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Research paper

Synthesis and electrochemical investigations of piperazines

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ABSTRACT

Sodium4-benzyl piperazine-1-carbodithioate and sodium4-benzhydryl piperazine-1-carbodithioate were synthesized and characterized by FT-IR and multinuclear NMR (^{1}H, ^{13}C) spectroscopy. The effects of scan rate, pH and concentration on the voltammetric response of the analytes were investigated for the evaluation of electrochemical and kinetic parameters of the electron transfer processes. Redox mechanisms of the compounds were proposed on the basis of results obtained from electrochemical investigations. Square wave voltammetry was used to determine the limits of detection and quantification. Moreover, various thermodynamic parameters of the electrode reactions were evaluated from the temperature responsive redox response of the synthesized piperazines.

1. Introduction

Piperazine is a heterocyclic compound having two nitrogen atoms at opposite positions in the six membered ring. No one can deny the significance of piperazines as these compounds find extensive applications in various medical and industrial fields [1–4]. The structure-activity relationships of this class of compounds have been documented to relate with their proton coupled electron transfer reactions [5,6]. The hydrogen bonding ability of piperazines allow them to develop supramolecular assemblies [7]. Diamine and cyclic nature of piperazines make these compounds suitable as promoters for the removal and recovery of CO_2 [8]. Piperazines are important constituents of various anthelmintic products used for inhibition of some intestinal worms of pets and livestocks [9]. Piperazinic compounds also find use as chelating agents due to their ability of forming complex with metal ions [10]. Different factors *i.e.* aging, pollution, poor diet and smoking *etc.* cause oxidation of lipids, proteins, or DNA and produce free radicals that lead to the onset of cancer, cardiovascular, autoimmune, inflammatory and age-related degenerative brain diseases [11]. Piperazines being potent antioxidants have the ability of scavenging free radicals [12]. This class of compounds has been reported to exert its antioxidant role by the donation of electrons and protons [13]. Several evidences are available that relate the biological activities of piperazines with their pH dependent redox reactions [12–14]. Therefore, the current work is focused on exploring the proton coupled electron transfer reactions of piperazines in media of different pH.

Though extensive literature is available on piperazines, however, investigation of their redox mechanistic pathways by a multitude of electrochemical techniques is scanty. To bridge this gap in literature, we explored two representative members of this class by cyclic, differential pulse and square wave voltammetry (CV, DPV and SWV). CV was used for getting a general portrait of the analytes. DPV was employed for the evaluation of number of electrons involved in redox events. It was also used for getting evidence about the involvement of protons during electron transfer processes. SWV was used to judge the reversibility or irreversibility of a redox process. Moreover, due to its higher sensitivity and faster speed of analysis this technique was used for analytical determination of the analytes. Finally, on the basis of experimental outcomes, the redox mechanistic pathways of the compounds were proposed which are expected to provide valuable insights into the understanding of the biochemical actions of piperazines.

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2. Experimental

2.1. Chemicals and general methods

Stock solutions of the compounds were prepared in ethanol. Fresh working solutions were prepared in a 50:50 Britton–Robinson (BR) buffer and ethanol mixture. Electrochemical experiments were carried out in the pH range 2-12. Eco Chemie Autolab PGSTAT 12 running with GPES 4.9 (Utrecht, The Netherlands) software package was used for voltammetric experiments. Glassy carbon with 0.071 cm^2 was used as working electrode. Pt wire and Ag/AgCl (4 M KCl) were employed as counter and reference electrodes respectively. Square wave voltammetry was performed at 100 mV s^{-1}. Differential pulse voltammetry was carried out at 5 mV s^{-1}. GCE electrode was cleaned by rubbing it on nylon buffering pad using alumina powder of 1 μm particle size followed by thorough washing with distilled water. To ensure reproducible experimental results, various voltammograms were obtained till the achievement of a steady state baseline. Electrochemical measurement cell was used to immerse in a water circulating bath (IRMECO I-2400 GmbH Germany) in order to control temperature.

2.2. Synthesis and structural confirmation of the compounds

The title compounds, sodium 4-benzylpiperazine-1-carbodithioate (SBPC) and sodium 4-benzhydrylpiperazine-1-carbodithioate (SBHPC) were synthesized by a slightly modified reported procedure [15]. A methanolic solution (30 mL) containing equimolar sodium hydroxide and corresponding piperazine precursors was allowed to react with constant stirring for 1 h, followed by a drop wise addition of equimolar amount of undiluted CS_2 instead of methanolic solution of CS_2 as reported in literature [15]. The reaction mixture was stirred for 4 h at 0 °C. The precipitate thus formed was filtered off, washed with cooled methanol and air dried (Scheme 1).

2.2.1. Sodium 4-benzylpiperazine-1-carbodithioate (SBPC)

Amount of reagents used: 1-benzylpiperazine 3.05 g, 17.34 mmol; sodium hydroxide 0.693 g 17.34 mmol, carbon disulfide 1.318 g, 17.34 mmol. Yield: 80.83%, m.p. 132–133 °C. Elemental analysis, % Calculated (Found) for $C_{12}H_{15}N_2S_2Na$: C, 52.53 (55.51); H, 5.51 (5.45); N, 10.21 (10.13); S, 23.37 (23.30). FT-IR (cm^{-1}): 1451 (C-N), 1213 (C=S), 955 (C-S). ^{1}HNMR ($CDCl_3$, 300 MHz, δ, ppm): Piperazine 2.50 (4H, t, $^3J^1_{H,}{}^1_H$ = 5.1 Hz), 2.25 (4H, t, $^3J^1_{H,}{}^1_H$ = 5.1 Hz); Methylene: 3.45 (2H, s); Phenyl: 7.22-7.37 (5H, m). ^{13}CNMR ($CDCl_3$, 75 MHz, δ, ppm): 214.2 (SCS), 53.2, 49.4 (Piperazine-carbons), 62.4 (methylene), 138.4,129.3, 128.4,127.4 (Phenyl-carbons).

2.2.2. Sodium4-benzhydrylpiperazine-1-carbodithioate (SBHPC)

Amount of reagents used: 3 g (11.90 mmol) 1-(diphenylmethyl) piperazine, 0.476 g (11.90 mmol) sodium hydroxide, 0.903 g (11.90 mmol) carbon disulfide. Yield: 75.23%, m.p. 230–231 °C. Elemental analysis, % Calculated (Found) for $C_{18}H_{19}N_2S_2Na$: C, 61.69 (61.60); H, 5.46 (5.41); N, 7.99 (7.90); S, 18.30 (18.24). FT-IR (cm^{-1}): 1410 (C-N), 1212 (C=S), 924 (C-S). ^{1}HNMR ($CDCl_3$, 300 MHz, δ, ppm): Piperazine: 2.22 (4H, t, $^3J^1_{H,}{}^1_H$ = 4.8 Hz); 2.50 (4H, t, $^3J^1_{H,}{}^1_H$ = 4.8 Hz); methine: 3.36 (1H, s); Phenyl: 7.16-7.44 (10H, m). ^{13}CNMR ($CDCl_3$, 75 MHz, δ, ppm): 214.2 (SCS), 52.1, 49.4 (Piperazine-carbons), 75.2 (methine-carbon), 143.1, 128.9, 128.2,127.3 (Phenyl-carbons).

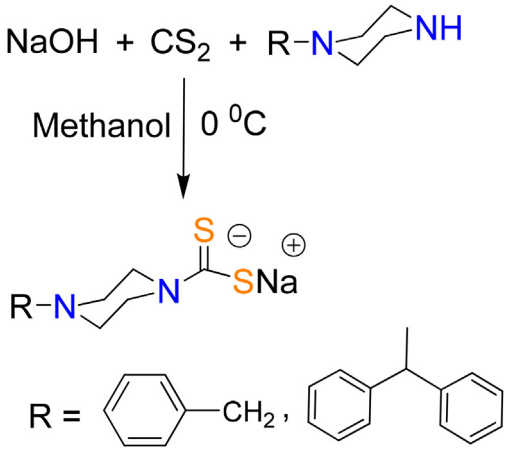
3. Results and discussion

3.1. Confirmation of the synthesis of SBPC and SBHPC

The absence of N-H peak of piperazine and the appearance of CS stretches around 1200 and 1000 cm^{-1} in the FT-IR spectra signified the formation of SBPC and SBHPC. Similarly, the disappearance of N-H peak in the ^{1}HNMR and the appearance of new signal due to CS in the ^{13}C NMR further confirmed the information obtained from IR analysis. Additionally, the number signals in ^{1}H NMR and ^{13}C NMR, the integration values of each peak (^{1}H NMR only) and theirs multiplicity (^{1}H NMR only) pattern are matched well with the expected structures of SBPC and SBHPC.

3.2. Differential pulse voltammetry

The electrochemical behaviour of sodium 4-benzyl piperazine-1-carbodithioate (SBPC) and sodium 4-benzhydryl piperazine-1-carbodithioate (SBPHC) was investigated over a wide pH range by differential pulse voltammetry. In neutral and alkaline conditions two anodic peaks corresponding to the oxidation of nitrogen atoms of SBPC appeared in the DPVs shown in Fig. 1. The absence of anodic signals in acidic media can be related to the surrounding and encapsulation of the oxidizable moiety of SBPC by H^+ ions that may prohibit the electron transfer from SBPC molecules to the electrode surface. The anodic peak current values increased significantly with elevation of pH due to closer accessibility of the electroactive moiety to the electrode surface. The number of electrons involved in the redox reaction was calculated from half peak width ($W_{1/2}$)



Scheme 1. Synthesis of SBPC and SBHPC.

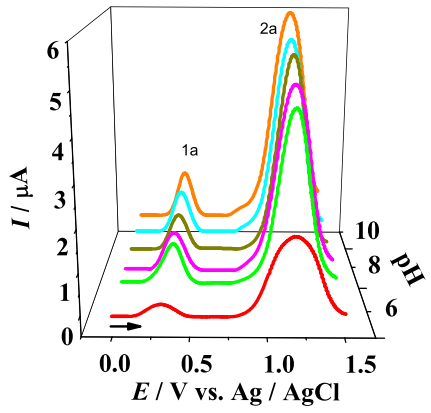


Fig. 1. DPVs (oxidation region) of 1 mM solution of SBPC obtained in solutions of pH 6–1 at a scan rate 5 mV/s.