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Electrochemical Synthesis of Sulfonamide Derivatives Based on the Oxidation of 2,5-Diethoxy-4-Morpholinoaniline in the Presence of Arylsulfinic Acids

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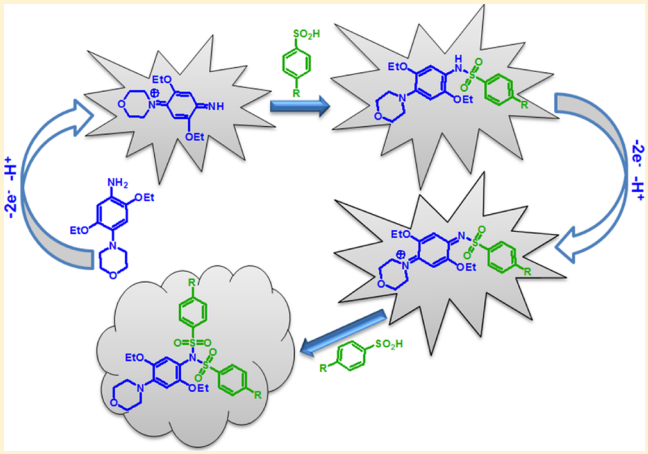
Supporting Information

ABSTRACT: Some new sulfonamide derivatives were synthesized in aqueous solutions via anodic oxidation of 2,5-diethoxy-4-morpholinoaniline in the presence of arylsulfinic acids using a commercial carbon anode. In addition, the formation mechanism of the products was discussed. The obtained data show that the electrogenerated quinone diimine undergoes a Michael-type addition reaction with arylsulfinic acids to yield the respective sulfonamide derivatives. In this work, two different types of products (mono- and disulfone derivatives) in the same precursor could be isolated just by controlling the exerted potentials.



Sulfonamides are a class of antibacterial compounds, all of which contain the sulfonamido group, $-SO_2NH$ (Figure 1). These compounds are used in both human and veterinary medicine. In human medicine they are widely used to treat various conditions including urinary tract infections, eye lotions, gut infections, and mucous membrane infections. Sulfonamides are classified in veterinary medicine as standard use, highly soluble, potentiated, and topical sulfonamides.[1,2] These drugs are preferred because of their wide spectrum of antimicrobial activity and noninterference with the host defense mechanism. Thus, the synthesis of new sulfonamide derivatives is a fascinating and informative area in medicinal chemistry.[2] Such properties have motivated a greater number of researchers to develop new methods for the synthesis of sulfonamide derivatives. In this way, many of these compounds have been synthesized and investigated against various protozoal, bacterial, and viral diseases.[2,3]

On the other hand, because of the high selectivity due to the in situ formation of the reactants at the electrode−electrolyte interface, the change of polarity using electron transfer reactions, and the formation of different types of products by control of the potential, electrochemistry can be considered as a powerful tool for the synthesis of complex organic molecules.[4] A literature review shows that contrary to the large number of reports on chemical synthesis, only a few papers on the electrolytic synthesis of the sulfonamide derivatives have been published.[5]

On the other hand, the presence of alkyl groups in the structures of drugs increases their hydrophobicity and makes it easier for them to cross the gut wall. One of the properties of such drugs is their lack of rapid excretion. Accordingly, we expected that the synthesis of new sulfonamide derivatives with one or two arylsulfinic groups might lead to the above-mentioned properties. To implement this idea, we synthesized some new sulfonamide derivatives by means of the anodic oxidation of 2,5-diethoxy-4-morpholinoaniline (**DEM**) in the presence of arylsulfinic acids (Figure 1).

The cyclic voltammogram of a solution of **DEM** in an aqueous solution containing perchloric acid (c = 0.1 M) is shown as curve a in Figure 2. As can be seen, one anodic peak (A_1) and two cathodic peaks (C_1 and C_0) were obtained. Anodic peak A_1 and cathodic peak C_1 are counterparts and correspond to the transformation of **DEM** to *p*-quinone diimine **QDI**, and vice versa within a reversible two-electron process.[6] In addition, cathodic peak C_0 corresponds to the reduction of 2,5-diethoxy-4-iminocyclohexa-2,5-dienone (formed from the hydrolysis of **QDI**) to 4-amino-2,5-diethoxyphenol.[6] The oxidation of **DEM** in the presence of *p*-toluenesulfinic acid (**TSA**) as a nucleophile was studied in some detail. As can be seen, I_{pC1} and I_{pC0} decrease and a new anodic peak (A_2) and corresponding cathodic peak (C_2) appear

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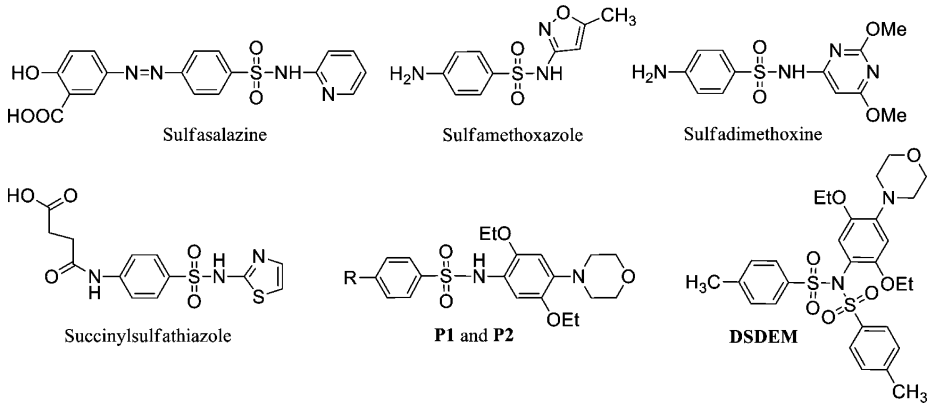


Figure 1. Structures of some available sulfonamides and sulfonamides synthesized in this work (**P1**, **P2**, and **DSDEM**).

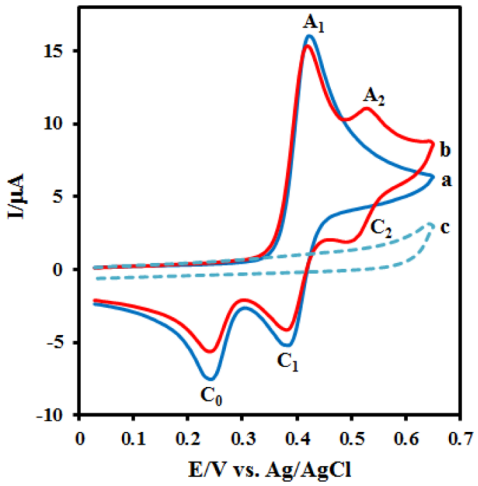


Figure 2. Cyclic voltammograms of (a) **DEM** (1.0 mM), (b) **DEM** (1.0 mM) in the presence of **TSA** (2.0 mM), and (c) **TSA** (2.0 mM) in the absence of **DEM** in aqueous solutions containing perchloric acid (0.1 M) at a glassy carbon electrode. Scan rate = 100 mV s^{-1}; t = 25 ± 1 °C.

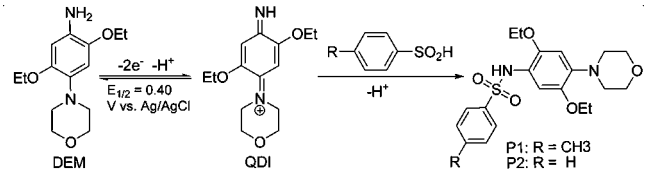
at more positive potentials (Figure 2, curve b). It should be noted that, under these conditions, no anodic or cathodic peaks were observed in the cyclic voltammogram of **TSA** (Figure 2, curve c).

The effect of the **TSA** concentration on the cyclic voltammogram of **DEM** was also studied. Our data show that when the **TSA** concentration is increased, (a) I_{pA1} remains constant, (b) I_{pC1} and I_{pC0} decrease, and (c) I_{pA2} and I_{pC2} increase (see Figure S1 in the Supporting Information).

The effect of the potential scan rate on the cyclic voltammogram of **DEM** in the presence of **TSA** was also studied. The obtained data show that with increasing scan rate, the peak current ratios (I_{pC1}/I_{pA1} and I_{pA1}/I_{pA2}) increase.

The time scale of a cyclic voltammetry experiment is determined by the scan rate, as increasing the scan rate decreases the experimental time scale and removes the effects of the following chemical reaction (the reaction of **QDI** with **TSA**) appearing as an increase in I_{pC1}/I_{pA1} and I_{pA1}/I_{pA2}.[7] Furthermore, the current function for peak A_1, $I_{pA1}/v^{1/2}$, changes only slightly with increasing scan rate, and such behavior is also adopted as indicative of the *EC* mechanism.[7] Controlled-potential coulometry was performed in an aqueous solution containing perchloric acid (c = 0.1 M), **DEM** (0.25 mmol), and **TSA** (0.25 mmol) at 0.40 V vs Ag/AgCl. Our results show that anodic peak A_1 disappeared when the charge consumption was about two electrons per molecule of **DEM**. The cyclic voltammetry and controlled-potential coulometry data accompanied by the spectroscopic data of the final product (see the Supporting Information) allow us to propose the mechanism shown in Scheme 1 for the electrochemical oxidation of **DEM** in the presence of **TSA** at 0.40 V vs Ag/AgCl.

Scheme 1. Proposed Mechanism for the Electrochemical Oxidation of DEM in the Presence of TSA and BSA



According to our results, it seems that the 1,4-addition (Michael addition) reaction of **TSA** to **QDI** leads to new derivative of 2,5-diethoxy-4-morpholinoaniline (**P1**) as a final product. The oxidation of **P1** is more difficult than the oxidation of **DEM** by virtue of the presence of the electron-withdrawing tolylsulfonyl group on **P1** as well as the insolubility of **P1** in aqueous solution. Our data also confirm that the new peaks A_2 and C_2 are related to oxidation of **P1** to its related *p*-quinone diimine ($\mathbf{P1_{ox}}$) and vice versa within a reversible two-electron process ($E_{1/2}$ = 0.51 V; see Scheme 2).

In the *EC* mechanism, the peak current ratios (I_{pA1}/I_{pC1} and I_{pA2}/I_{pA1}) are indications of the homogeneous reaction rate. An increase in the peak current ratio is an indicator of a high reaction rate. Comparison of the cyclic voltammogram of **DEM** in the presence of **TSA** with that of benzenesulfinic acid (**BSA**) shows that the rates of the reactions between arylsulfinic acids and **QDI** vary in the order **TSA** > **BSA** (Figure S2 in the Supporting Information). The observed trend is expected since **TSA** is much better nucleophile than **BSA** because of the presence of a methyl group with electron-donating character in the structure of **TSA**.[5b,c]

In order to synthesize the disulfone derivatives of **DEM**, electrochemical oxidation of **DEM** was studied in a 50/50 (v/v) water (phosphate buffer, pH 3.2)/acetonitrile mixture. Acetonitrile as a cosolvent was added to dissolve **P1**. Under these conditions, the cyclic voltammogram shows one anodic peak (A_1) and two cathodic peaks (C_1 and C_0) at 0.34, 0.21, and 0.08 V vs Ag/AgCl, respectively. In the presence of **TSA**,

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the cathodic peaks (C_1 and C_2) decreased and a new anodic/cathodic couple peak (A_2/C_2) appeared at 0.43 and 0.40 V vs Ag/AgCl, respectively. Controlled-potential coulometry was performed in a 50/50 (v/v) water (phosphate buffer, pH 3.2)/acetonitrile mixture containing **DEM** and **TSA** at 0.50 V vs Ag/AgCl. Monitoring the electrolysis progress by cyclic voltammetry synchronously during controlled-potential coulometry showed that as the coulometry progresses, I_{pA1} and I_{pA2} decrease (Figure 3). These peaks (A_1 and A_2) disappear when the charge consumption becomes about four electrons per molecule of **DEM.**

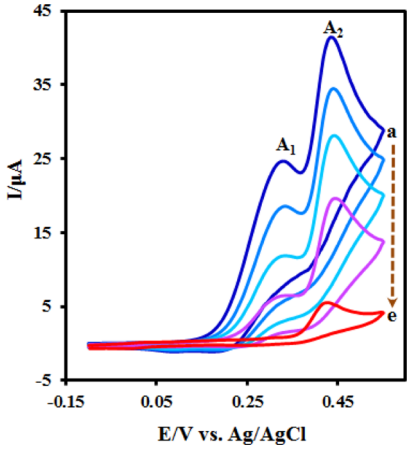
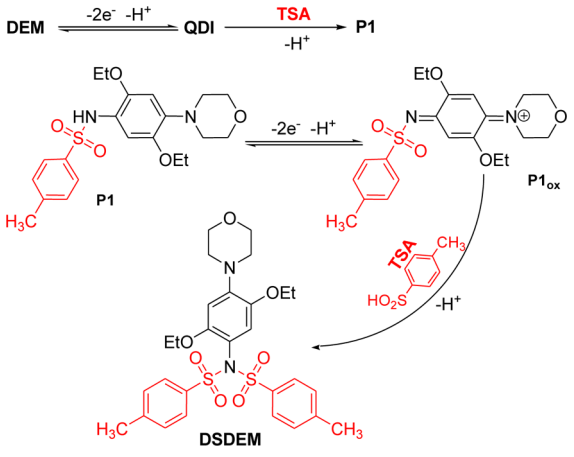


Figure 3. Cyclic voltammograms of **DEM** (0.30 mmol) in the presence **TSA** (0.60 mmol) during controlled-potential coulometry at 0.50 V vs Ag/AgCl in a 50/50 (v/v) water (phosphate buffer, pH 3.2)/acetonitrile mixture after the consumption of (a) 0 C, (b) 20 C, (c) 41 C, (d) 60 C, and (e) 110 C. Scan rate = 100 mV s^{-1}; t = 25 ± 1 °C.

Under these conditions, the generation of $\mathbf{P1}_{ox}$ is followed by a Michael-type addition reaction of **TSA** to produce disulfone derivative **DSDEM** as a final product (Scheme 2). The structure of **DSDEM** was further confirmed by single-crystal X-ray diffraction analysis, as shown in Figure 4.

The presented electrochemical method has some important advantages, including the use of electricity as the energy source instead of oxidative reagents, the ability to work at room temperature and pressure, technical feasibility, high atom economy (>99%), and selective synthesis of mono- or disulfone derivatives of **DEM** (**P1** or **DSDEM**) just by controlling the exerted potential during electrolysis. Finally, although one-pot reactions are performed potentiostatically on a millimolar scale in divided cells, there is little difficulty in producing larger quantities by using larger cells.

Scheme 2. Proposed Mechanism for the Electrochemical Synthesis of DSDEM



EXPERIMENTAL SECTION

Apparatus and Reagents. The working electrode used in the voltammetry experiments 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 macroscale electrolysis was an assembly of four ordinary soft carbon rods (6 mm in diameter and 4 cm in length), placed as single rods at the edges of a square with a distance of 3 cm. A large platinum gauze cylinder (25 cm^2 in area) constituted the counter electrode. The electrochemical oxidations were performed under constant-potential conditions in a cell with two compartments separated by an ordinary porous fritted-glass diaphragm (a tube with 1.5 cm diameter) and equipped with a magnetic stirrer. **DEM**, **TSA**, **BSA,** perchloric acid, and other solvents were obtained from commercial sources and used without further purification. More details are described in the previous paper.[8]

Electroorganic Synthesis of P1 and P2. In a typical procedure, 70 mL of 0.1 M perchloric acid solution containing **DEM** (0.25 mmol) and **TSA** or **BSA** (0.25 mmol) was subjected to electrolysis at 0.40 V vs Ag/AgCl in a divided cell. The electrolysis was terminated when the current decayed to 5% of its original value. The precipitated solid was collected by filtration and washed several times with water.

*N-(2,5-Diethoxy-4-morpholinophenyl)-4-methylbenzenesulfonamide ($C_{21}H_{28}N_2O_5S$, **P1**).* Isolated yield: 62% (0.065 g). Mp: 211−212 °C (dec). ^{1}H NMR (300 MHz, acetone-d_6): δ 1.23 (t, 3H), 1.44 (t, 3H), 2.38 (s, 3H), 3.89 (t, 4H), 3.95 (q, 2H), 4.00 (t, 4H), 4.15 (q, 2H), 7.39 (m, 4H), 7.76 (d, J = 8.2 Hz, 2H), 8.79 (NH, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 21.4, 55.4, 64.9, 66.2, 66.4, 107.4, 107.6, 125.1, 128.0, 130.2, 130.5, 137.9, 144.2, 145.0, 145.3. IR (KBr): 553.8, 576.0, 621.0, 709.7, 812.7, 908.6, 1043.1, 1089.5, 1122.0, 1210.5, 1265.7, 1340.2, 1399.5, 1453.0, 1511.2, 1598.8, 2989.8, 3243.1 cm^{-1}. MS: m/z (relative intensity) 420 (63, $[M]^+$), 265 (52), 246 (90), 172 (20), 155 (23), 139 (23), 123 (49), 107 (18), 91 (52), 45 (20). Anal. Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66; S, 7.63. Found: C, 59.82; H, 6.67; N, 6.64; S, 7.59.

*N-(2,5-Diethoxy-4-morpholinophenyl)benzenesulfonamide ($C_{20}H_{26}N_2O_5S$, **P2**).* Isolated yield: 57% (0.058 g). Mp: 213−214 °C (dec). ^{1}H NMR (300 MHz, acetone-d_6): δ 1.23 (t, 3H), 1.46 (t, 3H), 3.88 (m, 6H), 4.15 (t, 4H), 4.25 (q, 2H), 7.39 (s, 2H), 7.39 (m, 3H), 7.87 (d, J = 8.6 Hz, 2H), 8.76 (NH, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 53.1, 64.3, 65.2, 106.0, 108.4, 127.0, 129.2, 133.3, 144.1, 144.6. IR (KBr): 627.0, 692.6, 727.7, 764.7, 909.9, 1034.2, 1121.1, 1169.5, 1217.3, 1269.1, 1334.8, 1394.0, 1450.8, 1526.8, 2986.6, 3273.2 cm^{-1}. MS: m/z (relative intensity) 406 (100, $[M]^+$), 265 (98), 237 (58), 181 (25), 143 (58), 125 (72), 94 (35), 77 (86), 43 (35). Anal. Calcd for $C_{20}H_{26}N_2O_5S$: C, 59.09; H, 6.45; N, 6.89; S, 7.89. Found: C, 58.88; H, 6.76; N, 6.70; S, 7.63.

Electroorganic Synthesis of DSDEM. A 50/50 (v/v) water (phosphate buffer, c = 0.2 M, pH 3.2)/acetonitrile mixture (70 mL) containing **DEM** (0.25 mmol) and **TSA** (0.5 mmol) was subjected to electrolysis at 0.50 V vs Ag/AgCl. The electrolysis was terminated when the current decayed to 5% of its original value. The precipitated solid was collected by filtration and washed several times with water.

*N-(2,5-Diethoxy-4-morpholinophenyl)-N-(4-methylbenzenesulfonyl)-4-methylbenzenesulfonamide ($C_{28}H_{34}N_2O_7S_2$, **DSDEM**).* Isolated yield: 63% (0.090 g). Mp: 184−185 °C (dec). ^{1}H NMR (300 MHz DMSO-d_6): δ 0.94 (t, 3H), 1.2 (t, 3H), 2.43 (s, 6H), 3.08 (t, 4H), 3.74 (m, 8H), 6.36 (s, 1H), 6.46 (s, 1H), 7.42 (d, J = 8.2 Hz, 4H), 7.68 (d, J = 8.3 Hz, 4H). ^{13}C NMR (75 MHz DMSO-d_6): δ 14.1, 14.7, 21.1, 50.0, 63.8, 64.3, 66.3, 103.2, 113.6, 118.0, 128.3, 129.4, 136.6, 143.6, 144.5, 144.8, 151.9. IR (KBr): 489.8, 546.4, 607.3, 662.9, 689.7, 812.7, 902.1, 971.0, 1044.8, 1085.7, 1116.2, 1173.0, 1205.0, 1347.1, 1372.4, 1390.7, 1407.7, 1451.1, 1514.4, 1597.8, 2810.2, 2850.6,

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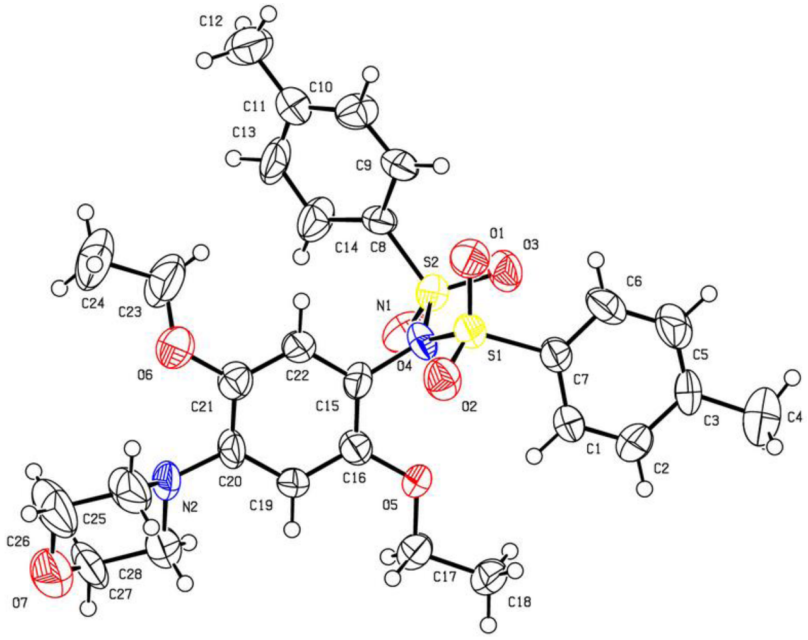

Figure 4. ORTEP view of the X-ray crystal structure of **DSDEM**.

2886.0, 2927.3, 2976.0 cm^{-1}. Anal. Calcd for $C_{28}H_{34}N_2O_7S_2$: C, 58.52; H, 5.96; N, 4.87; S, 11.16. Found: C, 58.20; H, 5.75; N, 4.82; S, 11.27.

■ ASSOCIATED CONTENT

Supporting Information

Cyclic voltammograms of **DEM** in the presence of **TSA** at various concentrations; cyclic voltammograms of **DEM** in the presence of **TSA** and **BSA**; FT-IR, ^1H NMR, ^{13}C NMR, and MS spectra for compounds **P1**, **P2**, and **DSDEM**; and crystallographic data for **DSDEM** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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