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A non-covalent complex based on catechol-benzoxazole moieties: Electrochemical Synthesis and Characterization†

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Electrochemical oxidation of 3,5-di-*tert*-butylcatechol has been studied in the presence of 2-methoxybenzylamine by means of cyclic voltammetry and controlled-potential coulometry. The results indicate that the electrogenerated 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione participates in a cyclization reaction with 2-methoxybenzylamine and converts to the corresponding benzoxazole (**4**). Afterward by a non-covalent interaction, a proton transfer complex is formed between benzoxazole **4** and 3,5-di-*tert*-butylcatechol.

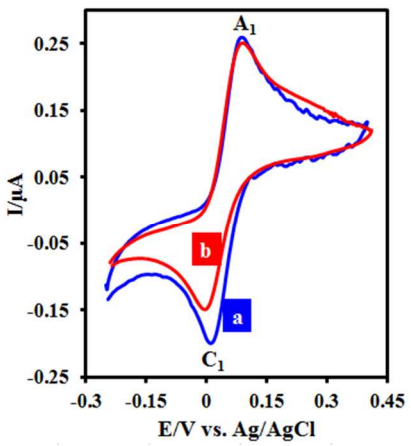
Introduction

As heteroaromatic systems, benzoxazole derivatives are important structural motifs in many biological, pharmaceutical and dye compounds.[1] They are used as cytotoxic agents,[2] cathepsin S inhibitors,[3] HIV reverse transcriptase inhibitors,[4] estrogen receptor agonists,[5] selective peroxisome proliferator activated receptor antagonists,[6] anticancer agents,[7] and orexin-1 receptor antagonists.[8]

In this connection, we have recently reported a new strategy for the electrochemical synthesis of some 5,7-di-*tert*-butyl-2-phenylbenzo[d]oxazole derivatives based on the reaction of benzylamine derivatives with 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione.[9] In the present work, we have studied the electrochemical oxidation of 3,5-di-*tert*-butylcatechol in the presence 2-methoxybenzylamine to represent an electrochemical synthesis of a new non-covalent complex containing 5,7-di-*tert*-butyl-2-(2-methoxyphenyl) benzo[d] oxazole and 3,5-di-*tert*-butylcatechol.

Results and discussion

Electrochemical oxidation of 3,5-di-*tert*-butylcatechol (**DTC**) in the absence and presence of 2-methoxybenzylamine (**MBA**) as a nucleophile was studied in some details. The cyclic voltammogram of **DTC** in aqueous phosphate buffer, (0.2 M, pH 7.5)/ethanol mixture (80/20 v:v) shows one anodic peak (A_1) and its counterpart cathodic peak (C_1) which correspond to the transformation of **DTC** to 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione (**DBQ**) and vice versa within a quasi-reversible two-electron process (Figure 1, curve a).[9,10] Curve b in Fig. 1 shows the cyclic voltammogram of **DTC** in the presence of **MBA**. The occurrence of a chemical reaction after the electrochemical oxidation is supported by decrease in the current of peak C_1 during the reverse scan, which could indicate that **DBQ** formed at the surface of the electrode is consumed by a chemical reaction with **MBA**.[9] More studies were performed by varying the potential sweep rate of cyclic voltammograms of **DTC** in the presence of **MBA**. The results indicate that the peak current ratio (I_{pC1}/I_{pA1}) increases by increasing sweep rate. With increasing potential scan rate, the time required for the reaction of **DBQ** with **MBA** is not enough, and consequently, the peak current ratio (I_{pC1}/I_{pA1}) increases.[9]



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*†Electronic Supplementary Information (ESI) available: FT-IR, ^{1}H NMR, ^{13}C NMR, MS spectra and X-ray data of compound **5**. See DOI: 10.1039/b000000x/*

Fig. 1 Cyclic voltammograms of **DTC** (0.1 mM): (a) in the absence and (b) in the presence of **MBA** (30 mM) at a glassy carbon electrode, in aqueous phosphate buffer, (0.2 M, pH 7.5)/ethanol mixture (50/20 v:v). Scan rate: 2.5 mV s^{-1}; t = 25 ± 1 °C.

Controlled-potential coulometry was performed in aqueous phosphate buffer (c = 0.1 M. pH = 7.5)/ethanol (v/v 80/20) mixture containing **DTC** and **MBA** at 0.15 V *versus* Ag/AgCl. Figure 2 presents the cyclic voltammograms during controlled potential coulometry. The plot of I_{pA1} vs Q is shown in the inset of figure 2. As can be seen, I_{pA1} and I_{pC1} decrease during coulometry and both disappear when the charge consumption becomes $2e^-$ per molecule of **DTC**.

Diagnostic criteria of cyclic voltammetry and controlled potential coulometry accompanied by ^{1}H NMR, ^{13}C NMR, MS (see **ESI**†) and X-ray spectra of final product (Fig. 3) allow us to propose the following mechanism for the electrochemical oxidation of **DTC** in the presence of **MBA** (Scheme 1). According to our results, the condensation reaction of **MBA** with electrogenerated **DBQ** at the most electrophilic carbonyl, leads to intermediate **1** (imine formation). Rearrangement then led to the formation of the Schiff base **2**. In the next step, via a cyclization reaction, **2** is converted to benzoxazoline **3**. Chemical or electrochemical oxidative dehydrogenation of **3** in the next step leads to the corresponding benzoxazole **4**. The affinity of the non-covalent interaction between **4** and **DTC** causes the formation of non-covalent complex **5**.

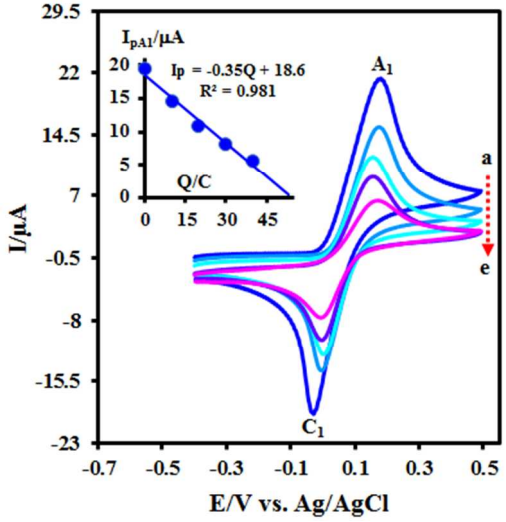


Fig. 2 Cyclic voltammograms of **DTC** (0.25 mmol) in the presence of **MBA** (0.25 mmol) during controlled potential coulometry at 0.15 V versus Ag/AgCl in aqueous phosphate buffer, (0.2 M, pH 7.5)/ethanol mixture (80/20 v:v), after consumption of: (a) 0, (b) 10, (c) 20, (d) 30 and (e) 40 C. Scan rate: 100 mV s^{-1}. Inset: Variation of I_{pA1} versus charge consumed during controlled potential coulometry.

Non-covalent complexes are highly useful for the development of new molecular electronic devices and optical sensors.[11] Quinhydrone is a well-known stable non-covalent complex formed between *p*-benzoquinone and 1,4-hydroquinone.[12] In this complex, the charge transfer and hydrogen-bonding interactions between the electron donor (hydroquinone) and the electron acceptor (quinone) stabilize the complex. In addition, another quinhydrone complex was described by the reaction of phenanthrene-9,10-dione with phenanthrene-9,10-diol (*ortho*-quinhydrone).[13] We also reported a non-covalent complex based on 3,5-di-*tert*-butylcatechol and its oxidized form, 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione.[10]

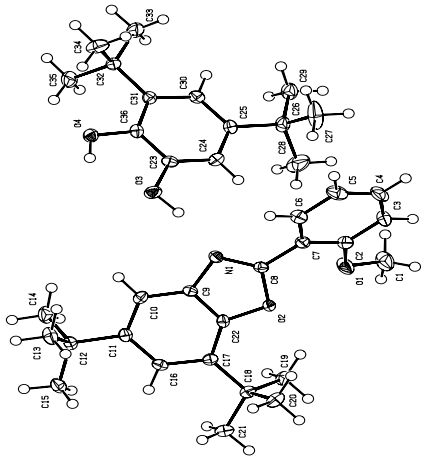


Fig. 3 Single-crystal X-ray diffraction of **5**.

Figure 4 compares the cyclic voltammograms of **DTC** and non-covalent complex **5**. As can be seen, the oxidation potential of 3,5-di-*tert*-butylcatechol moiety of **5** is more positive than that of **DTC** ($E_{pA2} > E_{pA1}$). In contrast, in the reverse scan, the potential of the two cathodic peaks (C_1) are nearly same. This is expected because the hydrogen bonding makes **5** difficult to oxidation. On the other hand, since there is no interaction between **DBQ** and benzoxazole **4**, both cathodic peaks have same potential.

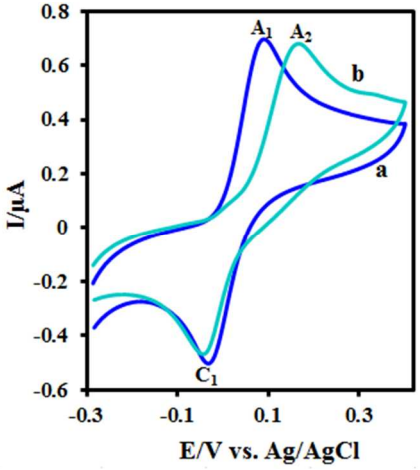
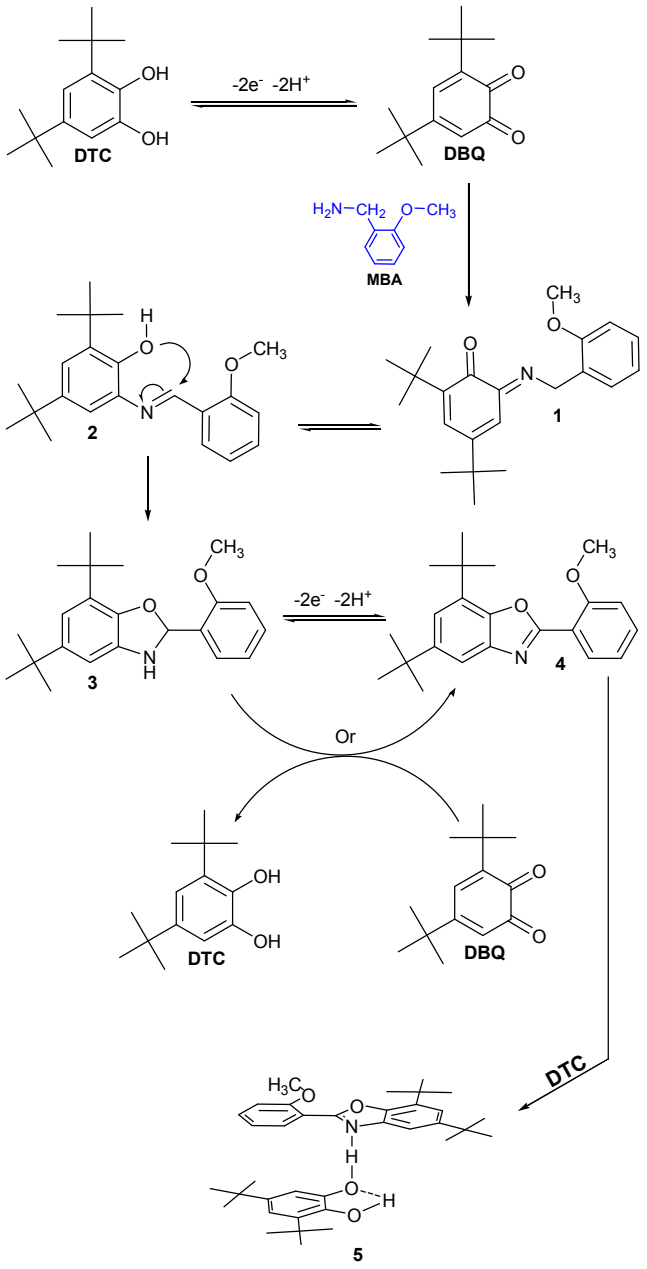


Fig. 4 cyclic voltammogram of (a) **DTC** (0.5 mM) and (b) non-covalent complex **5** 0.5 mM) at a glassy carbon electrode in aqueous phosphate buffer, (0.2 M, pH 7.5)/ethanol mixture (50/50 v:v). Scan rate: 10 mV s^{-1}; t=25 °C.

The effect of hydrogen bonding between **DTC** and benzoxazole moieties in **5** has been shown in its FT-IR spectrum. Analysis of the IR spectrum reveals two peaks at 3499 and 3188 cm^{-1} that are related to two OH groups of bonded **DTC** to benzoxazole **4**[10] (see **ESI**†).



Scheme 1 Proposed mechanism for the electrochemical oxidation of **DTC** in the presence of **MBA**.

Conclusion

This is the first report showing the formation of a complex between benzoxazole and catechol moieties via an intermolecular proton transfer reaction. Recently, we have shown that **DBQ** reacts with benzylamine derivatives to form 2-arylbenzoxazoles derivatives.[9] However, the results of this work revealed that electro-oxidation of **DTC** in the presence of **MBA** to afford non-covalent complex **5** whose structure was established by X-ray analysis.

Experimental

Cyclic voltammetry, controlled-potential coulometry and preparative electrolysis were performed using an Autolab model PGSTAT 30 potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disc (1.8 mm^2 area) and platinum wire was used as counter electrode. The working electrode used in controlled-potential coulometry and synthesis was an assembly of four carbon rods (31 cm^2) and large platinum gauze constitute the counter electrode. The working electrode potentials were measured versus Ag/AgCl/3M KCl (all electrodes from AZAR electrode). 3,5-di-*tert*-butylcatechol, 2-methoxybenzylamine and other solvents and reagents were reagent-grade materials from Aldrich. The glassy carbon electrode was polished using alumina slurry (from Iran Alumina Co.)

General procedure for synthesis of 5

For synthesis of **5**, a solution (80 mL) of water (phosphate buffer, pH = 7.5, *c* = 0.2 M)/ethanol (80/20, v/v) containing **DTC** (1.0 mmol) and **MBA** (0.5 mmol) was electrolyzed at 0.15 V versus Ag/AgCl, in a divided cell. The electrolysis was terminated when the decay of the current became more than 95% of the initial current. At the end of electrolysis, the precipitated solid was collected by filtration and recrystallized in *n*-hexane (71% yield). After recrystallization, products were characterized by: MS, IR and ^{1}H NMR, ^{13}C NMR and single-crystal X-ray diffraction (see **ESI**†). mp = 133–135 ◦C. IR(KBr, cm^{-1}): 3500, 2962, 2905, 2868, 1603, 1584, 1551, 1481, 1465, 1437, 1362, 1311, 1248, 1122, 1076, 1044, 1022, 968, 870, 855, 752, 655 and 496; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H *tert*-butyl), 1.38 (s, 9H *tert*-butyl), 1.46 (s, 9H *tert*-butyl), 1.58 (s, 9H *tert*-butyl), 4.00 (s, 3H CH_3), 5.98 (s, 1H NH), 6.80 (d, *J* = 2.0 Hz, 1H Ar), 6.88 (d, *J* = 2.0 Hz, 1H Ar), 7.10-7.17 (m, 2H Ar), 7.34 (d, *J* = 2.0 Hz, 1H Ar), 7.52-7.56 (m, 1H Ar), 7.61 (d, *J* = 1.6 Hz, 1H Ar), 8.17 (dd, J_d = 7.8, J_{dd} = 1.8 Hz, 1H Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.5, 147.7, 146.3, 143.0, 141.7, 141.5, 141.2, 135.3, 133.6, 132.8, 130.9, 120.7, 119.6, 116.0, 115.3, 114.1, 112.1, 110.6, 55.9, 35.1, 34.8, 34.4, 34.2, 31.8, 31.5, 29.9, 29.7; MS (*m/z*) (relative intensity): 337.3 (22), 322.3 (24), 222.2 (35), 207.2 (100), 179.1 (6), 82 (6).

Acknowledgements

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Graphical Abstract

Electrochemical synthesis of novel non-covalent complex was carried out via the electrooxidation of 3,5-di-*tert*-butylcatechol in the presence of 2-methoxybenzylamine.