid were added to the solution, and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and washed thoroughly with cold water. The precipitate was purified by column chromatography using ethyl acetate–hexane (50:50 V/V) as mobile phase. The products were characterized using $^1$H NMR, $^{13}$C NMR, DEPT, MS spectrometry, and FT-IR.

**Characterization of Products. 2a: 5*H*-Dibenzo[*a*,*d*]cycloheptene-5,10(11*H*)-dione ($C_{15}H_{10}O_4$):** Yield: 75%, mp 154–156 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.22 (s, 2H, methylene), 7.80 (d, $J = 4.5$ Hz, 1H, aromatic hydroquinone ring), 7.86–7.96 (m, 5H, aromatic + 1H–OH), 8.01 (d, $J = 4.5$ Hz, 1H, aromatic hydroquinone ring), 9.73 (s, 1H, –OH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 43.5, 123.1, 123.4, 123.6, 125.2, 129.7, 131.7, 134.2, 135.4, 135.5, 145.9, 155.6, 157.5, 209.8, 211.2. DEPT 135: $\delta$ 43.5, 123.1, 123.4, 123.6, 131.7, 134.2, 134.4. MS: $m/e$ (relative intensity): 254 ($M^+$, 45), 226 (52), 212 (38), 178 (63), 150 (77), 90 (52), 76 (89), 50 (52). FT-IR (KBr): 3395, 3295, 2954, 1696, 1525, 1450, 1262, 825 cm$^{-1}$.

**2b: 2-Methyl-5*H*-dibenzo[*a*,*d*]cycloheptene-5,10(11*H*)-dione ($C_{16}H_{12}O_4$):** Yield: 68%, mp 157–159 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.62 (s, 3H, methyl), 4.23 (s, 2H, methylene), 7.81 (t, $J = 4.5$ Hz, 1H, aromatic), 7.87 (s, 1H, aromatic hydroquinone ring), 7.90 (t, $J = 4.5$ Hz, 1H, aromatic), 8.00 (s, 1H, –OH), 8.02 (d, $J = 4.5$ Hz, 1H, aromatic), 8.08 (d, $J = 4.5$ Hz, 1H, aromatic), 9.74 (s, 1H, –OH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 30.9, 43.5, 123.1, 123.4, 123.6, 125.4, 131.7, 134.2, 135.4, 140.4, 141.3, 141.7, 145.9, 155.4, 201.1, 205.6. DEPT 135: $\delta$ 30.9, 43.5, 123.4, 123.6, 131.7, 134.2, 135.4. MS: $m/e$ (relative intensity): 269 ($M^+$, 100), 241 (75), 193 (42), 165 (85), 151 (44), 146 (25), 134 (42), 133 (45), 104 (20), 90 (35), 76 (62), 50 (36). FT-IR (KBr): 3385, 3274, 2956, 1656, 1585, 1252, 976, 785 cm$^{-1}$.

**2c: 1-Methyl-5*H*-dibenzo[*a*,*d*]cycloheptene-5,10(11*H*)-dione ($C_{16}H_{12}O_4$):** Yield: 55%, mp 160–161 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.63 (s, 3H, methyl), 4.23 (s, 2H, methylene), 7.80 (t, $J = 4.5$ Hz, 1H, aromatic), 7.85 (s, 1H, aromatic hydroquinone ring), 7.90 (t, $J = 4.5$ Hz, 1H, aromatic), 8.02 (d, $J = 4.5$ Hz, 1H, aromatic), 8.04 (s, 1H, –OH), 8.07 (d, $J = 4.5$ Hz, 1H, aromatic), 9.76 (s, 1H, –OH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 33.3, 47.5, 123.1, 123.4, 123.7, 125.6, 131.6, 134.2, 135.4, 140.4, 142.1, 142.6, 145.8, 155.4, 200.4, 202.2. DEPT 135: $\delta$ 33.3, 47.5, 123.4, 123.7, 131.6, 134.2, 135.4. MS: $m/e$ (relative intensity): 269 ($M^+$, 69), 241 (67), 227 (35), 193 (100), 165 (25), 151 (25), 151 (25), 146 (37), 134 (45), 133 (56), 104 (44), 90 (95), 76 (46), 50 (16). FT-IR (KBr): 3326, 3217, 2952, 1682, 1576, 1487, 1265, 825 cm$^{-1}$.

## Results and Discussion

**Electrochemical Oxidation of Catechols in the Presence of 1,3-Indandione.** Cyclic voltammogram of 1.0 mM CAT (Fig. 1a) in aqueous solution containing 0.15 M sodium acetate as the supporting electrolyte showed one anodic peak ($A_0$) at 0.232 V and a corresponding cathodic peak ($C_0$) at 0.142 V, which corresponds to the transformation of CAT to *o*-benzoquinone (BQ) and vice versa (Scheme 1) within a quasireversible two-electron process (Fig. 1a). A peak current ratio ($I_p(C_0)/I_p(A_0)$) of nearly unity, particularly during the repetitive recycling of the potential, is considered to be a criterion for the 4MBQ produced at the surface of electrode under the experimental conditions. This result shows that hydroxylation or dimerization is too slow to be observed on the time scale of experiment.[18–21] The oxidation of CAT in the presence of 1,3-indandione as nucleophile was studied in some details. Figure 1b shows the cyclic voltammogram obtained for a 1.0 mM solution of CAT in the presence of 1.0 mM 1,3-indandione. The voltammogram showed only one anodic peak ($A_0$) at 0.418 V, and the corresponding cathodic peack was not

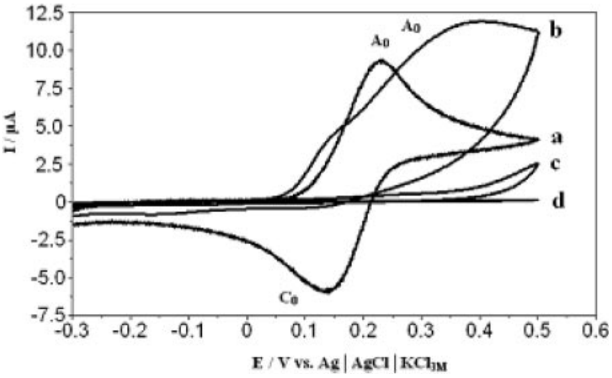
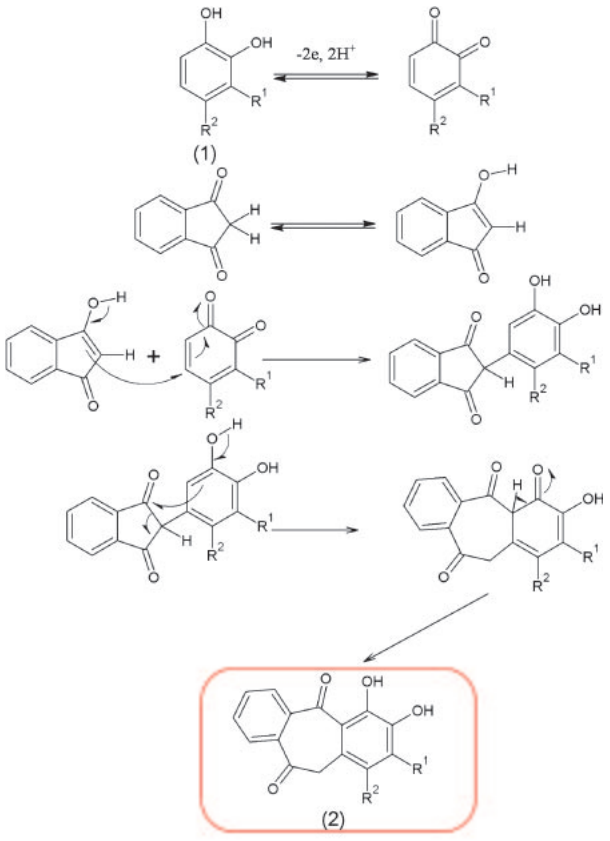


Fig. 1. Cyclic voltammograms of 1.0 mM CAT in the absence (a) and in the presence of 1.0 mM 1,3-indandione (b) at scan rate of $50\,mV\,s^{-1}$ in water (0.15 M sodium acetate) at the surface of GC electrode. Voltammograms (c) and (d) represent the electrochemical behavior of 1,3-indandione and pure buffer solution.



1a, 2a $R^1=R^2=H$
1b, 2b $R^1=CH_3$, $R^2=H$
1c, 2c $R^1=H$, $R^2=CH_3$

Scheme 1. Proposed mechanism for anodic oxidation of CAT, 3MCAT, and 4MCAT in the presence of 1,3-indandione in aqueous solution.

observed. The anodic shift in $A_0$ in the presence of 1,3-indandione (Fig. 1b) is probably, because of 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.[22,23] In Fig. 1, curves c and d are the voltammograms of 1,3-indandione and pure supporting electrolyte in this range of potential.

Similar behavior was observed for the electrochemical oxidation of 3MCAT and 4MCAT in the presence of 1,3-indandione; however, electrooxidation of these two compounds occurred at a more negative potential compared to that of CAT. This shift in oxidation potential can be explained easily considering electron-donating characteristics of the methyl group.

**Effect of 1,3-Indandione Concentration on the Cyclic Voltammetric Response of the Catechols.** The effect of 1,3-indandione concentration on the cyclic voltammograms of CAT, 4MCAT, and 3MCAT was studied. Figure 2A shows cyclic voltammograms of a 1.0 mM solution of 3MCAT in the presence of different concentrations of 1,3-indandione. As can be seen in Fig. 2A(b), 3MCAT in the presence of 0.5 mM of 1,3-indandione, exhibited an anodic peak ($A_0$) at 0.203 V in the forward potential scan and a clear corresponding cathodic peak ($C_0$) at 0.066 V in the reverse potential scan. It can be deduced from the $(I_p(C_0)/I_p(A_0)) = 0.7$ that at a low concentration ratio of 1,3-indandione to 3MCAT (1:2), the nucleophilic attack of 1,3-indandione to 3MBQ does not occur to a great extent. The $C_0$ current decreased with an increase in the concentration of 1,3-indandione from 0.5 to 3.0 mM. Using these voltammograms, $I_p(C_0)/I_p(A_0)$ was extracted and plotted versus the 1,3-indandione concentration (Fig. 2B). These results indicate that the nucleophilic attack of 1,3-indandione to 3MBQ increases with an increase in the concentration of 1,3-indandione. The dependence $I_p(C_0)/I_p(A_0)$ on the 1,3-indandione concentration shows the dependence of f chemical reaction rate on the 1,3-indandione concentration.

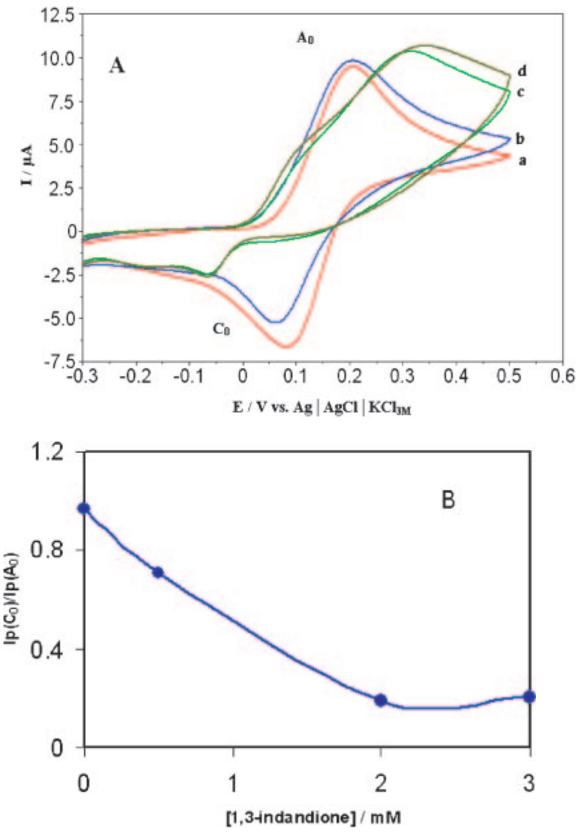


Fig. 2. (A) Cyclic voltammograms of 1.0 mM of 3MCAT in the presence of various concentrations of 1,3-indandione: (a) 0 mM, (b) 0.5 mM, (c) 2.0 mM, and (d) 3.0 mM. Scan rate is 50 mV $s^{-1}$, and solution similar to that was in Fig. 1. (B) Plot of $I_p(C_0)/I_p(A_0)$ versus 1,3-indandione concentration.

**The Effect of Scan Rate on Cyclic Voltammetry Response of Catechols in the Presence of 1,3-Indandione.** The effect of potential scan rate on electrochemical behavior of CAT, 3MCAT, and 4MCAT in the presence of 1,3-indandione was also studied. Figure 3 shows the cyclic voltammograms obtained for a 1.0 mM 3MCAT in the presence of 1.0 mM of 1,3-indandione at different potential scan rates. As the scan rate increased, the height of $C_0$ increased. The current function for $A_0$, $I_p(A_0)/v^{1/2}$, decreased as the scan rate increased (Fig. 3B). On the other hand, a plot of $I_p(C_0)/I_p(A_0)$ versus the scan rate, indicates that as the scan rate increases, nucleophilic attack of 1,3-indandione to 3MBQ decreases.

Considering the above results, in order to elucidate the structure of the products obtained, a general pathway for the reaction leading to the major products in the electrooxidation

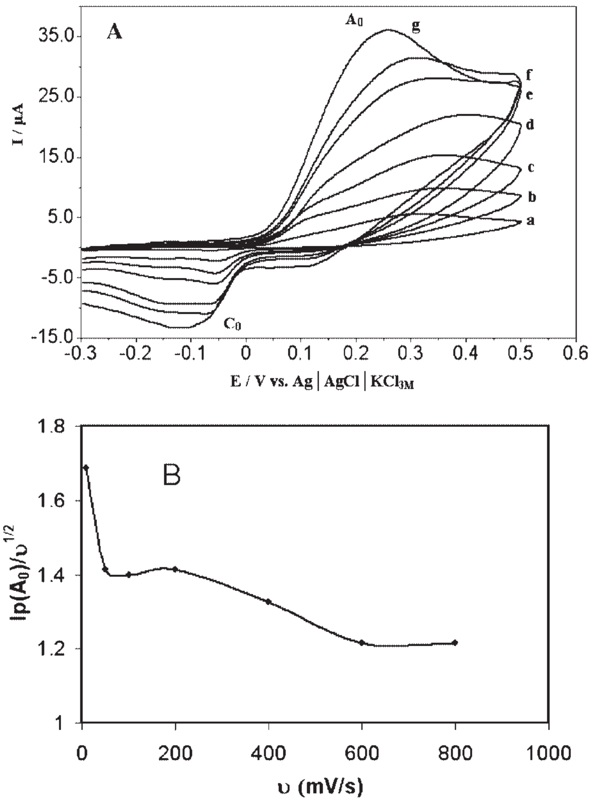


Fig. 3. (A) Cyclic voltammograms of 1.0 mM of 3MCAT in the presence of 1 mM of 1,3-indandione at various scan rates: (a) 10, (b) 50, (c) 100, (d) 200, (e) 400, (f) 600, and (g) 800 mV s$^{-1}$. (B) ($I_p(A_0)/v^{1/2}$) versus the scan rate.

of CAT, 3MCAT, and 4MCAT in the presence of 1,3-indandione is illustrated in Scheme 1 from the viewpoint of an EC mechanism. According to the structure of the products, which has been characterized by spectroscopic data, it seems that first 1,3-indandione attacks the electrogenerated *o*-benzoquinone through a Michael addition reaction to form intermediate 3, which then attacks the carbonyl group through hydroquinone ring at the ortho position to form the final product. Tabaković et al. have been studied anodic oxidation of catechol in the presence of some nucleophiles such as 1,3-indandione; however, they have identified a different product.[24,25] Because it is very difficult to distinguish between two products considering only IR and MS spectrometry data, taking into account other spectroscopic data, such as $^{1}$H NMR, $^{13}$C NMR, and especially DEPT NMR (negative peak at 43 or 47.5 ppm), it was deduced that the product had a –CH$_2$– (methylene group) group, which is in accordnce with the identified structure.

## Conclusion

In conclusion, we described an efficient carbon–carbon bond-forming reaction at the 5- and 6-positions of a catechol skeleton in water which is a green solvent. Based on the results CAT, 3MCAT, and 4MCAT are oxidized in aqueous solution to their respective *o*-benzoquinones. The benzoquinones are then attacked by 1,3-indandione through a Michael addition reaction. The overall reaction mechanisms for anodic oxidation of CAT, 3MCAT, and 4MCAT in the presence of 1,3-indandione as nucleophile was presented. The galvanostatic electrolysis of catechols was carried out in the presence of 1,3-indandione in an undivided cell, and the products **2a**, **2b**, and **2c** were obtained in high yield. The product yield order was **3a** > **3b** > **3c** can be explained by the steric factor of the methyl group on the catechol ring.

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