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Kinetics study and electrochemical synthesis of arylsulfinic acid derivatives of clozapine in green media

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ABSTRACT

The electrochemical oxidation of clozapine (CLZ) has been studied in the presence of toluenesulfinic acid (TSA) and benzenesulfinic acid (BSA) as nucleophiles in aqueous solution, using cyclic voltammetry and controlled-potential coulometry. The results indicate the participation of electrochemically produced dibenzodiazepine in the Michael addition type reaction with TSA or BSA to form the corresponding new dibenzodiazepin derivatives. On the basis of the EEC mechanism, the observed homogeneous rate constants (k_{obs}) of the chemical reaction between oxidized clozapine with TSA and BSA were estimated by comparing the experimental cyclic voltammograms with the digitally simulated results. Also the effective parameters such as type of nucleophile, scan rate and pH on the rate constants of chemical reactions are investigated. The electrochemical synthesis of new dibenzodiazepine derivatives (**3a** and **3b**) has been successfully performed in an undivided cell at biological pH. The product has been characterized by IR, ^{1}H NMR, ^{13}C NMR and MS methods.

1. Introduction

Electrochemistry provides a very versatile means for electrosynthesis, mechanistic and kinetics studies [1–3]. Furthermore, cyclic voltammetry is known as a powerful technique for the investigation of electrochemical reactions that are coupled with chemical reactions. In addition, general treatment of the reaction mechanism is probably best carried out through digital simulations [4–9]. The reaction mechanism is depending on some parameters such as nature of the electroactive species (electron withdrawing or donating), and electrolysis medium (solvent, acidity or pH) [10]. Mechanistic analyses of reactions in which electron transfer is coupled to proton transfer [11,12] as well as electrochemical investigation of deprotonation of the radical cation followed by the coupling reactions [13] have attracted special attention.

Clozapine, 8-chloro-11-(4-methylpiperazine-1-yl)-5H Dibenzo [b,e] [1,4] diazepine, is a dibenzodiazepine derivative with atypical antipsychotic drug. This drug is very effective against both the negative and positive symptoms of schizophrenia and has been successfully used in patients who are “non-responder” to the classical neuroleptic drugs [14,15]. Clozapine use, however, is restricted because of the incidence of hematological disorders, mainly agranulocytosis, in about 0.8% patients receiving this drug treatment [16,17]. The mechanism of the agranulocytosis is still unclear, with studies demonstrating that the toxicity might be due to a metabolite of CLZ, i.e., a nitrenium cation (CLZox) [18]. Fischer et al. [19] concluded from studies with human myeloperoxidase and horseradish peroxidase (HRP) that CLZ activation possibly yields free radical metabolites. Maggs et al. studied the generation of chemically reactive metabolites, expressed by the covalent binding to cellular protein, depletes intracellular GSH and formation of thioether adducts, both in vitro and in vivo. They found the bioactivated reactive intermediate of CLZ to be either a radical cation or the nitrenium ion [20].

Some electrochemical techniques such as: cyclic voltammetry using diagnostic criteria derived by Nicholson and Shain for various electrode mechanisms and controlled-potential coulometry were used. These methods provide a powerful independent route for quantitative characterization of complex electrode processes [21–23]. Controlled-potential coulometry is a useful method for studying the mechanisms of electrode reactions and for determining the n-value for an electrode reaction without prior knowledge of the electrode area or diffusion coefficient. However, because the time scale of coulometric measurements is at least one or two orders of magnitude longer than that of voltammetric methods, the perturbing homogeneous chemical reactions that follow the electrode transfer, which might not affect the voltammetric measurement, may be important in coulometry [4,24].

In this work, we obtained two dibenzodiazepine derivatives by controlling potential during electrolysis. In this direction we investigated the electrochemical oxidation of clozapine (**1**) in the presence of toluenesulfinic acid (**2a**) and benzenesulfinic acid (**2b**) as nucleophiles and we have reported a facile and one-pot electrochemical method for

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the synthesis of new dibenzodiazepine derivatives in aqueous solutions and in an undivided cell. Also this work represents kinetics and mechanistic study of the electrochemical oxidation of CLZ in the presence of TSA and BSA as nucleophiles and the estimation of the observed homogeneous rate constants (k_{obs}) of the reaction of electrochemically generated CLZox with these nucleophiles by digital simulation of cyclic voltammograms.

2. Experimental

2.1. Apparatus and reagents

Cyclic voltammetry and controlled-potential coulometry were performed using an Autolab model PGSTAT 12 potentiostat/golvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disk (1.8 mm diameter), and platinum wire was used as counter electrode. The working electrode used in controlled-potential coulometry was an assembly of four carbon rods (6 mm diameter and 4 cm length) and a large platinum gauze constitute the counter electrode. The working electrode potentials were measured versus SCE (all electrodes from AZAR electrode). An undivided cell was used for coulometry. The IR spectra were recorded on a Shimadzu model IR Prestige 21 FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometer operating at 400 and 100 MHz, respectively. The mass spectra were obtained using Agilent Technologies (HP) 5973 Network mass selective detector.

Clozapine was pharmaceutical grade material (purity > 99%) is received from Sobhan pharmaceutical company from Iran. TSA and BSA were of analytical reagent grade from Fluka. Phosphate salts were of pro-analysis grade from E. Merck. Solutions were prepared in distilled water. The total concentrations of prepared buffers are 0.2 M. All experiments were conducted at room temperature.

2.2. Digital simulation

The cyclic voltammograms have been analyzed by a commercial digital simulation program (DIGIELCH 4, software) [25] to estimate the observed homogeneous rate constants (k_{obs}) of the reaction of CLZ with TSA (**2a**) and BSA (**2b**). To verify the reaction mechanism for the electrochemical oxidation of CLZ in the absence and presence of the TSA (**2a**) and BSA (**2b**), the cyclic voltammograms have been analyzed to find the best-fit between experimental and simulated cyclic voltammograms.

2.3. Electroorganic synthesis procedure

In a typical procedure, 80 mL of phosphate buffer solution (0.2 M, pH 7.2) containing 0.3 mmol of CLZ (**1**) and 0.3 mmol of TSA (**2a**) (or BSA (**2b**)) was electrolyzed at 0.5 V vs. SCE in an undivided cell. The solution was stirring by a magnetic stirrer during electrolysis. The process was interrupted during the electrolysis and the carbon anode was washed in acetone in order to reactivate it. The electrolysis was terminated when the current decayed to 10% of its original value. For the synthesis of **3a** and **3b,** at the end of electrolysis, cell was placed in refrigerator overnight, and then the precipitated solid was collected by filtration and was washed several times with water. After recrystallization in ethanol the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS methods.

2.4. Characteristics of 3a-3b

Compound **3a** ($C_{25}H_{26}ClN_4O_2S$): M.p = 203–205 °C. $IR_{(KBr)}$ = 3412, 3288, 2359, 1600, 1475, 1161 cm^{-1}. MS: m/z (relative intensity); 481 (M^+, 6.8), 472 (9), 410 (13), 326 (11.6), 268 (10), 256 (62), 243 (66), 227 (38), 192 (90), 164 (29.6), 99 (33.4), 70 (55.5), 42 (100). ^{1}H NMR (400 MHz, DMSO-d_6,): δ_H (ppm) 2.20 (3H, s, NCH_3), 2.38 (3H, s, CH_3), 2.49 (4H, m, $2CH_2$), 2.94 (4H, m, $2CH_2$), 3.36 (1H, s, NH), 6.84–7.62 (10H, m, H–Ar). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 21.55 (CH_3), 46.05 (NCH_3), 54.60 (CH_2), 54.78 (CH_2), 121.83, 123.45, 125.20, 126.45, 127.12, 129.36, 130.25, 131.32, 133.81, 137.87, 142.34, 142.64, 144.22, 146.99, 154.46, 159.15, 163.22.

Compound **3b** ($C_{24}H_{23}ClN_4O_2S$): M.p = 188–190 °C. $IR_{(KBr)}$ = 3422, 3285, 2372, 1560, 1470, 1150 cm^{-1}. MS: m/z (relative intensity); 467 (M^+,15.6), 396 (29.4), 384 (19.9), 325 (36), 268 (18.4), 255 (23.7), 226 (13.6), 191 (19), 164 (5.4), 99 (15.7), 83 (100), 70 (53), 42 (27.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 2.36 (3H, s, NCH3), 2.52 (4H, m, 2CH2), 3.49 (4H, m, $2CH_2$), 3.92 (1H, s, NH), 6.62–7.31 (11H, m, H–Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 46.17 (NCH_3), 47.23 (CH_2), 55.02 (CH_2), 118.94, 120.01, 120.09, 123.08, 123.12, 123.42, 123.81, 126.77, 127.86, 128.30, 129.07, 130.30, 131.91, 140.40, 141.77, 152.71, 162.83.

3. Results and discussion

Cyclic voltammetry of 1.0 mmol/L of CLZ (**1**) in aqueous solution containing 0.2 M phosphate buffer (pH 7.2) shows one anodic (A_1) in the positive-going scan and two cathodic peak (C_1 and C_2) in the negative-going scan (Fig. 1 curve a), which C_1 is counterpart of A_1, (peak current ratio (IpC_1/IpA_1) deviates from unity). The anodic peak (A_1) corresponds to the two-electron oxidation of the compound and peak C_1 corresponds likely to the reduction of CLZox, i.e., the nitrenium ion of CLZ, while the second reduction peak, C_2, was attributed to reduction of the product of a chemical reaction, likely hydroxylation, subsequent to the clozapine oxidation [26–28].

The oxidation of CLZ in the presence of TSA (**2a**) or BSA (**2b**) as nucleophile was studied in details. Fig. 1 (curve b) shows the cyclic voltammogram obtained for a 1.0 mmol L^{-1} solution of CLZ (**1**) in the presence of 1.0 mmol L^{-1} of **2a** and curve d shows the cyclic voltammogram obtained for a 1.0 mmol L^{-1} solution of CLZ (**1**) in the presence of 1.0 mmol L^{-1} **2b**. Comparison of these voltammograms with cyclic voltammogram of CLZ (**1**) in the absence of **2a** or **2b**, Fig. 1 (curve a) shows that the anodic peak A_1 is decreased and in the reverse scan, reduction peaks C_1 and C_2 disappeared completely. These observations indicate that a chemical reaction follows the electron transfer process and **1**ox, formed at the surface of the electrode by the two-electron oxidation of CLZ (**1**), is consumed in a reaction with the nucleophiles **2a** or **2b**. In this figures, curve c and e are the voltammograms of TSA and BSA respectively.

Fig. 2 shows cyclic voltammograms of CLZ in the presence of various concentration of **2a**. As shown, proportional to the augmentation of concentration of **2a**, the height of peaks A_1, C_1 was decreased and peak C_2 was disappeared. The peak current ratio (IpC_1/IpA_1) is strongly dependent on the concentration of **2a** or **2b** and decreases with increasing of them. The dependence of the peak current ratio (IpC_1/IpA_1) on the concentration of **2a** or **2b** indicates on a chemical reaction after electron transfer process. More voltammetric studies were performed by variation of the potential scan rate. In these conditions, cyclic voltammogram of 1.0 mmol/L of CLZ (**1**) in the presence of 1.0 mmol/L of **2a** (Fig. 3) and **2b** (data not shown) was recorded at different scan rates. The peak current ratio (IpC_1/IpA_1) depends on the scan rate and increases with increasing scan rate which shows a chemical reaction following the electron-transfer step [29]. The plot of the peak current ratio (IpC_1/IpA_1) versus scan rate for a mixture of CLZ (**1**) with **2a** (Fig. 3 insets a) or **2b** confirms the reactivity of **1**ox towards **2a** or **2b**. On the other hand, to prove the mechanism, the current function for peak A_1, ($IpA_1/v^{1/2}$), versus scan rate was plotted (data not shown). The peak current function shows a decreasing parallel to decreasing of scan rates. Such a behavior points to a chemical reaction following the electron transfer [3].

Finally the electrolysis was performed in phosphate buffer solution (c = 0.2 mol/L, pH 7.2) containing 0.3 mmol of CLZ (**1**) and 0.3 mmol of **2b** (or **2a**) at 0.5 V versus SCE. The monitoring of electrolysis progress