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Electrochemical oxidation of catechol in the presence of indole: a facile and one-pot method for the synthesis of trisindolyl-*o*-benzoquinone

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Abstract

The electrochemical oxidation of catechol has been studied in the presence of indole as the nucleophile in water/acetonitrile (50:50) using cyclic voltammetry and controlled-potential coulometry methods. The results revealed that the quinone derived from the oxidation of catechol participates in Michael addition reactions with indole, and via a novel ECECECE mechanism, converts it to the trisindolyl-*o*-quinone in a good yield via electrochemical oxidation under controlled-potential conditions without any toxic reagents at the carbon electrode in a two-compartment cell.

Keywords: ECECECE mechanism; Electrochemical oxidation; Michael addition; Indole; Catechol; 3,4,5-Tri(1*H*-indol-3-yl)cyclohexa-3,5-diene-1,2-dione

It has been found that indolyldihydroxyquinones serve as useful lead molecules for drug discovery and for further cell-based studies on the role of Cdc25s in cell cycle control.[1] Also it is recognized that the 3-indolylbenzoquinone fragment is a core structure in a number of biologically active natural products such as asterriquinones.[2] The asterriquinones and demethylasterriquinones exhibit a wide spectrum of biological activities including antitumor properties, and are inhibitors of HIV reverse transcriptase.[3] Asterriquinone A1, has been shown to arrest the cell cycle in G1 and promote apoptotic cell death.[4] Bis-indolylquinones exhibit a range of biological activities against cancer and diabetes.[5] These compounds have been isolated from a wide range of fungi, including *Aspergillus terreus*, *Chaetomium* sp., and *Pseudomassaria* sp.[6] All these properties apparently stem from the ability of asterriquinones to either promote or prevent protein–protein interactions. The importance of these compounds has motivated many workers to synthesize a number of them, and numerous methods have been developed for their preparation.[1,7] A literature survey reveals that, in contrast to the widely studied, mono and bisindolyl-*p*-quinones, no paper has reported the synthesis of a trisindolyl-*o*-quinone (Fig. 1). To the best of our knowledge, there is no report on the preparation of trisindolyl-*o*-quinone through electrochemical routes.

Following our experience in electrochemical oxidation of catechols in the presence of nucleophiles,[8] we envisaged that the attachment of an *o*-quinone ring to an indole might cause an enhancement of pharmaceutical properties and medicinal activities. This idea prompted us to investigate the electrochemical oxidation of catechol in the presence of indole as the nucleophile and we have discovered an easy and one-pot electrochemical method for the synthesis of 3,4,5-tri(1*H*-indol-3-yl)cyclohexa-3,5-diene-1,2-dione (**8a**) in high yield and purity, using this environmentally friendly method with high atom economy.

The cyclic voltammogram of 1 mM catechol (**1**) in water/acetonitrile (50:50) solution shows one anodic peak (A_1) at 0.37 V and the corresponding cathodic peak at

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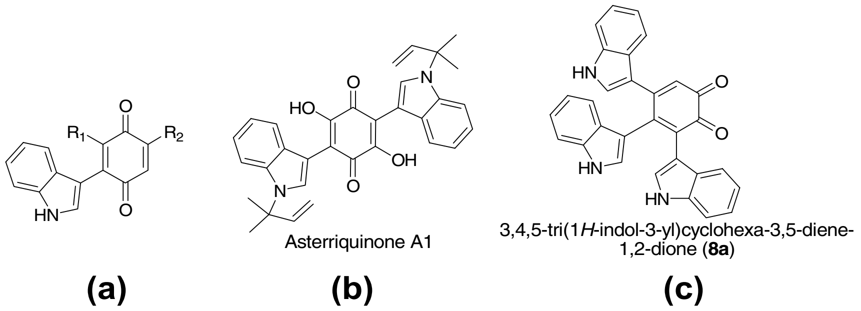


Fig. 1. Structures of mono (**a**), bis (**b**), and trisindolylquinones (**c**).

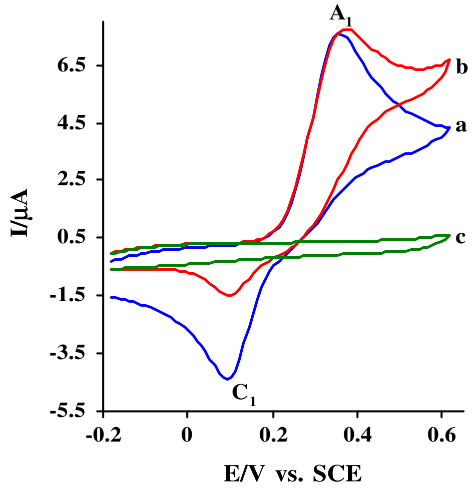


Fig. 2. Cyclic voltammograms of (a) 1 mM catechol (**1**) in the absence of indole, (b) 1 mM catechol (**1**) in the presence of 20 mM of indole (**2**), and (c) 20 mM indole in the absence of catechol at a glassy carbon electrode in water/acetonitrile (50:50) solution containing acetate buffer ($c = 0.2$ M, pH 5). Scan rate: 25 mV s^{-1}; $t = 25 \pm 1$ °C.

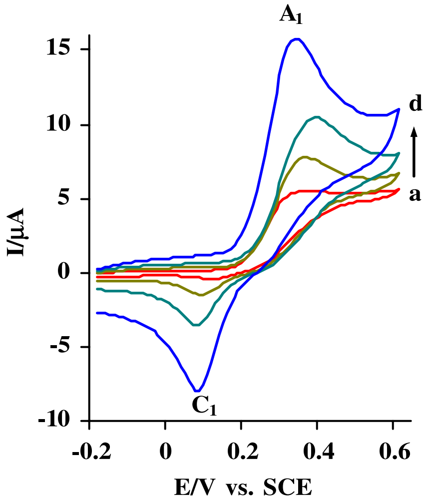


Fig. 3. Typical cyclic voltammograms of 1 mM catechol (**1**) in the presence of 20 mM indole (**2**) in water/acetonitrile (50:50) solution containing acetate buffer ($c = 0.2$ M, pH 5) at a glassy carbon electrode and at various scan rates. Scan rates from (a) to (d) are 10, 25, 50, and 100 mV s^{-1}, respectively; $t = 25 \pm 1$ °C.

0.08 V, which correspond to the transformation of catechol (**1**) to *o*-benzoquinone (**1a**) and vice versa within a quasi-reversible two electron process (Fig. 2 curve a). A peak current ratio (I_p^{C1}/I_p^{A1}) of nearly unity, particularly during the repetitive recycling of the potential, can be considered as a criterion for the stability of the *o*-benzoquinone (**1a**) produced at the surface of the electrode under the experimental conditions.[8] The oxidation of catechol (**1**) in the presence of indole (**2**) as a nucleophile was studied in some detail. In Figure 2, curve b shows the cyclic voltammogram obtained for a 1 mM solution of **1** in the presence of 20 mM of indole (**2**). The votammogram exhibits the same anodic peak (A_1), whereas, the cathodic counterpart of the anodic peak (A_1) decreases. In Figure 2, curve c shows the cyclic voltammogram of indole.

Furthermore, it is seen that, proportional to the increase in the potential sweep rates the height of C_1 increases (Fig. 3 curves a–d). In other words, the peak current ratio (I_p^{C1}/I_p^{A1}) versus scan rate for a mixture of catechol (**1**) and indole (**2**) increases with increasing scan rate. A similar situation is observed when the indole (**2**) to **1** concentration ratio is decreased (Fig. 4).

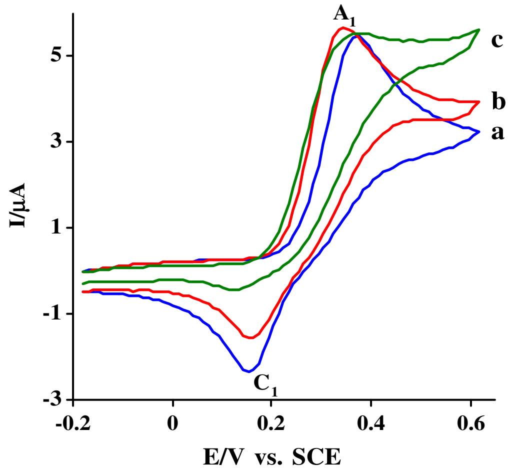
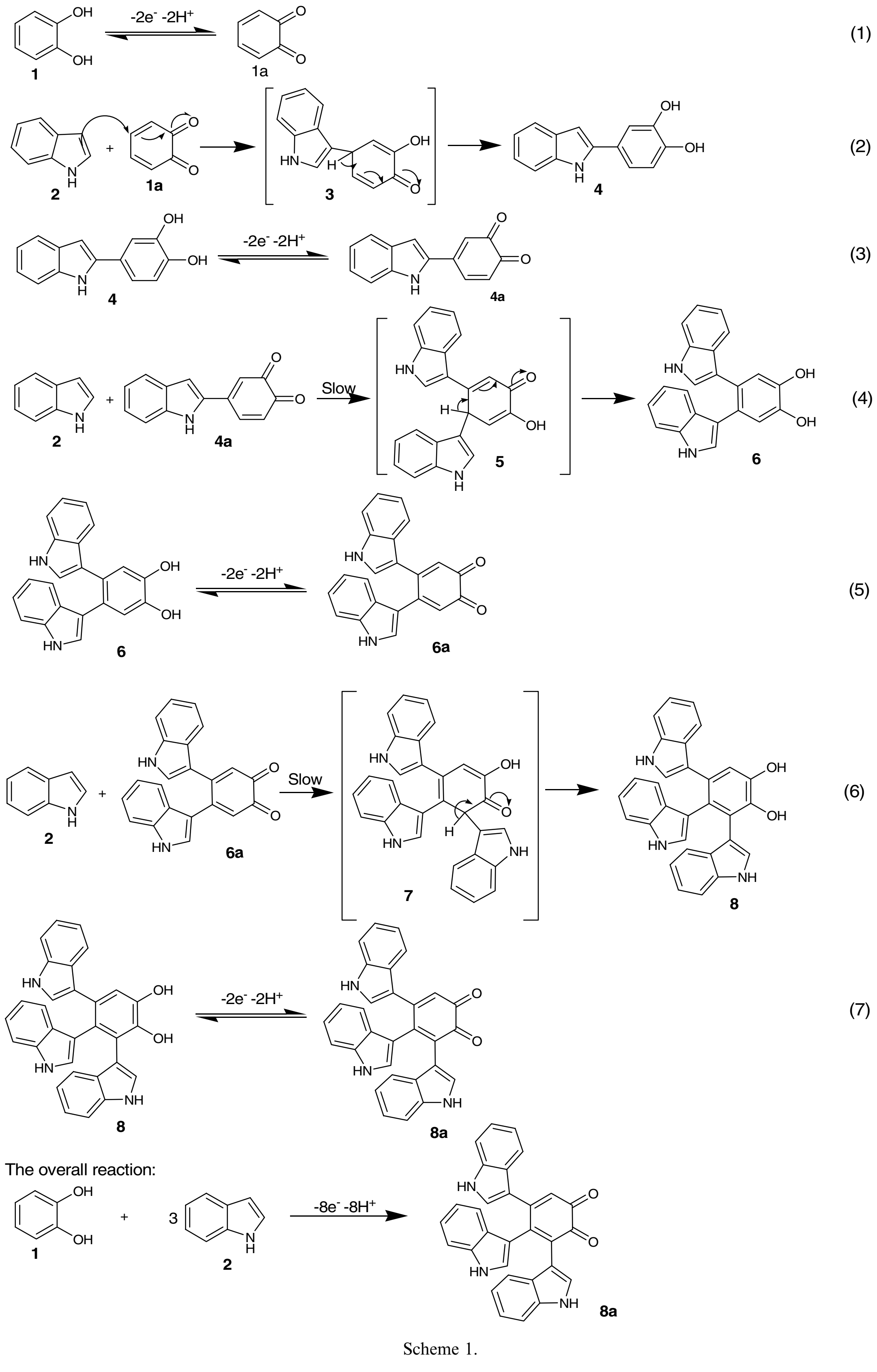
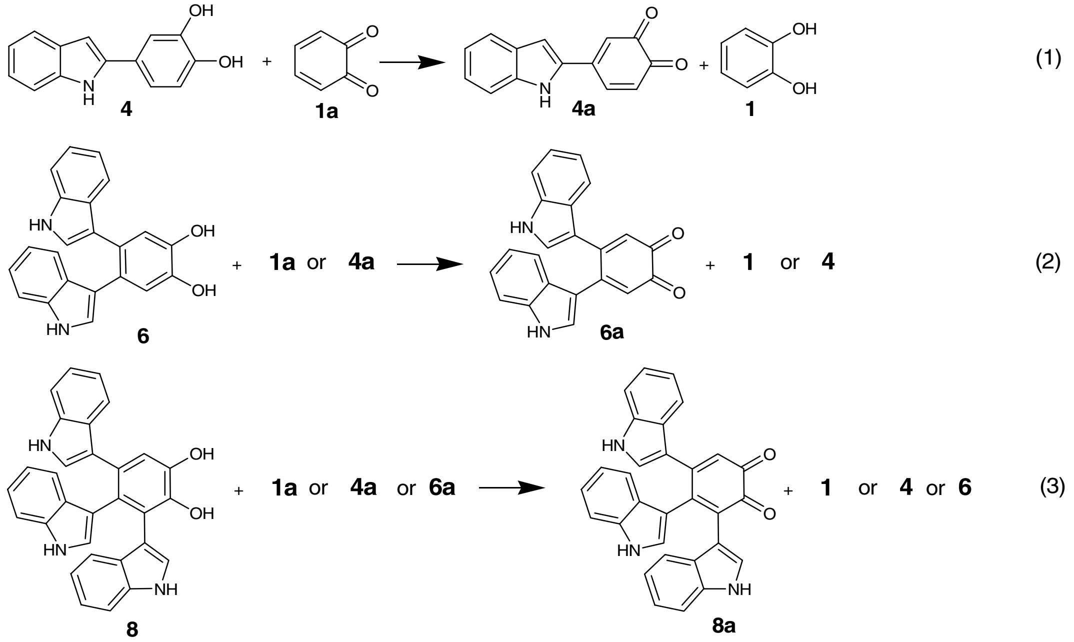


Fig. 4. Cyclic voltammograms of 1 mM catechol (**1**) in the presence of various amounts of indole (**2**) in water/acetonitrile (50:50) solution containing acetate buffer ($c = 0.2$ M, pH = 5) at a glassy carbon electrode. Concentrations of indole from (a) to (c) are 1, 5, and 20 mM, respectively. Scan rate: 10 mV s^{-1}; $t = 25 \pm 1$ °C.

Controlled-potential coulometry was performed in a water/acetonitrile (50:50) solution, containing 0.25 mmol of catechol (**1**) and 0.75 mmol of indole (**2**) at 0.40 V versus the SCE. The electrolysis progress was monitored using cyclic voltammetry. It was shown that, proportional to the advancement of coulometry, the anodic peak A_1 and



Scheme 1.



Scheme 2.

the cathodic peak C_1 decreased. The anodic and cathodic peaks disappeared when the charge consumption became about 8e$^-$ per molecule of **1**.

Diagnostic criteria of cyclic voltammetry, the consumption of eight electrons per molecule of catechol (**1**), and the mass spectra of the isolated products, indicated that the reaction mechanism of electrooxidation of catechol (**1**) in the presence of indole (**2**) is ECECECE ('E' represents an electron transfer at the electrode surface, and 'C' represents a homogeneous chemical reaction) (Scheme 1). According to our results, it seems that the Michael addition reaction of **2** to *o*-benzoquinone (**1a**) (Eq. 2) is faster than other side reactions and leads to intermediate **4**. The oxidation of compound **4** is easier than the oxidation of catechol (**1**) by virtue of the presence of an electron-donating group (Eq. 3). In the next step, *o*-quinone **4a**, via a Michael reaction, is converted to intermediate **6** (Eq. 4). Another oxidation (Eq. 5) and Michael addition (Eq. 6) transforms intermediate **6** to intermediate **8**. Further oxidation converts intermediate **8** into the final product **8a**.

Accordingly, the anodic peak A_1 pertains to the oxidation of catechol **1** to the *o*-benzoquinone **1a**. Obviously, the cathodic peak C_1 corresponds to the reduction of the *o*-benzoquinone **1a**. The presence of electron-donating group(s) on *o*-quinones **4a** and **6a** reduced the reactivity of these *o*-quinones toward Michael reactions, so the rate of reactions (Eqs. 4 and 6) are low and the effects of these reactions are not observed because of the time scale of the cyclic voltammograms obtained and the times of these chemical reactions are not comparable. However, in controlled-potential coulometry with a longer time scale, the effect of these reactions is observed as an increase in the number of electrons per molecule ($n = 8$). In addition, it is possible that the oxidation of intermediates **4**, **6**, and **8** takes place through solution electron transfer (SET) reactions (Scheme 2).

Electroorganic synthesis of **8a**: In a typical procedure, 80 ml of an acetate buffer solution ($c = 0.2$ M, pH 5) in water/acetonitrile (50:50) was pre-electrolyzed at 0.40 V versus the SCE in a two-compartment cell, and then 1 mmol of catechol (**1**) and 3 mmol of indole (**2**) were added to the cell. The electrolysis was terminated when the current decayed to 5% of its original value. The process was interrupted during electrolysis and the graphite anode was washed with acetone to reactivate it. At the end of electrolysis, to achieve better precipitation, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The solid precipitated was collected by filtration and was washed several times with water. The isolated yield of 3,4,5-tri(1*H*-indol-3-yl)cyclohexa-3,5-diene-1,2-dione (**8a**) was 68%, mp = 284–286 °C (dec). IR (KBr): ν (cm^{-1}) = 3399, 3057, 1736, 1704, 1613, 1559, 1458, 1417, 1365, 1229, 744. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.43 (s, 1H, quinone ring), 7.00–8.52 (m, 12H, aromatic), 10.14 (br, 1H, –NH), and 10.95 (br, 2H, –NH). MS (EI): *m*/*z* (relative intensity): 453 [M]$^+$. (100), 435 (23), 338 (24), 217 (19). Anal. Calcd for $C_{30}H_{19}N_3O_2$; C 79.45; H 4.22; N 9.27. Found: C 79.68; H 4.01; N 9.49.

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