Electro-organic synthesis of dibenzylaminodioxocyclohexa-dienecarboxylic acids

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Abstract
Electrochemical oxidation of dihydroxybenzoic acids **1a–c** has been studied in the presence of dibenzylamine (**3**) as nucleophile in water/acetonitrile (90:10) solution using cyclic voltammetry and controlled-potential coulometry. The quinones **2a–c** derived from dihydroxybenzoic acids participate in Michael addition reactions with dibenzylamine (**3**), and via ECE mechanism convert to the corresponding (dibenzylamino)dioxocyclohexadienecarboxylic acids **5a–c**.

Keywords: Dihydroxybenzoic acid, electrooxidation, cyclic voltammetry, (dibenzylamino)dioxocyclohexadienecarboxylic acid

Introduction

Alkylaminoquinones are of considerable interest because they exhibit antitumor and antimalarial activities[1,2] and many of them are also involved in enzyme inhibition and DNA cross-linking.[3] 1,2-Benzoquinone derivatives have been less extensively studied than the 1,4-benzoquinone derivatives because they are more difficult to prepare.[2,4,5] The importance of amino derivatives of quinones has encouraged us to study[6] and synthesize[7] a number of these compounds. However, no report has been published so far about the chemical or electrochemical synthesis of (dibenzylamino)dioxocyclohexadienecarboxylic acids. Therefore, we have investigated the electro-oxidation of *ortho* and *para* dihydroxybenzoic acids in the presence of dibenzylamine as N-nucleophile. The present work has led to the development of a facile and environmentally friendly electrochemical method for the synthesis of some new (dibenzylamino)dioxocyclohexadienecarboxylic acids in a two-compartment cell with high atom economy and good yields.

Results and Discussion

Electrochemical study of 2,3-dihydroxybenzoic acid (1a)

Cyclic voltammograms of 2,3-dihydroxybenzoic acid (**1a**) in the absence and in the presence of dibenzylamine (**3**) in water/acetonitrile mixture (90:10, v/v) containing 0.2 M phosphate buffer (pH 7.0) are shown in Figure 1. The cyclic voltammogram of **1a** in the absence of dibenzylamine (**3**) (curve a) shows one anodic peak (A_1) at 0.28 V and the corresponding cathodic peak (C_1) at 0.22 V, which correspond to the transformation of 2,3-dihydroxybenzoic acid (**1a**) to related *o*-benzoquinone (5,6-dioxocyclohexa-1,3-dienecarboxylic acid, **2a**) and vice versa within a quasi-reversible two-electron process.[8] At this condition, the peak-current ratio (I_p^{C1}/I_p^{A1}) is nearly unity; this can be considered as a criterion for the stability of *o*-benzoquinone **2a** produced at the surface of the electrode under the experimental conditions. In other words, hydroxylation[9] or dimerization[10] reactions are too slow to be observed on the time scale of cyclic voltammetry.

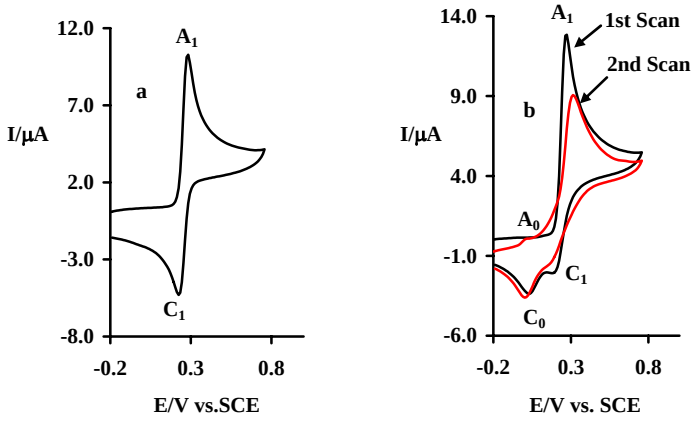


Figure 1. Cyclic voltammograms of (a) 1.0 mM 2,3-dihydroxybenzoic acid (**1a**), (b) first and second cycles of 1.0 mM 2,3-dihydroxybenzoic acid (**1a**) in the presence of 1.0 mM dibenzylamine (**3**) at a glassy carbon electrode in water/acetonitrile (90:10) solution containing 0.2 M phosphate buffer (pH 7.0). Scan rate: 50 mVs^{-1}; t = 25±1 °C.

Figure 1 (curve b) shows the first cycle voltammogram obtained for a 1 mM solution of **1a** in the presence of 1 mM dibenzylamine (**3**). The voltammogram exhibits two cathodic peaks C_1 (0.18 V versus SCE (Saturated Calomel Electrode)) and C_0 (0.03 V versus SCE). In the second cycle, a new peak (A_0) appears with an E_p value of 0.01 V versus SCE. This new peak is related to oxidation of intermediate **4a**.

Controlled-potential coulometry was performed in water/acetonitrile mixture (90:10, v/v) (phosphate buffer, c = 0.2 M, pH = 7.0) containing 0.30 mmol of 2,3-dihydroxybenzoic acid (**1a**) and 0.30 mmol of dibenzylamine (**3**) at peak A_1 potential. Cyclic voltammetric analysis carried out during the electrolysis shows the progressive formation of new anodic peak (A_0), parallel to

the disappearance of the A_1 peak (Figure 2). The anodic peak (A_1) and cathodic peak (C_1) disappear when the charge consumption becomes about $4e^-$ per molecule of **1a**.

These observations are indicative of an ECE (Electron transfer–Chemical reaction-Electron transfer) mechanism[11] and allows to propose the pathway for the electro-oxidation of 2,3-dihydroxybenzoic acid (**1a**) in the presence of dibenzylamine (**3**) (Scheme 1). Accordingly, the 1,4-addition (Michael) reaction of dibenzylamine (**3**) to the *o*-benzoquinone derivative **2a** leads to intermediate **4a**. The oxidation of **4a** is easier than the oxidation of **1a** by virtue of the presence of more electron-donating groups. Since $E_{1/2}^{A1\ and\ C1} > E_{1/2}^{A0\ and\ C0}$, the occurrence of solution electron transfer (Scheme 2) is possible. So, we think that both mechanisms (ECE and Disp (disproportionation)) are participating in electrochemical oxidation of benzoic acid derivatives in the presence of dibenzylamine.

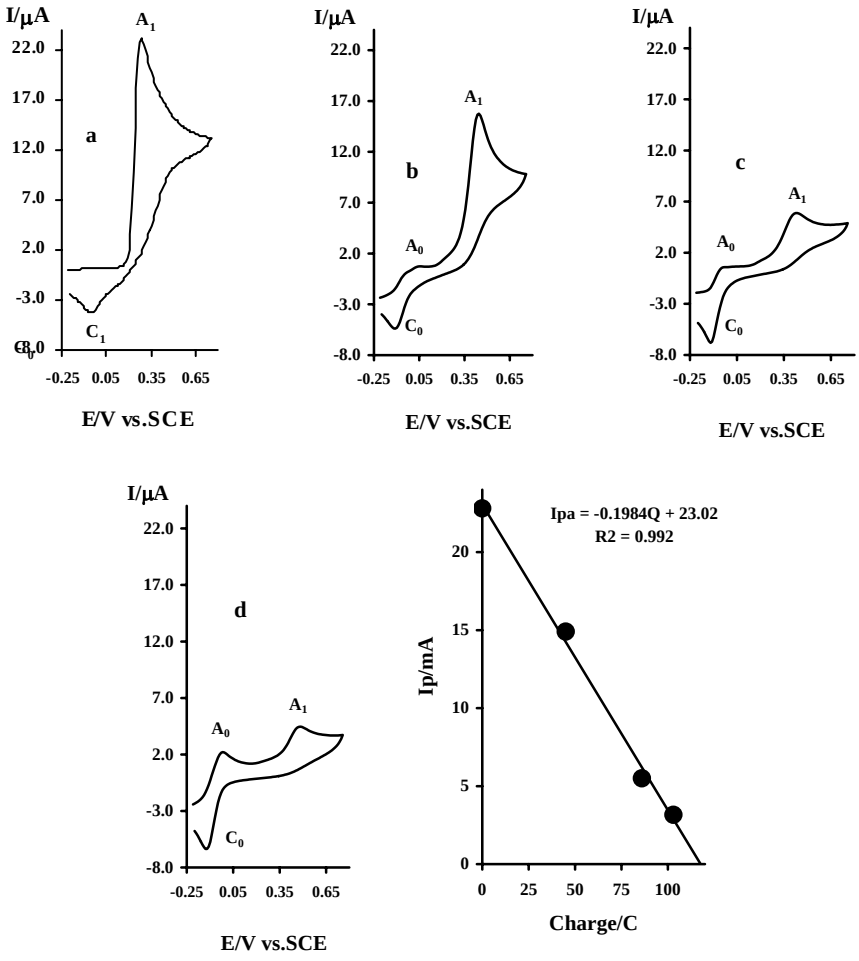
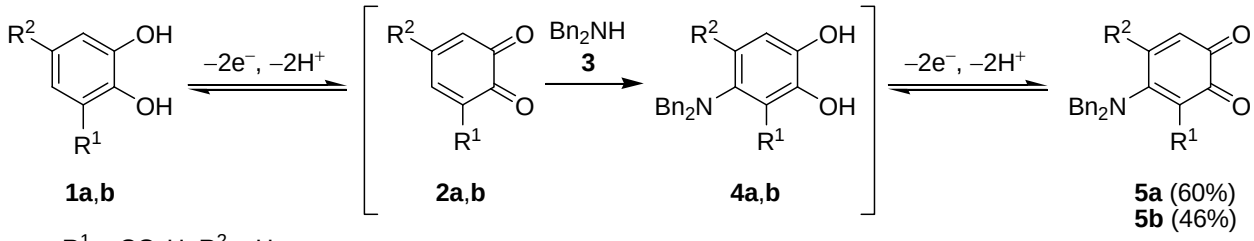
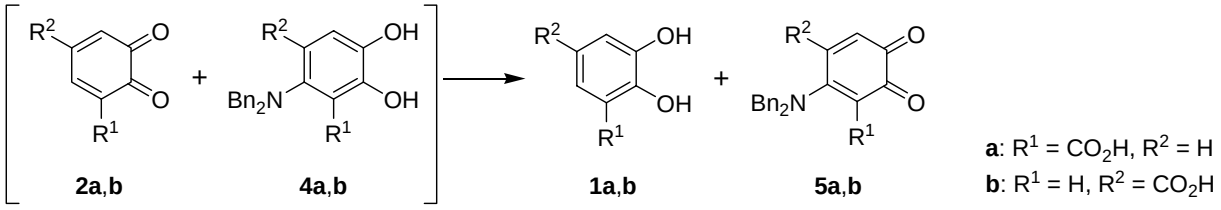


Figure 2. Cyclic voltammograms of 0.30 mmol 2,3-dihydroksybenzoic acid (**1a**) in the presence of 0.30 mmol of dibenzylamine (**3**) in water/acetonitrile (90:10) mixture, containing 0.2 M phosphate buffer (pH 7.0) at a glassy carbon electrode during controlled-potential coulometry at 0.45 V vs. SCE. After consumption of (a) 0, (b) 45, (c) 86 and (d) 103 C. (e): variation of peak current (Ipa_1) vs. charge consumed. Scan rate 50 mVs^{-1}; t = 25±1 °C.



Scheme 1



Scheme 2

The 1,4-addition (Michael) reaction of dibenzylamine (**3**) to the *ortho*-quinone intermediate **2a** can conceivably occur at C-2 and C-3 resulting in products **5a** or **6a**, respectively (Figure 3). The ^{1}H NMR spectrum of the isolated product displays two doublet peaks with vicinal coupling constants (δ 6.50 and 6.76) in support of structure **5a**.

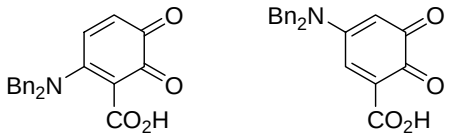


Figure 3

The electro-oxidation of 3,4-dihydroxybenzoic acid (**1b**) in the presence of dibenzylamine (**3**) in water/acetonitrile (90:10) solution in phosphate buffer (pH 7.0, 0.2 M) proceeds similarly (Scheme 1). Two ^{1}H NMR singlet peaks (δ 5.40 and 5.80) provide evidence of product structure **5b** resulting from the 1,4-addition of dibenzylamine (**3**) at C-6 of intermediate **4b**.

Electrochemical study of 2,5-dihydroxybenzoic acid (1c)

Under the same conditions the electrochemical oxidation of 2,5-dihydroxybenzoic acid (**1c**) in the presence of dibenzylamine (**3**) was performed using cyclic voltammetry. In comparison with the cyclic voltammogram of **1a** the *p*-benzoquinone intermediate **2c** formed by oxidation of **1c** is

less reactive toward the Michael addition reaction. A decreased peak current ratio (I_p^{A1}/I_p^{C1}) shows this behavior. Time-dependent absorption spectra of the mixture of 2,5-dihydroxybenzoic acid (**1c**; 0.5 mM) and dibenzylamine (**3**; 0.5 mM) were recorded during a controlled-potential coulometry at 0.20 V vs. SCE (Figure 4). In the course of the coulometry experiment an absorption peak at λ_{max} 534 nm keeps growing due to the formation of 2-dibenzylamino-3,6-dioxocylohexa-1,4-dienecarboxylic acid (**5c**).

The electro-oxidation of 2,5-dihydroxybenzoic acid (**1c**) in the presence of dibenzylamine (**3**) (Scheme 3) is considered to involve the Michael acceptor 3,6-dioxocyclohexa-1,4-diene-carboxylic acid (**2c**) as an intermediate that could be attacked at positions C-2, C-4 or C-5 to yield **5c**, **6c**, **7c**, respectively (Figure 5). The ^{1}H NMR spectrum of the isolated product exhibits two doublet peaks with vicinal coupling constants (δ 6.62 and 7.02) confirming structure **5c**.

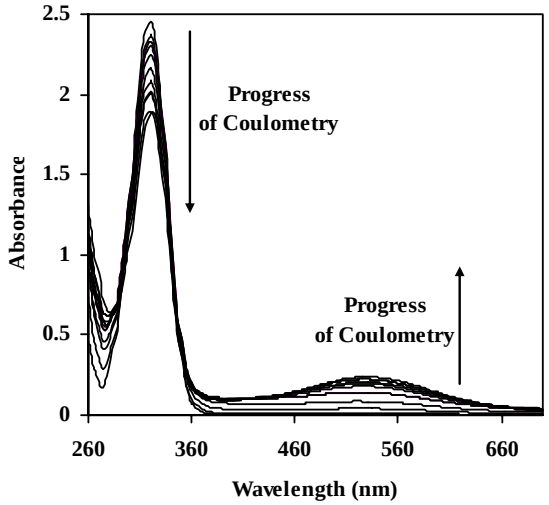
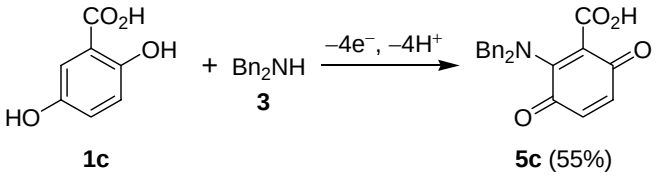


Figure 4. Absorption spectra of the mixture of 2,5-dihydroxybenzoic acid (**1c**) (0.5 mM) and dibenzylamine (**3**) (0.5 mM) during controlled-potential coulometry at 0.20 V vs. SCE in aqueous solution containing 0.2 M phosphate buffer (pH 7.0).



1c **5c** (55%)

Scheme 3

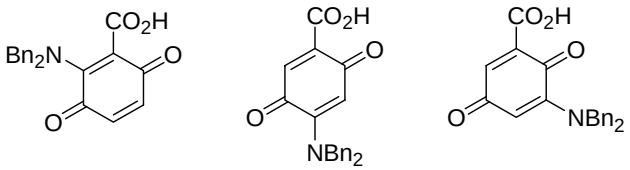


Figure 5

The ^{13}C NMR spectra of **5a** and **5c**, contrary to that of **5b**, show only one downfield peak at δ 172.8 and 172.7, respectively. This can be related to the formation of intramolecular hydrogen bonds in **5a** and **5c** (Figure 6).[12]

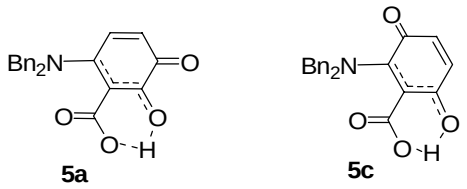


Figure 6

The mass spectra of compounds **5a–c** show strong protonated molecular ion peaks [M+2H] (and [M+3H] in **5c**) due to protonation of quinone, amino, and carbonyl groups.[7,13]

Conclusions

This work reports the electro-oxidation of dihydroxybenzoic acids (**1**) in water/acetonitrile solution to the corresponding quinones **2**, which in turn, add dibenzylamine (**3**) to form (dibenzylamino)dioxocyclohexadienecarboxylic acids **5**. The advantage of dibenzylamine (**3**) as a bulky nucleophile is the formation of monoamino-substituted benzoquinones as final products (Schemes 1 and 3). The present work has led to the development of a one-pot electrolytic method for the synthesis of new (dibenzylamino)dioxocyclohexadienecarboxylic acids **5a-c** as final products, in good yields.

Experimental Section

General Procedures. 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 experiment was a glassy carbon disc (1.8 mm

diameter) and a platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and macro-scale electrolysis was an assembly of four carbon rods (6 mm diameter and 4 cm length) and large platinum gauze constituted the counter electrode. In controlled-potential coulometry, the counter electrode compartment was separated from the working electrode with porous membrane electrode shape that involving counter electrode. The working electrode potentials were measured versus SCE (all electrodes were obtained from AZAR Electrodes). All experiment was carried out at a temperature of 25 ± 1 °C. Melting points of all synthesized compounds were determined in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on IFS66 Bruker FT-IR spectrometer. ^{1}H and ^{13}C, NMR spectra (DMSO-d_6) were recorded on JEOL JNM-EX90A spectrometer operating at 90 and 22.6 MHz, respectively and BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8, MHz, respectively. Mass spectra were recorded on a QP-1100EX Shimadzu Mass spectrometer operating at an ionization potential of 70 eV.

General procedure for the synthesis of (dibenzylamino)dioxocyclohexadienecarboxylic acids 5a–c. A solution of phosphate buffer (ca. 80 mL; c = 0.2 M, pH = 7.0) in water/acetonitrile (90:10; 80 mL) solution containing dihydroxybenzoic acid (**1a**–**c**; 154.1 mg, 1 mmol) and dibenzylamine (**3**; 197.3 mg, 1 mmol) was electrolyzed in a two-compartment cell at 0.3 V vs. SCE. The electrolysis was terminated when the current decreased by more than 95%. The process was interrupted during the electrolysis and the graphite anode was washed in acetone in order to reactivate it. After electrolysis, the precipitated solid was collected by filtration. The products were purified by column chromatography (silica gel; chloroform for **5a,b**, chloroform/ether for **5c**). After purification, the products were characterized by UV, IR, ^{1}H NMR, ^{13}C NMR and MS.

2–(Dibenzylamino)-5,6-dioxocylohexa-1,3-dienecarboxylic acid (5a). The product **5a** was obtained as violet crystals**,** (208.4 mg, 60% yield); mp 170–172 °C. ^{1}H NMR (90 MHz, DMSO-d_6): δ 10.02 (broad, 1H), 7.26-7.40 (m, 10H), 6.76 (d, J = 7.1, 1H), 6.50 (d, J = 7.5, 1H), 4.53 (s, 4H). ^{13}C NMR (22.6 MHz, DMSO-d_6): δ 172.8, 150.6, 145.8, 131.7, 130.5, 129.8, 128.5, 120.3, 117.36, 115.8, 110.7, 59.4. IR (KBr): $\tilde{\nu}$ 3134, 3034, 2834, 1601, 1555, 1500, 1479, 1456, 1387, 1319, 1265, 1190, 1072, 1017, 977, 844, 752, 696 cm^{-1}. UV-Vis (acetonitrile, c = 5×10^{-4} mol dm^{-3}): λ_{max} (ε) 514, 406 nm (576 mol^{-1} dm^{3} cm^{-1}). EI-MS: *m*/*z* (%) 349 (61) [M+2H], 313, 305(98), 258(12), 244(24), 228(46), 214(99), 196(25), 167(46), 152(47), 136(38), 109(41), 106(100), 91(90), 77(86), 65(84). Anal. Found. C 72.61; H 4.93; N 4.03. Calcd. For $C_{21}H_{17}NO_4$; C 72.60; H 4.91; N 4.05.

6–(Dibenzylamino)-3,4-dioxocylohexa-1,5-dienecarboxylic acid (5b). The product **5b** was obtained as red-orange crystals**,** (159.8 mg, 46% yield); mp 165–167 °C. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.25-7.45 (m, 10H), 5.80 (s, 1H), 5.40 (s, 1H), 4.77 (s, 4H). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 181.1, 176.9, 164.0, 154.6, 136.9, 129.0, 127.5, 127.0, 104.5, 104.2, 57.0. IR (KBr): $\tilde{\nu}$ 3059, 2986, 2927, 1668, 1625, 1545, 1442, 1359, 1307, 1262, 1233, 1183, 1111, 1027, 945, 905, 802, 730, 697 cm^{-1}. UV-Vis (acetonitrile, c = 5×10^{-4} mol dm^{-3}) λ_{max} (ε) 481, 327 nm

(451.6 mol^{-1} dm^3 cm^{-1}). EI-MS: *m*/*z* (%) 349 (14) [M+2H], 256 (12), 228 (17), 91 (100). Anal. Found. C 72.61; H 4.93; N 4.03. Calcd. For $C_{21}H_{17}NO_4$; C 72.58; H 4.89; N 4.01.

2–(Dibenzylamino)-3,6-dioxocylohexa-1,4-dienecarboxylic acid (5c). The product **5a** was obtained as pink crystals**,** (191.1 mg, 55% yield); mp 209–210 °C. ^{1}H NMR (90 MHz DMSO-d_6): δ 10.01 (broad, 1H), 7.20-7.49 (m, 10H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 4.69 (s, 4H). ^{13}C NMR (22.6 MHz, DMSO-d_6): δ 172.7, 154.5, 145.0, 132.3, 130.5, 128.8, 128.4, 126.6, 122.2, 117.9, 110.8, 56.3. IR (KBr): $\tilde{\nu}$ 3033, 2977, 1633, 1589, 1494, 1458, 1350, 1293, 1275, 1226, 1143, 1081, 1030, 983, 911, 865, 836, 802, 752, 729, 697, 642, 569 cm^{-1}. UV-Vis (acetonitrile, $c = 5\times10^{-4}$ mol dm^{-3}) λ_{max} (ε) 456, 334 nm (506.4 mol^{-1} dm^3 cm^{-1}). EI-MS: *m*/*z* (%) 350 (98) [M+3H], 332 (12), 258 (34), 240 (24), 91 (100), 65 (22). Anal. Found. C 72.61; H 4.93; N 4.03. Calcd. For $C_{21}H_{17}NO_4$; C 72.63; H 4.90; N 4.06.

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