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# A facile electrochemical method for the synthesis of phenazine derivatives via an ECECC pathway

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ABSTRACT

Electrochemical oxidation of 2,3-dimethylhydroquinone **1** has been studied in the presence of *o*-phenylenediamines **3a–c** as nucleophiles in aqueous solution, using cyclic voltammetry and controlled potential coulometry. The results indicate that the quinone **2** derived from 2,3-dimethylhydroquinone participates in Michael addition and imine condensation reactions with *o*-phenylenediamine via an ECECC mechanism, and is converted to the corresponding phenazine derivatives **7a–c** and **7′b**. The electrochemical synthesis of compounds **7a–c** and **7′b** has been performed successfully at a carbon rod electrode in an undivided cell with good yields and high purities.



Nitrogen-containing heterocycles are abundant in Nature and exhibit diverse and important biological properties.[1] Phenazine derivatives are an important class of nitrogen-containing heterocycles which exhibit a wide range of biological activities.

A classic method for the synthesis of phenazine is via the reaction of nitrobenzene and aniline using the Wohl–Aue reaction.[2] The phenazine may be obtained by distilling the barium salt of azobenzoate by passing aniline vapor over lead oxide[3] or by the oxidation of dihydrophenazine, which is prepared by heating pyrocatechin with *o*-phenylenediamine. It can also be formed when *o*-aminodiphenylamine is distilled over lead peroxide. Many phenazine compounds are found in Nature and are produced by bacteria such as *Pseudomonas* spp, *Streptomyces* spp, and *Pantoea agglomerans*. These phenazine natural products have been implicated in the virulence and competitive fitness of the parent organisms.[4] These compounds show numerous biological activities such as antibacterial, antifungal, antiviral, and antitumor properties.[5,6]

Regarding the importance of phenazine derivatives in biological systems and following our previous work[7–14] in this area, we report a simple electrochemical method for the synthesis of several novel phenazine derivatives from 2,3-dimethylhydroquinone **1** and *o*-phenylenediamines **3a–c** in excellent yields.

A cyclic voltammogram of a solution of 1.0 mM 2,3-dimethylhydroquinone **1** in water/acetonitrile (85/15) containing phosphate buffer (pH 7, $c = 0.2$ M) shows one anodic peak ($A_1$) and the corresponding cathodic peak ($C_1$), which represent the transformation of **1** to 2,3-dimethyl-*p*-benzoquinone **2** and vice versa within a quasi-reversible two-electron process[15] (Fig. 1, curve a, Scheme 1). A peak current ratio ($Ip^{C1}/Ip^{A1}$) of nearly unity, particularly during recycling of the potential, can be considered as a criterion for the stability of 2,3-dimethyl-*p*-benzoquinone **2** produced at the surface of the electrode under the experimental conditions. Thus, any side reactions such as hydroxylation,[16] dimerization,[17] or

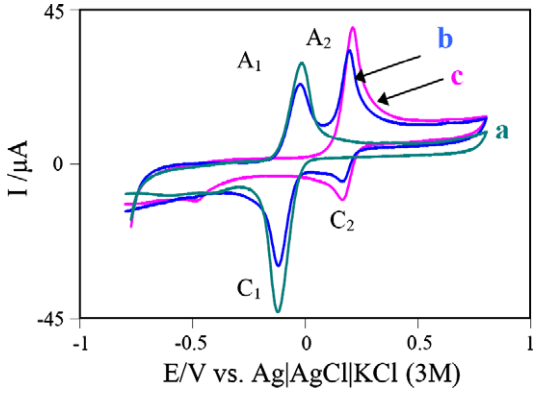


**Figure 1.** Cyclic voltammograms of (a) 1 mM of **1**, (b) 1 mM of **1** in the presence of 1 mM of **3a**, and (c) 1 mM of **3a**, at a glassy carbon electrode (1.8 mm diameter) in water/acetonitrile (85/15) containing phosphate buffer (pH 7, $c = 0.2$ M); scan rate = 100 mV $s^{-1}$; room temperature.

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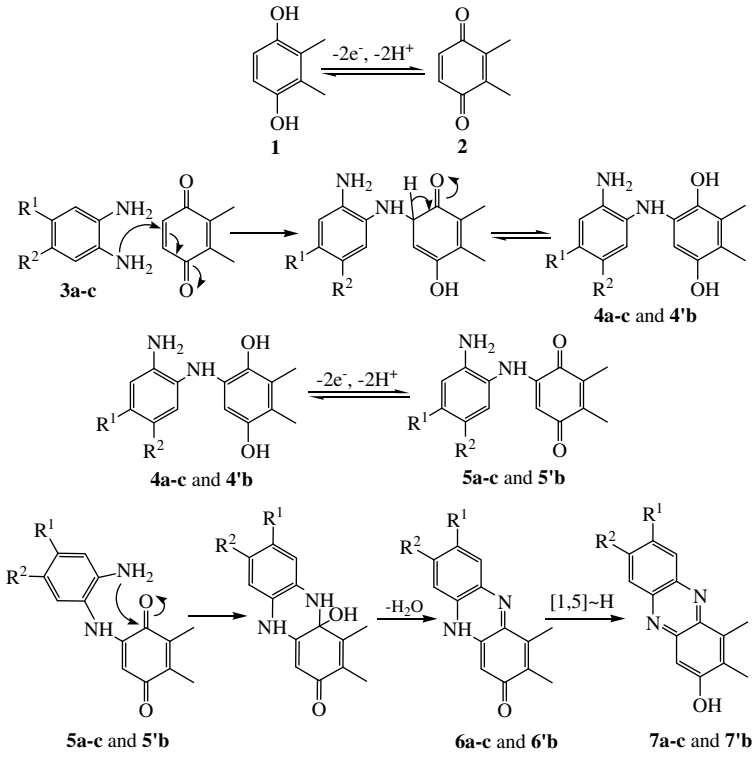



**Scheme 1.** Proposed mechanism for the electrooxidation of 2,3-dimethylhydroquinone in the presence of *o*-phenylenediamines.

radical formation[18–20] are too slow to be observed on the time scale of cyclic voltammetry. The oxidation of 2,3-dimethylhydroquinone **1** in the presence of 3,4-dimethyl-*o*-phenylenediamine **3a** was studied in detail. The cyclic voltammogram obtained for a 1.0 mM solution of **1** in the presence of 1 mM 3,4-dimethyl-*o*-phenylenediamine **3a** is shown in Figure 1 (curve b). The voltammogram exhibits two anodic peaks ($A_1$ and $A_2$) and their relative cathodic peaks ($C_1$ and $C_2$), respectively. The $A_2$ and $C_2$ peaks correspond to 3,4-dimethyl-*o*-phenylenediamine. A comparison of the $C_1$ peaks in the absence and presence of **3a** shows a decrease in current of this peak for the latter. This indicates the reactivity of electrochemically generated *p*-benzoquinone **2** toward **3a**. In this figure, curve c is the voltammogram of **3a** in the absence of **1**.

Multicyclic voltammetry of **1** in the presence of **3a** shows that, in the second and third cycles, parallel to the shift of the $A_1$ peak in a positive potential direction, a new peak ($A_0$) appears (Fig. 2). This new peak is related to electrochemical oxidation of intermediate **4a** (Scheme 1). The positive shift of the $A_1$ peak in the presence of 3,4-dimethyl-*o*-phenylenediamine is due to the formation of a thin film of product on the surface of the electrode, which inhibits, to a certain extent, the performance of the electrochemical process.

Controlled-potential coulometry were performed in water/acetonitrile (80/20) containing 0.2 M phosphate buffer (pH 7), 0.5 mmol of **1**, and 0.5 mmol of **3a** at 0.15 V versus Ag/AgCl/KCl (3 M). All the anodic and cathodic peaks disappeared when the charge consumption was about 4e$^-$ per molecule of **1**.

The fluorescence spectra of **7a** were recorded in chloroform. Figure 3 shows the fluorescence of **7a** when excitation wavelengths $\lambda$ = 263.5 nm and 375.5 nm were used. These spectra show that **7a** exhibits good photoluminescence (PL).

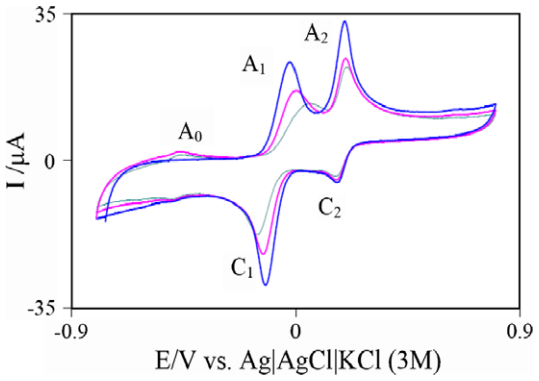



**Figure 2.** Multicyclic voltammograms of 1 mM 2,3-dimethylhydroquinone **1** in the presence of 1 mM 3,4-dimethyl-*o*-phenylenediamine **3a**, at a glassy carbon electrode (1.8 mm diameter) in water/acetonitrile (85/15) containing phosphate buffer (pH 7, *c* = 0.2 M); scan rate = 100 mV s$^{-1}$; room temperature.

The spectroscopic data ($^1$H and $^{13}$C NMR spectra, molecular mass, elemental analysis) supported the structure and aromaticity of **7a**, which is yellow in color. These observations allow us to propose the pathway in Scheme 1 for the electrochemical oxidation of **1** in the presence of **3a**. According to our results it seems that the Michael addition reaction of **3a** to *p*-benzoquinone **2** is faster than other secondary reaction, leading to the intermediate **4a**. The oxidation of this compound is easier than the oxidation of the parent-starting molecule **1** by virtue of the presence of an electron-donating group.[21] Thus, as the chemical reaction proceeds, the apparent

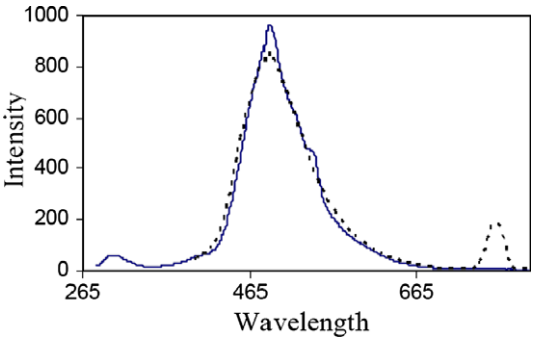
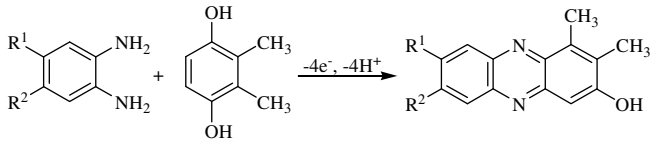



**Figure 3.** Photoluminescence (PL) spectra of a $2 \times 10^{-5}$ M solution of **7a** in chloroform at 263.5 nm excitation (solid line) and 375.5 nm excitation (dotted line).

**Table 1**
Electrochemical synthesis of products **7**




| Product | $R^1$ | $R^2$ | Yield[a] |
|---|---|---|---|
| **7a** | $CH_3$ | $CH_3$ | 90 |
| (**7b**:**7′b**) | (H:$CH_3$) | ($CH_3$:H) | 90 (50:50) |
| **7c** | H | H | 79 |

[a] Isolated yield.

number of electrons transferred increases from the limit of $n = 2$ to 4 electrons per molecule of **1**. Intramolecular cyclization of *p*-benzoquinone **5a** followed by elimination of one molecule of $H_2O$ leads to **6a**. Finally, a [1,5] hydrogen shift leads to 3,4,7,8-tetramethylphenazin-2-ol **7a**.

In conclusion, the results of this work show that 2,3-dimethylhydroquinone is oxidized to its respective *p*-benzoquinone. The *p*-benzoquinone is then attacked by phenylenediamine via an ECECC electrochemical mechanism. The process involves an intermolecular Michael addition reaction of *p*-benzoquinone and an intramolecular cyclization followed by elimination of $H_2O$ and a [1,5] hydrogen shift to afford highly conjugated phenazine **7a** as the final product. When 4-methyl-*o*-phenylenediamine **3b** was used as the nucleophile in the presence of **1**, two products **7b** and **7′b** were obtained. This was due to the asymmetrical structure of **3b**. The percentage of each isomer **7b** and **7′b** was calculated from $^1$H NMR spectra (Table 1).[22] Phenazine **7c** was prepared from **3c** in an analogous manner.[22]

## Acknowledgment

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22. *Apparatus and reagents* Cyclic voltammetry (CV) and preparative analysis were performed using a μAutolab potentiostat/galvanostat type III. The working electrode (WE) used in the voltammetry experiment was a glassy carbon disc (1.8 mm diameter, 2.5 $mm^2$ area) and platinum wire was used as the counter electrode (CE). The WE used in milli scale electrolysis was an assembly of three carbon rods (8 mm diameter and 4 cm length, 25 $cm^2$ area) and a large platinum gauze ($3 \times 3$ $cm^2$) constituted the CE. The WE potentials were measured versus Ag/AgCl/KCl (3 M) as a reference electrode.
*Electro-organic synthesis of products* **7**: In a typical procedure, 100 ml of a mixture of water/acetonitrile (80/20) containing phosphates ($KH_2PO_4/K_2HPO_4$) as the buffer and supporting electrolyte (pH 7, $c = 0.2$ M) was pre-electrolyzed at 0.15 V versus Ag/AgCl/KCl (3 M) in an undivided cell. Subsequently, 1 mmol of 2,3-dimethylhydroquinone **1** and 1 mmol of nucleophile **3** were added to the cell, and the electrolysis was performed using the same potential. Initially, the current density was 2 mA/$cm^2$ and the electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted several times during the electrolysis and the carbon anode was washed in acetone in order to reactivate it. At the end of electrolysis, the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and then washed several times with distilled water. The products were characterized by using IR, $^1$H NMR, $^{13}$C NMR, elemental analysis, and MS. *3,4,7,8-Tetramethylphenazin-2-ol* (**7a**): mp > 260 °C. IR (KBr) $\nu$ ($cm^{-1}$): 3380, 2919, 2573, 1663, 1634, 1606, 1534, 1469, 1416, 1388, 1332, 1221, 1190. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.36 (s, 3H, $CH_3$), 2.47 (s, 6H, $CH_3$), 2.75 (s, 3H, $CH_3$), 7.20 (s, 1H, CH), 7.81 (s, 1H, CH), 7.90 (s, 1H, CH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ (ppm): 12.8, 19.5, 20.5, 128.2, 128.6, 132.8, 134.6, 137.9, 139.0, 140.9, 141.1, 148.7, 166.1. MS (EI, 70 eV) $m/z$ (relative intensity): 252 (100), 223 (34), 209 (25), 186 (5), 136 (5). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.10; H, 6.45; N, 11.31.
*3,4,8-Trimethylphenazin-2-ol* (**7b**) *and 3,4,7-trimethyl-phenazin-2-ol* (**7′b**): mp > 260 °C. IR (KBr) $\nu$ ($cm^{-1}$): 3385, 2917, 2577, 1630, 1605, 1527, 1469, 1416, 1380, 1296, 1213, 1187. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.37 (s, 6H, $CH_3$), 2.57 (s, 6H, $CH_3$), 2.85 (s, 6H, $CH_3$), 7.22 (s, 2H, CH), 7.60 (d, $^3J_{HH}$ = 8.6 Hz,1H, CH), 7.65 (d, $^3J_{HH}$ = 8.6 Hz,1H, CH), 7.83 (s, 1H, CH),7.93 (s, 1H, CH), 7.97 (d, $^3J_{HH}$ = 8.6 Hz,1H, CH), 8.04 (d, $^3J_{HH}$ = 8.6 Hz,1H, CH),10.92 (broad, 2H, OH (exchangeable)). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ (ppm): 13.7, 13.75, 13.8, 21.9, 22.1, 104.6, 126.8, 128.1, 128.2, 129.6, 131.5, 132.4, 132.9, 133.1, 135.2, 135.4, 138.7, 138.9, 139.2, 139.4, 140.5, 140.6, 141.4, 142.7,143.7, 144.2, 158.9, 159.2. MS (EI, 70 eV) $m/z$ (relative intensity): 238 (100), 209 (87), 195 (76), 89 (25), 63 (28), 39 (42). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found C, 75.42; H, 5.78; N, 11.49.
*3,4-Dimethylphenazin-2-ol* (**7c**): mp >260 °C. IR (KBr) $\nu$ ($cm^{-1}$): 3422, 1692, 1624, 1610, 1522, 1457, 1406, 1374, 1334, 1231, 1092. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.40 (s, 3H, $CH_3$), 2.80 (s, 3H, $CH_3$), 7.26 (s, 1H, CH), 7.82 (m, 2H, CH), 8.13 (m, 2H, CH), 10.45 (broad, 1H, OH (exchangeable)). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ (ppm): 24.2, 24.7, 122.3, 124.5, 127.7, 129.6, 133.9, 135.0, 139.1, 143.7, 158.3. MS (EI, 70 eV) $m/z$ (relative intensity): 224 (100), 195 (68), 97 (22), 70 (24), 45 (70). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 75.25; H, 5.66; N, 12.23.