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Electrochemical Method for the Synthesis of Disulfides of 2-(Benzo[*d*]thiazol(or oxazol)-2-ylamino)-5-morpholinobenzenethiol

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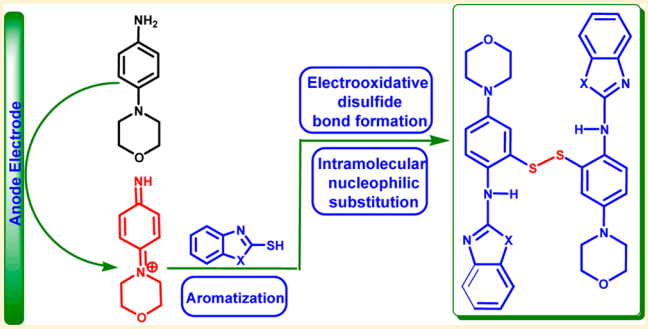
Supporting Information

ABSTRACT: Electrochemical synthesis of two new disulfides of 2-(benzo[*d*]thiazol(or oxazol)-2-ylamino)-5-morpholinobenzene thiols was carried out via the electrooxidation of 4-morpholinoaniline in the presence of 2-mercaptobenzothiazole and 2-mercaptobenzoxazole. Our results indicate that electrogenerated *p*-quinonediimine participated in a Michael-type addition reaction with 2-SH-benzazoles and after intramolecular nucleophilic substitution reaction and electrooxidative disulfide bond formation were converted to the corresponding disulfide compounds.



The disulfide bond is a covalent bond, usually derived by the coupling of two thiol groups. These compounds are potentially interesting from biological and synthetic point of view.[1−5] They are also essential moieties of biologically active compounds for peptide and protein stabilization.[6] Disulfides are also, useful reagents in organic synthesis.[7,8] Compounds containing a disulfide linkage used for the preparation of catenanes,[9] macrocycles,[10] carceplexes,[11] dendrimers,[12] rotaxanes, and micelles.[13]

The most common method for the preparation of disulfides is the oxidation of the appropriate thiols. Most of the existing methods involve the use of reagents such as molecular oxygen,[14] metal ions,[15] $Bu_3SnOMe/FeCl_3$,[16] nitric oxide,[17] halogens,[18] sodium perborate,[19] borohydride exchange resin (BER)-transition metal salt system,[20] morpholine iodine complex,[21] ammonium persulfate,[22] $KMnO_4/CuSO_4$,[23] H_2O_2,[24] permanganate,[25] $PVP–N_2O_4$,[26] and electrochemical methods.[27] Some of these methods suffer from one or more of disadvantages such as tedious workup of products, low yields, heavy metal contamination, toxicity, use of stoichiometric excess amounts of the reagents for successful oxidation, requirements of strong oxidizing agents, and cost-effective reagents or catalysts. Benzothiazoles are important fragments in medicinal chemistry because of the existence of a thiazole ring in their structure. One of the biologically active molecules bearing a benzothiazole nucleus is zopolrestat, which is used for the treatment of diabetic complications.[28] Benzothiazole and benzoxazole compounds were also studied for their antitumor, antiviral, and antimicrobial activities.[29] Flunoxaprofen is a well-known drug with benzoxazole moiety.[30] This drug is a chiral nonsteroidal anti-inflammatory drug. It has been shown to significantly improve the symptoms of osteoarthritis and rheumatoid arthritis.[30] In this work, we thought that the synthesis of disulfide compounds containing benzothiazole or benzoxazole moieties would be useful from the point of view of pharmaceutical properties.[31] This idea prompted us to investigate electrochemical oxidation of 4-morpholinoaniline (**1**) in the presence of 2-mercaptobenzothiazole (**2a**) and 2-mercaptobenzoxazole (**2b**) as nucleophiles and represent a facile and one-pot reagentless electrochemical method for the synthesis of new disulfide compounds containing benzothiazole or benzoxazole moieties. This reaction proceeds in a single step with an environmentally friendly method in ambient conditions and in a divided cell using a carbon electrode.

The oxidation of 4-morpholinoaniline (**1**) in the presence of 2-mercaptobenzothiazole (**2a**) as a nucleophile was studied in some detail. The cyclic voltammogram (first cycle) of 1.0 mM of 4-morpholinoaniline (**1**) in aqueous (phosphate buffer, 0.2 M, pH 2.0)/acetonitrile (80/20 v/v) mixture shows one anodic (A_1) and corresponding cathodic peak (C_1), which corresponds to the transformation of **1** to *p*-quinonediimine (**1ox**) and vice versa within a quasi-reversible two-electron process (Figure 1, curve a).[32] A peak current ratio (I_{pC1}/I_{pA1}) of nearly unity, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *p*-quinonediimine (**1ox**) produced at the surface of electrode under the experimental conditions. Figure 1, curve b, shows the cyclic voltammogram obtained for **1** in the presence of **2a**. Comparison of this voltammogram with cyclic voltammogram of **1** in the absence of **2a** shows that (a) the cathodic peak C_1 decreased intensively, (b) the anodic peak A_1 increased, (c) a new cathodic peak (C_0) appeared at less positive potentials, and (d) in the second cycle, a new peak (A_0) appears as a shoulder. More studies were performed by varying the potential scan rate of **1** in the presence of **2a**. The results indicate that the peak

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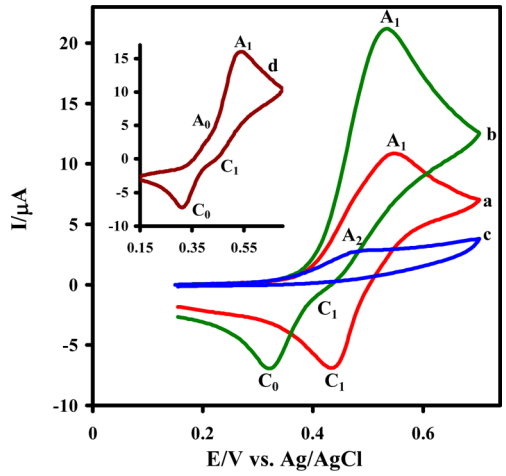


Figure 1. Cyclic voltammograms of (a) 1.0 mM 4-morpholinoaniline (**1**), (b) 1.0 mM **1** in the presence of 1.0 mM 2-mercaptobenzothiazole (**2a**), (c) 1.0 mM **2a** in the absence of **1**, (d) second cycle of cyclic voltammogram of 1.0 mM 4-morpholinoaniline (**1**) in the presence of 1.0 mM 2-mercaptobenzothiazole (**2a**) at a glassy carbon electrode in water (phosphate buffer, c = 0.2 M, pH = 2.0)/acetonitrile (80/20 v/v). Scan rate, 100 mV s^{-1}. t = 25 ± 1 °C.

current ratio (I_{pC1}/I_{pA1}) is dependent on the potential scan rate and increases with increasing it.

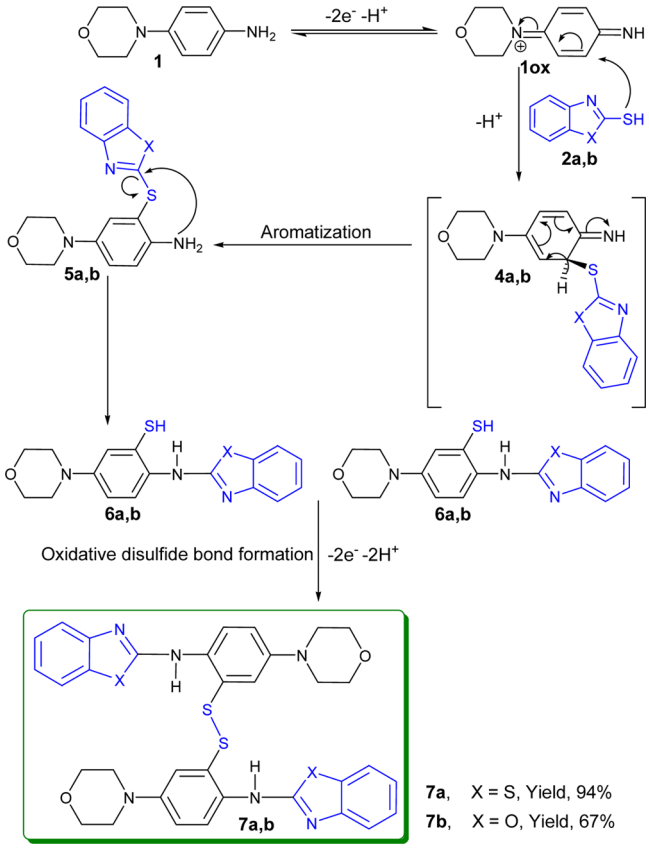
The occurrence of a chemical reaction after electron-transfer process is supported by the decreasing of peak C_1 during the reverse scan which could indicate that the *p*-quinonediimine (**1ox**) formed at the surface of the electrode is consumed by a chemical reaction with **2a**. On the other hand, with increasing the potential scan rate, the time required for the reaction of **2a** with **1ox** is not enough, and consequently, the peak current ratio (I_{pC1}/I_{pA1}) increases with increasing scan rate.[33]

The cyclic voltammetry results accompanied by the spectroscopic data of final product obtained from exhaustive oxidation of **1** in the presence of **2a** by applying 0.50 V versus SCE (Supporting Information) allow us to propose the following mechanism for the electrochemical oxidation of **1** in the presence of **2a** (Scheme 1).

According to our results, it seems that the 1,4-(Michael) addition reaction of **2a** to *p*-quinone-diimine (**1ox**) (Scheme 1, step 2) is faster than other secondary reactions (and after aromatization), leading to the intermediate **5a**. In the next step, intramolecular nucleophilic substitution reaction converts intermediate **5a** to thiol **6a**.[34,35] The oxidation of **6a** is easier than the oxidation of **1**; therefore, at the applied potential (0.50 V vs SCE) it can be oxidized. Thus, the apparent number of electrons transferred increases from the limits of n = 2 to 3 electrons per molecule **1**. Coupling of the two oxidized molecules of **6a** and disulfide linkage[36] leads to the disulfide **7a** as the final product.

According to our data, we can conclude that in Figure 1 (a) the cathodic peak C_1 decreased because of the consumption of electrochemically generated *p*-quinone-diimine (**1ox**) by a chemical reaction with **2a**, (b) the anodic peak A_1 increased because of the overlapping of peaks A_1 and A_2 as well as an increase of the apparent number of electrons transferred from n = 2 to n = 3 electrons per molecule **1**, and (c) a new cathodic and its anodic counterpart (C_0 and A_0) appeared. These new peaks are related to electrooxidation of intermediate **6a** to related *p*-quinonediimine (**6aox**) (Scheme 2). In Figure 1, curve c is the voltammogram of 2-mercaptobenzothiazole (**2a**).

Scheme 1. Proposed Mechanism for the Electrochemical Oxidation of 4-Morpholinoaniline (1) in the Presence of the 2-SH-Benzazoles



Wittstock and co-workers reported that the main product in the oxidation of 2-mercaptobenzoxazole is bis(benzoxazolyl) disulfide.[37]

The overall reaction mechanism for the anodic oxidation of 4-morpholinoaniline (**1**) in the presence of 2-mercaptobenzothiazole (**2a**) is an ECCEC mechanism. In intramolecular nucleophilic substitution reaction, the $-NH_2$ group at the intermediate **5a** attacks the carbon linked to sulfur in benzothiazole moiety and via a rearrangement converts to thiol **6a**. Oxidative disulfide bond formation converts thiol **6a** to disufide **7a**.

The biosynthetic formation of the disulfide bond is an important step in the maturation of the extracellular domains of both membrane and secreted proteins in eukaryotic and prokaryotic cells.[38] The formation of a disulfide bond from two thiols is a two-electron, two-proton reaction that requires an electron acceptor or oxidant. This work is a one-pot work, that in it, the formation of disulfide bond takes place directly at the surface of carbon electrode. The structure of **7a** is further confirmed by single-crystal X-ray diffraction analysis.

The oxidation of 4-morpholinoaniline (**1**) in the presence of 2-mercaptobenzoxazole (**2b**) as a nucleophile was also studied. Spectroscopic data of final product obtained from exhaustive oxidation of **1** in the presence of **2b** by applying 0.50 V versus SCE shows us the same disulfide compound (**7b**). The unambiguously determined structure of **7a** via single-crystal X-ray diffraction also lent support to the proposed structures of another related compound (**7b**).

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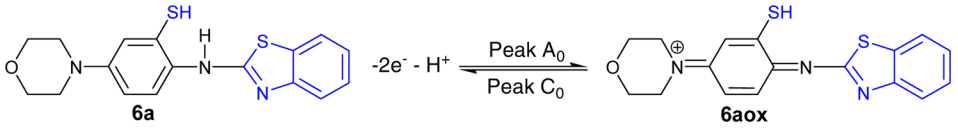
Scheme 2. Electrochemical Oxidation of Intermediate 6a



The presented electrochemical method has some important advantages. Clean synthesis, use of electricity as energy instead of oxidative reagents, one-pot reaction, room temperature and pressure conditions, technical feasibility, and especially dramatically high atom economy (>99%) are preeminent advantages of this work.

EXPERIMENTAL SECTION

Apparatus and Reagents. The working electrode used in the voltammetry experiments was a glassy carbon disk (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 carbon rods (6 mm diameter and 4 cm length), placed as single rods in the edges of a square with a distance of 3 cm. And a large platinum gauze cylinder (25 cm^2 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. 4-Morpholinoaniline, 2-mercaptobenzothiazole, 2-mercaptobenzoxazole, phosphoric acid, other solvents were obtained from commercial sources. These chemicals were used without further purification. More details are described in the previous work.[39]

Electroorganic Synthesis of 7a,b. A mixture of phosphate buffer solution (c = 0.2 M, pH = 2.0)/acetonitrile (45/15) containing 4-morpholinoaniline (**1**) (0.25 mmol) and 2-mercaptobenzothiazole (**2a**) (or 2-mercaptobenzoxazole, **2b**) (0.25 mmol) was subjected to electrolysis at 0.50 V vs SCE in a divided cell. The electrolysis was terminated when the current decayed to 5% of its original value. At the end of electrolysis, the precipitated solid was collected by filtration and was washed with water. Precipitated solid was dissolved in a chloroform solvent, and n-hexane solvent was added slowly. The crystallization container was placed in a dark place overnight.

7a: yield 94% (0.160 gr); mp 216−218 °C dec; IR (KBr) (cm^{-1}) 3451, 3062, 2950, 2813, 1606, 1538, 1445, 1234, 1121, 949, 750, 725; ^{1}H NMR, δ ppm (90 MHz, DMSO-d_6) 2.99 (s, 4H), 3.62 (s, 4H), 6.8−7.8 (m, 7H), 9.86 (s, 1H); ^{13}C NMR, δ ppm (22.5 MHz, DMSO-d_6) 48.0, 65.6, 114.0, 115.0, 118.0, 120.3, 120.8, 121.3, 125.5, 126.8, 130.1, 132.3, 149.4, 151.6, 165.4; MS (m/z) (relative intensity) 343 (100), 310 (40), 285 (35), 252 (80), 225 (50), 108 (20).

7b: yield 67% (0.11 gr); mp 205−207 °C dec; IR (KBr) (cm^{-1}) 3445, 2959, 2854, 1639, 1582, 1524, 1459, 1306, 1236, 1120, 950, 743; ^{1}H NMR, δ ppm (300 MHz, DMSO-d_6) 3.00 (m, 4H), 3.65 (m, 4H), 7.28 (m, 7H), 9.74 (s, 1H); ^{13}C NMR, δ ppm (100 MHz, DMSO-d_6) 48.7, 66.5, 109.3, 115.1, 115.3, 115.9, 116.6, 121.5, 124.3, 124.9, 127.3, 128.3, 132.4, 148.3, 150.0; MS (m/z) (relative intensity) 327 (2), 269 (5), 255 (4), 176 (18), 63 (18), 52 (25), 28 (100). Anal. Calcd for $C_{34}H_{32}N_6O_4S_2$: C, 62.56; H, 4.94; N, 12.87; S, 9.82. Found: C, 62.19; H, 4.84; N, 12.70; S, 9.67.

ASSOCIATED CONTENT

Supporting Information

FT-IR, ^{1}HNMR, ^{13}CNMR, and MS spectra for compounds **7a** and **7b** andX-ray data for compound **7a** (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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