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Electrochemical oxidation of substituted catechols in the presence of pyrazol-5-ones: characterization of products and reaction mechanism

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ABSTRACT

The electrochemical oxidation of substituted catechol derivatives has been investigated in the presence of pyrazol-5-ones as C–H acid nucleophiles by using constant current technique in acetate buffer solution. The results indicate that different reaction mechanisms are involved and not only 1,4-Michael adducts but also 1,6-Michael adducts are formed, depending on the nature of the starting catechols and the nucleophiles, as well as the reaction conditions.

1. Introduction

Catechols and their quinone derivatives have drawn considerable attention due to their abundance in nature and important roles in many biological systems. Moreover, most of compounds incorporating catechol moiety exhibit antioxidant,[1] anticarcinogenic,[2,3] antifungous,[4] and antibacterial activities[5,6] or are used as HIV integrase inhibitors.[7–9] For example, dopamine is a neurotransmitter in the central nervous system of human and other vertebrate animals,[10] whereas, dicaffeoyltartaric acid[7] and dicaffeoylquinic acid[7,8] exhibit HIV integrase inhibitory activity.

On the other hand, electroorganic synthesis[11] is regarded as an environmental friendly strategy for chemical transformation, wherein electrons are used as oxidants and thus the utilization of toxic metal-based reagents is avoid. Also, such transformation is generally performed under mild conditions. Indeed, catechols and their quinone derivatives can be achieved by the electrochemical synthesis of *o*-benzoquinones and their in situ transformation[12–23] since the electro-generated *o*-benzoquinones are active intermediates and readily undergo Michael addition reaction,[12–15,18–23] with nucleophiles or [4+2] cycloaddition with dienes[16,17] to form various products. In this respect, electrochemical oxidation of catechols in the presence of nucleophiles (such as amines,[13] thiols[14] or sulfuric acids[15]) leads to the formation of substituted catechols or substituted *o*-benzoquinones.

C–H acids are common nucleophiles and therefore also are employed in the nucleophilic attack to the electro-generated *o*-benzoquinones.[18–23] However, most of the C–H acids employed are confined to acyclic and cyclic 1,3-dicarbonyl derivatives, such as barbituric acids,[18] acetylacetone,[19] cyclohexanediones,[20] acetoacetates,[21] 4-hydroxycoumarins[12,22] and Meldrum's acid,[23] and mainly lead to the formation of benzofurans and coumestans. Moreover, it is observed that only 1,4-Michael addition products are isolated in these electrochemical transformations.

As a continuous work toward the development of potential HIV-1 integrase inhibitors derived from polyhydroxylated aromatics, we have investigated the electrochemical synthesis of polyhydroxylated aromatics.[24–29] In the present work, we report the electrochemical oxidation of catechols **1** in the presence of pyrazol-5-ones **2** as C–H acids by constant current technique (Fig. 1). The outcomes indicate that different reaction mechanisms (not only 1,4-Michael addition, but also 1,6-addition) are involved, which demonstrates that a wide spectrum of products may be produced by simply tuning the natures of the starting catechols and nucleophiles, and reaction conditions.

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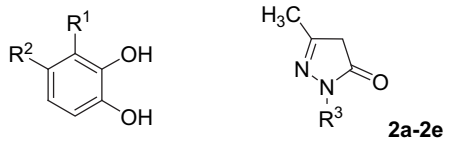


1a-1d

1a: $R^1 = OCH_3$, $R^2 = H$
1b: R^1= H, R^2 = *t*-Bu
1c: R^1 = H, $R^2 = CH_3$
1d: $R^1 = CH_3$, R^2 = H

2a-2e

2a: R^3 = H,
2b: R^3 = Ph
2c: R^3 = *p*-CH_3-Ph
2d: R^3 = *p*-OCH_3-Ph
2e: R^3 = *p*-Cl-Ph

Fig. 1. Structures of starting substituted catechols **1** and pyrazol-5-ones **2**.

2. Results and discussion

2.1. Cyclic voltammetric studies

The electrochemical behavior of catechols **1** in the absence and presence of pyrazol-5-ones was examined at room temperature in water containing 0.2 M acetate buffer (pH 7.0) as the supporting electrolyte by cyclic voltammetry (CV).

Taking 4-methylcatechol (**1c**) as an example, as shown in Fig. 2, upon scanning anodically, 4-methylcatechol exhibits a well defined quasi-reversible oxidation wave (peak A) at +0.51 V versus Ag/AgCl (KCl 3 M) and its corresponding cathodic peak (C) at+0.30 V. Peak A is attributed to the oxidation of 4-methylcatechol to the corresponding 4-methyl *o*-benzoquinone and peak C to the reduction of the quinone. The ratio of the current amplitudes between the oxidation and reduction processes is equal to unity (I_p^{ox}/I_p^{red}), indicating that the *o*-benzoquinone produced at the surface of the electrode is stable under pH 7 acetate buffer and that side-reactions, such as hydroxylation or dimerization reactions are too slow to be observed on the time scale of the cyclic voltammetry.[13–23]

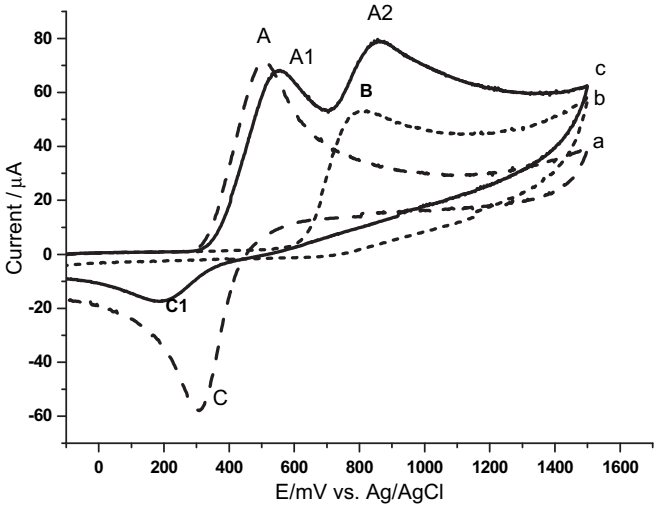
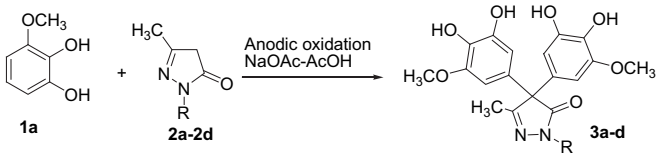


Fig. 2. Cyclic voltammograms of (a) 2 mM of 4-methylcatechol (**1c**), (b) 2 mM of 3-methyl-1*H*-pyrazol-5-one (**2a**), and (c) a mixture of 2 mM of **2a** and 2 mM of **1c**, at a glassy carbon working electrode, platinum wire counter, and Ag/AgCl reference electrodes, in acetate buffer (0.2 M, pH 7) solution; scan rate: 100 mV/s.

When 1 equiv amount of 3-methyl-1*H*-pyrazol-5-one **2a** was added, the voltammogram of the mixture exhibits two anodic peaks A_1 (+0.55 V vs Ag/AgCl) and A_2 (+0.86 V vs Ag/AgCl), whereas the cathodic peak shift to 0.19 V versus Ag/AgCl and its cathodic current decreases dramatically (curve c, Fig. 2). Curve b in Fig. 2 is the CV of 3-methyl-1*H*-pyrazol-5-one **2a**, where one irreversible anodic wave at 0.80 V is observed. The observation that the cathodic current of the corresponding *o*-benzoquinone decrease indicates that the electro-generated *o*-benzoquinone intermediate undergoes follow-up chemical reactions under these conditions.

2.2. Electrochemical oxidation of substituted catechols in the presence of 3-methylpyrazol-5-ones

After examining the electrochemical properties of substituted catechols in the absence and presence of pyrazol-5-one, preparative scale of electrolyzes were carried out. At the outset, 3-methoxy catechol **1a** was subjected to anodic oxidation in the presence of 3-methylpyrazol-5-ones. Thus, in a pilot experiment, a solution of an equimolar quality of **1a** and **2a** was electrolyzed at constant current of 12 mA (~4 mA/cm^2) at pH 7.0 acetate buffer. The reaction mixture afforded *C*,*C*-dicatechol pyrazol-5-one derivative **3a** in 42% yield (Scheme 1).



3a: R = H; **3b**: R = Ph;
3c: R = *p*-CH_3-Ph;
3d: R = *p*-OCH_3-Ph;

Scheme 1. Anodic oxidation of 3-substituted catechol **1a** in the presence of 3-methylpyrazol-5-ones **2a**–**d**.

Subsequently, phenyl-substituted 3-methylpyrazol-5-ones **2b**–**d** were employed as C–H acid nucleophiles to react with the electro-generated 3-methoxy *o*-benzoquinone (Scheme 1). Here, due to the low solubility of phenyl-substituted 3-methylpyrazol-5-ones, acetonitrile was added as a co-solvent. Accordingly, a mixed solvent of acetate buffer solution and acetonitrile (3:1 ratio of acetate buffer to acetonitrile, pH 7) was used as supporting electrolyte. It was found that analogous reaction pattern occurred with respect to these 3-methyl-pyrazol-5-ones. As shown in Scheme 1, when the nucleophiles were **2b**–**d**, corresponding **3b**, **3c**, and **3d** were isolated in 23%, 20%, and 29%, respectively. Interestingly, an unexpected compound **4** was also isolated in 11% yield (Fig. 3), along with **3b**, from the anodic oxidation of the mixture of **1a** and **2b**. It is noteworthy that, structurally, compounds **3** and **4** are 1,4-Michael addition products. For example, compounds **3** may stem from the 1,4-Michael addition of pyrazol-5-ones to two molecules of the electro-generated 3-methoxy *o*-benzoquinone.

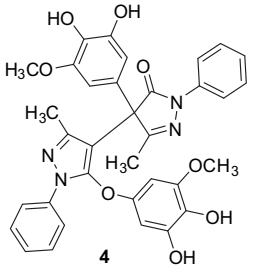


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Fig. 3. Structure of compound **4**.

To investigate the limitation and scope of the anodic oxidation of substituted catechols in the presence of pyrazol-5-ones, next, 4-*tert*-butylcatechol (**1b**) was subjected to constant current electrolysis in the presence of 3-methylpyrazol-5-ones **2a**–**e** (Scheme 2). However, the benzoquinone generated from this catechol behaved in a way quite different from o-benzoquinone generated from 3-methoxy catechol: 1,6-addition occurred on the former instead of 1,4-addition on the later. It is noticed that the formation of the type of 1,6-addition has not been obtained in the oxidations of catechols