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Electrochemical S_N^H(An) functionalization of 1,2- and 1,4-dihydroxybenzenes

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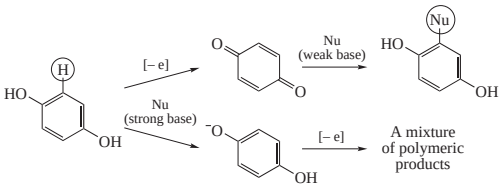
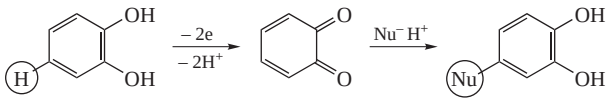
The regularities of electrochemical S_N^H(An) functionalization of 1,2- and 1,4-dihydroxybenzenes with nucleophiles of various strength and basicity are characterized.



Dihydroxybenzenes (DHB) are constituents of various pharmacologically active compounds.[1–4] Their electrochemical modification with various nucleophiles (azides,[5] alcohols,[6] amines,[7] thiols,[1] *etc*.) using an anode as a 'green oxidizing agent' has been intensely studied in recent years. Such processes should be considered[8,9] as electro-induced nucleophilic substitution of hydrogen in an arene [S_N^H(An)] occurring through generation of a quinone followed by Michael addition (Scheme 1).



Scheme 1

Scheme 1 describes the process just formally. It is no coincidence that neutral or weakly acidic (but not alkaline) solutions are actually more beneficial for DHB electrofunctionalization in aqueous media (see *e.g.* ref. 7). However, the studies cited above did not give proper attention to analysis of the reasons why the acidic properties of the medium, *i.e.*, DHB as such, as well as the basic properties of the Nu, affect the course of the process. Here, we made an attempt to clarify these problems.

We took into consideration data on controlled potential electrolysis (CPE) of hydroquinone **1** and pyrocatechol as DHB in MeCN in the presence of some representative nucleophiles (Figure 1), as well as data on cyclic voltammetry (CV) of these co-reagents under the same conditions. As nucleophiles with various basic properties, the following compounds were chosen: 2-mercaptobenzothiazole **3**, 4-nitropyrazole sodium salt **4** and 3,5-dimethylpyrazole **5**.† The results are summarized in Table 1.

As seen from Table 1, the efficiency of the process (see Scheme 1) diminishes with an increase in the oxidation peak potential (E_p^{ox}) of Nu, whose nucleophilicity should decrease with rising E_p^{ox} (*cf.* refs. 10, 11). In total, the efficiency of the process turned to be substrate dependent.

Mercaptobenzotriazole **3** with lowest E_p^{ox} = 1.3 V was the most efficient among other nucleophiles and the yields of its derivatives **6** and **9** were reasonable (see Table 1). Let us also note that the reactivity of electrogenerated poorly stable *o*-benzoquinone towards **3** was much higher than that in the case of *p*-benzoquinone. That is why the final solutions contain, along

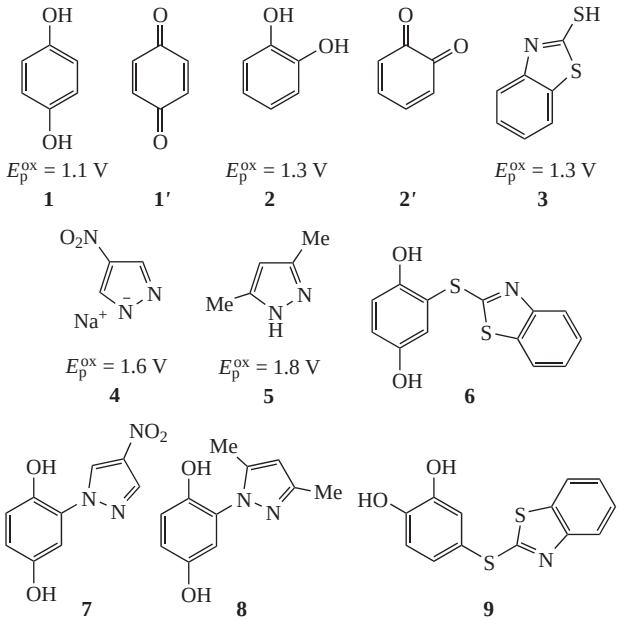


Figure 1 Reactants **1**–**5** with their oxidation potentials *vs*. SCE and products **6**–**9** obtained.

† ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 300 instrument (300.13 MHz). Mass spectra were recorded using a Finnigan MAT INCOS 50 instrument. Voltammetric (CVA) studies were carried out in a temperature-controlled (25 °C) cell (V = 10 ml) using an Elins P30JM potentiostat (the scan rate was 0.1 V s^{-1}). A platinum wire 1 mm in diameter in a Teflon casing was used as the working electrode. A saturated calomel electrode (SCE) separated from the solution by a salt bridge filled with the supporting electrolyte (0.1 M $NaClO_4$ in MeCN) was used as the reference electrode. A platinum plate (S = 3 cm^2) was used as the counter electrode.

Light petroleum, EtOAc, MeCN, MeOH, $NaClO_4$, hydroquinone **1**, pyrocatechol **2**, 2-mercaptobenzothiazole **3**, 4-nitro-1*H*-pyrazole, 3,5-dimethyl-1*H*-pyrazole **5**, Bu^{t}OK and silica gel (0.035–0.070 mm, 60 Å) for column chromatography were purchased from Acros Organics. Sodium 4-nitropyrazolate **4** was obtained according to a reported procedure.[14]

Electrolysis of DHB in the presence of a nucleophile (Table 1, entries 1 and 3). A solution of $NaClO_4$ in MeCN (50 ml, 0.1 M) containing 0.001 mol of DHB and 0.002 mol of a nucleophile was placed in the anodic space of a spatially divided (by a diaphragm made of tracing paper)

Table 1 Electrolysis of DHB in the presence of nucleophiles.

Entry	Substrate	E_{CPE}/V	Product with nucleophiles [yield (%)]		
			3	**4**	**5**
1	**1**	1.1	**6** (13,[a] 10[b])	–[c]	**8** (6[a])
2	**1′**[d]	–	**6** (10,[a] 8[b])	**7** (4[a])	**8** (5[a])
3	**2**	1.3	**9** (35,[a] 30[b])	–[c]	–[c]

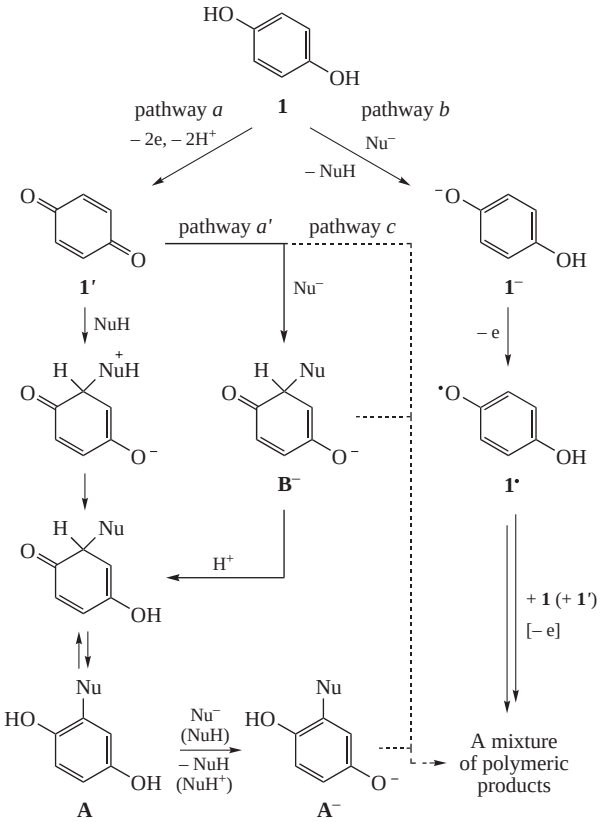
[a] NMR yield. [b] Isolated yield. [c] A complex mixture of products; the same result was obtained at E_{CPE} = 0.4 V. [d] *p*-Benzoquinone **1′** was preliminarily generated from **1** followed by addition of Nu.

with the target thioether **6**, up to 85% of non-reacted **1′**, whereas no unreacted **2′** was found in the final solution in the preparation of thioether **9**.

On can believe that oxidative functionalization of *p*(*o*)-DHBs in the presence of **3** occurs through pathway *a* (Scheme 2). The initial stage of this process corresponds to the electrogeneration of quinone **1′**, which adds NuH and, according to the published data,[12] gives the target product **A**.

If the nucleophile is charged (Nu^-), then, depending on its basicity, the process can occur either by pathway *b* or by pathway *a′* (see Scheme 2). In the latter case, product **A** can be deprotonated with Nu^-, and the resulting anion $\mathbf{A}^-$ (a tautomer of anion $\mathbf{B}^-$) can undergo subsequent transformations, *e.g.*, *via* pathway *c*. Let us note that deprotonation can also occur in the case of a non-charged but sufficiently basic NuH. Thus, the role of acid-base properties of the co-reactant (and also medium) is an important factor (see pathways *a*, *a′*, *b* and *c*).

Unlike thiol **3**, the nitropyrazole salt **4** is not only a weaker nucleophile (E_p^{ox} = 1.6 V, see Figure 1), but also, much more important, has higher basicity (CV data, see below). Its processing apparently occurs by pathway *b* (see Scheme 2), the first stage of which (**1** → $\mathbf{1}^-$) corresponds to deprotonation of the starting **1**. Anion $\mathbf{1}^-$ is oxidized much more easily than the starting **1**, and the resulting radical $\mathbf{1}^{\bullet}$ undergoes various transformations (by



Scheme 2

reactions with the starting **1**, with quinone **1′**, *etc*.). This, as a rule, gives a complex mixture of products. This mechanism agrees with the experimental results provided below.

The CV data for mixtures of **1** (pK_a = 9.85)[7]/**4** and **2** (pK_a = = 9.27)[13]/**4** confirmed that the anion of salt **4** had the properties of a base (Scheme 3). In fact, the heights of *o*(*p*)-DHBs oxidation peaks in the presence of this anion would decrease (see, *e.g.*, *o*-DHB **2**, peak *1*, Figure 2), and a new peak *2* with E_p^{ox} = 0.4 V

thermally controlled (25 °C) cell (V = 60 ml) with coaxial cylindrical Pt electrodes (S_{anode} = 26 cm^2, $S_{cathode}$ = 10 cm^2). In the tests with salt **4**, MeOH (2 ml) was added to ensure complete dissolution. A 0.1 M solution of $NaClO_4$ in MeCN (10 ml) was placed in the cathodic space. Electrolysis was carried out in a flow of nitrogen with vigorous stirring at oxidation potentials of 1.1 V (**1**), 1.3 V (**2**) or 0.4 V [*p*(*o*)-DHB$^-$ anions]. The process was stopped at regular intervals for reactivation of the Pt electrodes by calcination and for addition of fresh portions of the catholyte. After passing 2 F of electricity (as required for a 2-electron process of DHB oxidation), electrolysis was stopped and the mixture was stirred for 2 h. The solvent was distilled off *in vacuo*, then water (10 ml) was added and the mixture was sequentially extracted with toluene (2 × 30 ml) and Et_2O (2 × 30 ml). The extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was analyzed by mass spectrometry and ^{1}H NMR spectroscopy with addition of dioxane as the standard (all experiments) or purified by column chromatography on SiO_2 using the light petroleum/EtOAc system (experiments with **3**). In the first case, the product yield was determined from ^{1}H NMR data by comparison of the integral intensities of the signals of CH-protons in the product (in the range of δ 5.5–7.2) and CH_2-protons in dioxane (at δ 3.70). Identification of the products was performed using their characteristics reported previously (in the case of products **6** and **9**),[15,16] or (for new compounds **7** and **8**) based on the known characteristics of compounds with similar structures, namely: 2-bromobenzene-1,4-diol,[17] 1-(2,5-dimethoxyphenyl)-4-nitro-1*H*-pyrazole and 1-(2,5-dimethoxyphenyl)-3,5-dimethyl-1*H*-pyrazole.[18]

Electrosynthesis of benzoquinone **1′** *followed by the nucleophile addition (Table 1, entry 2)*. The process was carried out under the conditions described above, in two stages: (1) electrolysis of 0.001 mol of **1** by passing 2 F electricity (as required for 2-electron oxidation); (2) addition of 0.002 mol of a nucleophile (**3**–**5**) with stirring for 2 h. The resulting mixture was treated and analyzed as above.

2-(1,3-Benzothiazol-2-ylsulfanyl)benzene-1,4-diol **6**: white solid, mp 224–226 °C. ^{1}H NMR, δ: 6.88 (dd, 1H, C^{5}H, $J_{5,6}$ 8.8 Hz, $J_{5,3}$ 2.7 Hz), 6.93 (dd, 1H, C^{6}H, $J_{6,5}$ 8.8 Hz, $J_{6,3}$ 0.6 Hz), 7.02 (dd, $J_{3,5}$ 2.7 Hz, $J_{3,6}$ 0.6 Hz), 7.29 (ddd, 1H, C$^{6'}$H, 2-$C_7H_4NS_2$, $J_{6',7'}$ 8.2 Hz, $J_{6',5'}$ 7.1 Hz, $J_{6',4'}$ 1.1 Hz), 7.42 (ddd, 1H, C$^{5'}$H, 2-$C_7H_4NS_2$, $J_{5',4'}$ 8.1 Hz, $J_{5',6'}$ 7.1 Hz, $J_{5',7'}$ 1.2 Hz), 7.82 (ddd, 1H, C$^{4'}$H, 2-$C_7H_4NS_2$, $J_{4',5'}$ 8.1 Hz, $J_{4',6'}$ 1.1 Hz, $J_{4',7'}$ 0.7 Hz), 7.90 (ddd, 1H, C$^{4'}$H, 2-$C_7H_4NS_2$, $J_{7',6'}$ 8.2 Hz, $J_{7',5'}$ 1.2 Hz, $J_{7',4'}$ 0.7 Hz), 9.20 (br. s, 1H, 4-OH), 9.68 (s, 1H, 1-OH). MS, *m*/*z*: 275 (M^+). Found (%): C, 56.82; H, 3.19; N, 5.14. Calc. for $C_{13}H_9NO_2S_2$ (%): C, 56.71; H, 3.29; N, 5.09.

*2-(4-Nitro-1*H*-pyrazol-1-yl)benzene-1,4-diol* **7**: ^{1}H NMR, δ: 6.70 (dd, 1H, C^{5}H, $J_{5,6}$ 8.8 Hz, $J_{5,3}$ 2.6 Hz), 6.91 (d, 1H, C^{6}H, $J_{6,5}$ 8.8 Hz), 7.09 (d, 1H, C^{3}H, $J_{3,5}$ 2.6 Hz), 8.48 (s, 1H, 2-$C_3H_2N_3O_2$, C$^{5'}$H), 9.16 (s, 1H, 2-$C_3H_2N_3O_2$, C$^{3'}$H), 9.21 (br. s, 1H, 4-OH), 9.98 (br. s, 1H, 1-OH). MS, *m*/*z*: 221 (M^+).

*2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)benzene-1,4-diol* **8**: ^{1}H NMR, δ: 2.07 (s, 3H, 2-$C_5H_7N_2$, 5′-Me), 2.15 (s, 3H, 2-$C_5H_7N_2$, 3′-Me), 5.98 (s, 1H, 2-$C_5H_7N_2$, C$^{4'}$H), 6.60 (d, 1H, C^{3}H, $J_{3,5}$ 2.3 Hz), 6.69 (dd, 1H, C^{5}H, $J_{5,6}$ 8.8 Hz, $J_{5,3}$ 2.3 Hz), 6.81 (d, 1H, C^{6}H, $J_{6,5}$ 8.8 Hz), 9.50 (br. s, 2H, 1-OH, 4-OH). MS, *m*/*z*: 204 (M^+).

4-(1,3-Benzothiazol-2-ylsulfanyl)benzene-1,2-diol **9**: pale yellow solid, mp 196–198 °C. ^{1}H NMR, δ: 6.93 (dd, 1H, C^{6}H, $J_{6,5}$ 8.2 Hz, $J_{6,3}$ 0.7 Hz), 7.07 (dd, 1H, C^{5}H, $J_{5,6}$ 8.2 Hz, J_{5-3} 2.2 Hz), 7.14 (dd, 1H, C^{3}H, $J_{3,5}$ 2.2 Hz, $J_{3,6}$ 0.7 Hz), 7.29 (ddd, 1H, C$^{6'}$H, 2-$C_7H_4NS_2$, $J_{6',7'}$ 8.2 Hz, $J_{6',5'}$ 7.1 Hz, $J_{6',4'}$ 1.2 Hz), 7.41 (ddd, 1H, C$^{5'}$H, 2-$C_7H_4NS_2$, $J_{5',4'}$ 8.2 Hz, $J_{5',6'}$ 7.1 Hz, $J_{5',7'}$ 1.2 Hz), 7.80 (ddd, 1H, C$^{4'}$H, 2-$C_7H_4NS_2$, $J_{4',5'}$ 8.2 Hz, $J_{4',6'}$ 1.1 Hz, $J_{4',7'}$ 0.7 Hz), 7.89 (ddd, 1H, C$^{4'}$H, 2-$C_7H_4NS_2$, $J_{7',6'}$ 8.1 Hz, $J_{7',5'}$ 1.2 Hz, $J_{7',4'}$ 0.7 Hz), 9.57 (br. s, 1H, 4-OH), 9.77 (s, 1H, 1-OH). MS, *m*/*z*: 275 (M^+). Found (%): C, 56.84; H, 3.16; N, 5.17. Calc. for $C_{13}H_9NO_2S_2$ (%): C, 56.71; H, 3.29; N, 5.09.

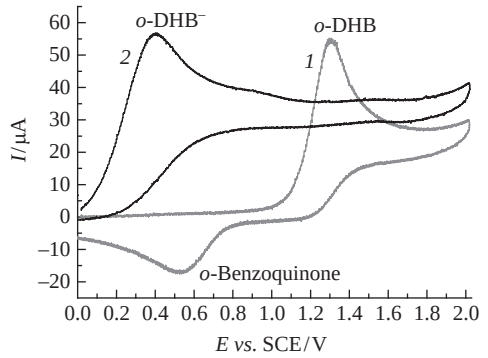
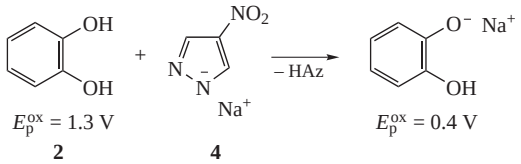


Figure 2 CV of *o*-DHB **2** (*c* = 0.002 M) on a Pt electrode (*1*) in 0.1 M $NaClO_4$ solution in MeCN and (*2*) in the presence of an excess of salt **4** (*c* = 0.008 M).

appeared simultaneously. With a 4-fold excess of salt **4** the oxidation peaks of *o*(*p*)-DHBs completely disappeared, whereas the peak with E_p^{ox} = 0.4 V remained. A similar CV analysis of *o*(*p*)-DHB solutions with the addition of Bu^tOK confirmed that the anodic peak with E_p^{ox} = 0.4 V corresponded to *o*(*p*)-DHB$^-$ monoanions oxidized at the same potential.



Scheme 3

Note that on addition of an excess of salt **4** to a solution of *o*(*p*)-DHB in MeCN, the solution turned dark red, which indicated that *o*(*p*)-DHB$^-$ ions were formed (see Scheme 3). Electrolysis of these mixtures (see Table 1, entries 1 and 3) gave resinous products. Thus, it is undesirable to perform the process by pathway *b* (see Scheme 2) involving *o*(*p*)-DHB$^-$ anions. An attempt to redirect the process from pathway *b* to pathway *a'* by preliminary electrogeneration of quinone followed by addition of salt **4** did not lead to a noticeable success, either. Apparently, protons are scavenged in the anolyte by the excess basic anion of **4**, which inhibits the protonation stage (pathway *a'*). As a consequence, intermediate anion **B**$^-$ undergoes various reactions (*e.g.*, reacts with quinone) to give resinous products. For these reasons, azolation product **7** was detected in the reaction mixture by ^{1}H NMR spectroscopy and mass spectrometry, although in trace amounts, and only in the case of the more stable benzoquinone **1′** (see Table 1, entry 2).

Even if one assumes that product **A** can be formed (see Scheme 2), then, due to the acceptor properties of the nitropyrazole substituent, this product should undergo deprotonation more easily than the starting DHB, with generation of anion **A**$^-$ followed by its resinification, *e.g.*, by pathway *c*. On the other hand, as expected, suppression of the basic properties of salt **4** anion by addition of an acid resulted in its nearly complete deactivation.

As expected, in the case of pyrazole **5** (E_p^{ox} = 1.8 V) the efficiency of reactions with DHBs was low (see Table 1). In fact, electrolysis of *p*-DHB **1** in the presence of **5** (or addition of **5** to benzoquinone **1′**) affords the azolation product **8** in only 5–6% yields, along with up to 80% unreacted **5** (see Table 1). This result is apparently a consequence of both the insufficient nucleophilicity of **5** and its weaker basic properties in comparison with anion of salt **4**. The absence of **5** in the reaction mixture after the electrolysis of *o*-DHB **2** (entry 3) indicates that **5** is consumed somehow to give polymeric products.

In conclusion, without optimizing the conditions of studied S_N^H(An) processes involving DHB/Nu pairs, their main regularities were established. In general, one of the important conditions for successful electrofunctionalization of DHB is that the substituting reactant should be not only a strong nucleophile but also a rather weak base which cannot deprotonate either the starting DHB or their functionalization products. The balance of the acid-base properties of nucleophile, DHB, and the medium are the key factor here. This balance should be regarded thoroughly in each case to develop an efficient process of DHB functionalization.

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