Electrochemical Behaviors and Determinations of Some 2,5-Disubstituted Benzoxazole Compounds at the Hanging Mercury Drop Electrode

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Abstract: The electrochemical behaviors of *N*-(2-benzylbenzoxazol-5-yl)benzamide (B1), *N*-(2-benzylbenzoxazol-5-yl)-4-nitrobenzamide (B2) and *N*-(2-(4-chlorobenzyl)benzoxazol-5-yl)-4-nitrobenzamide (B3) were investigated by cyclic voltammetry (CV), square wave voltammetry (SWV), differential puls voltammetry (DPV), chronoamperometry (CA) and bulk electrolysis (BE) techniques in dimethylsulfoxide (DMSO) containing 0.1 M tetrabutylammonium tetrafluoroborate (TBATFB). The number of electrons transferred and diffusion coefficients were calculated by using chronoamperometry and bulk electrolysis techniques. Standard heterogeneous rate constants for the electrochemical reduction were calculated by Klingler-Kochi technique. The data obtained showed that the quantitative determination of benzoxazoles could be done by using DPV and SWV rapidly and sensitively. For the DPV technique, linear working ranges for B2 and B3 were found to be (6.0×10^{-7}-4.0×10^{-4}) M and (1.0×10^{-6}-2.0×10^{-4}) M respectively. The corresponding ranges for these compounds found by SWV were (6.0×10^{-7}-4.0×10^{-4}) M and (1.0×10^{-6}-2.0×10^{-4}) M. The detection limits for B2 obtained from DPV and SWV were calculated to be 1.33×10^{-7} M and 1.76×10^{-7} M respectively. The detection limits with B3 deplicted to be almost the same.

Keywords: Benzoxazoles derivatives, Voltammetry, Differential-pulse voltammetry, Square-wave voltammetry.

1. INTRODUCTION

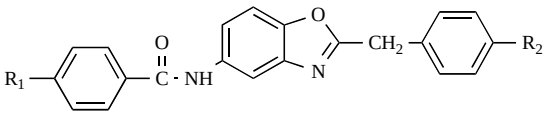
In recent years, benzoxazoles have drawn some attention due to their antibacterial and antifungal activity [1, 2], potential use as anticancer agents [3, 4] and laser dyes [5]. A bis (benzoxazole) isolated from the mycelial cake of the soil bacteria actinomycete (a strain of streptomyces) was shown to possess a remarkable antitumor activity [6]. This compound has been nicknamed as UK-1 and studied extensively in relation to its metal chelating ability and Mg(II)-intervened binding to DNA chains [7]. Syntheses of analogies of UK-1 were also reported to be underway to go a step further in making use of the DNA-binding capacity of the related structures [8].

Although UK-1 is a unique natural compound in that it has no antimicrobial, or antifungal activity–an unusual feature for cancer active natural product chemistry-many benzoxazole derivatives are reported to be of antimicrobial activity [9-11]. As an example, a series of *N*-(2-benzylbenzoxazole-5-yl)benzamide derivatives were prepared and tested for their antimicrobial activity [9].

As this class of compounds has shown of prospects of being used as drugs, their electrochemical characteristics may be of value in either understanding the mechanism of their action or determining their concentration. Especially the nitro-derivatives appear to be suitable for electrochemical studies as the nitro group is electroactive.

Numerous nitro-bearing drugs have been studied from electrochemical point of view [12-28]. In cases where the compounds involved were water-soluble mixed solvents [13, 15, 16, 24-27], dimethylformamide (DMF) [15, 24-26] and dimethylsulfoxide (DMSO) [12, 14, 17, 18, 24] were used as the reaction media. Water-soluble compounds were tested in aqueous medium [16, 21, 22]. The nitro derivatives investigated have all been reported to interact with the current through reduction mechanisms on the nitro group.

The structure of the title compounds investigated in this study is shown in Fig. (**1**). All the three compounds are water-insoluble and DMSO was the solvent of choice:



B1: R_1= H ; R_2= H, *N*-(2-benzylbenzoxazol-5-yl)benzamide
B2: R_1= NO_2 ; R_2= H , *N*-(2-benzylbenzoxazol-5-yl)-4-nitrobenzamide
B3: R_1= NO_2 ; R_2= Cl, *N*-(2-(4-chlorobenzyl)benzoxazol-5-yl)-4-nitrobenzamide

Fig. (1). The structures of *N*-(2-benzylbenzoxazol-5-yl)benzamide and its derivatives.

As will be described in the section results and discussion, the parent molecule coded B1 has proved to be electroinactive in the 0.00-(-1.90) V range, therefore by concentrating the nitro-bearing derivatives. Several electrochemical characteristics including CV-peak potentials, peak currents,

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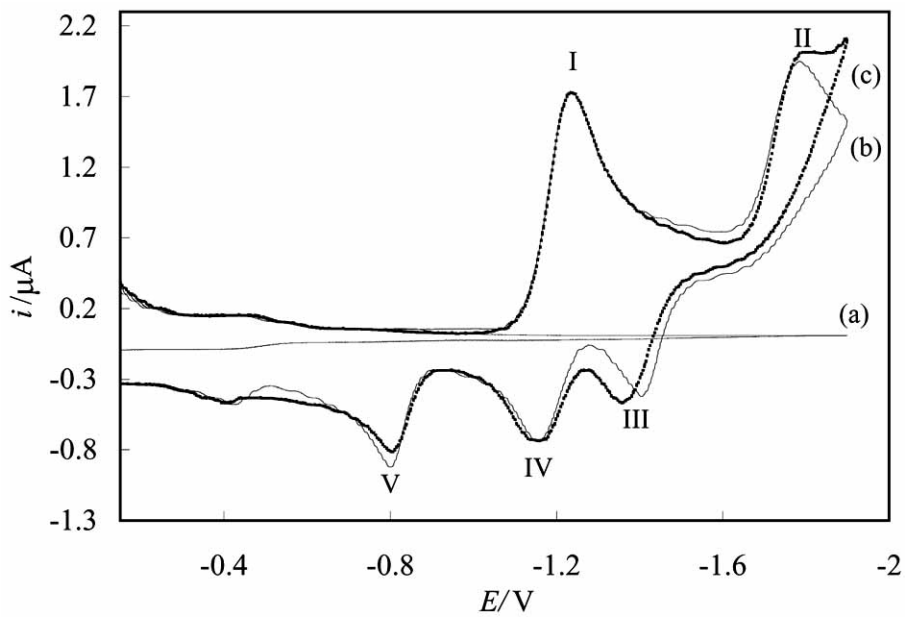

Fig. (2). Cyclic voltammograms of (a) B1, (b) B2 and (c) B3 in DMSO containing 0.1 M TBATFB at HMDE at a scan rate of 0.10 Vs^{-1} (*vs.* Ag^{+}/Ag).

diffusion coefficients, electrode rate constants and number of electrons transferred were determined. In addition, differential pulse voltammetric (DPV) and square wave voltammetric (SWV) methods for the quantitative determination of these benzoxazoles bearing nitro group were developed.

2. EXPERIMENTAL

2.1. Reagents

N-(2-benzylbenzoxazol-5-yl)benzamide and its derivatives were synthesized as described in the literature [9]. In the same work, the compounds were characterized by IR and NMR analysis. All chemicals were of analytical reagent grade (Merck and Sigma). Stock solutions of each compound were prepared at a concentration of 1.0×10^{-3} M in dimethylsulfoxide (DMSO). Voltammetric working solutions were prepared by diluting the stock solutions to obtain the desired concentrations. The supporting electrode tetrabutylammonium tetrafluoroborate (TBATFB) was purchased from Fluka (21796-4) and was used without further purification. The DMSO used was a dry (water≤0.01%) batch of Fluka (41648) kept on beads of a molecular sieve.

All solutions were protected from light and were used within 24 h in order to avoid decomposition.

2.2. Apparatus

The voltammograms were recorded with CH instrument 760B (CH Instruments, Inc., Austin, USA). For CV, DPV and SWV experiments, a hanging mercury drop electrode (HMDE) was used as working electrode with a silver wire in contact with 0.01 M $AgNO_3$ as the reference electrode. The 0.01 M $AgNO_3$ in the reference electrode was dissolved in DMSO containing 0.1 M TBATFB as the supporting electrolyte. The counter electrode was a platinum wire (BAS MW-1032). All solutions were deaerated for 10 minutes with pure argon.

All the measurements were taken at room temperature, 20±1°C. Differential-pulse voltammetry conditions were: pulse amplitude 0.05 V; pulse width 0.05 V; potential step 0.004V and square-wave pulse voltammetry conditions were: pulse amplitude 0.025 V; frequency 15 Hz; and potential step 0.004 V.

2.3. Coulometry

Coulometric studies on B2 and B3 were carried out on a BAS 100W/B instrument (Bioanalytical Systems, Inc., Indiana, USA) with a working electrode of mercury pool (55.4 cm^2) in DMSO containing 0.1 M TBATFB at a controlled potential of -1.55 V, being slightly more negative than the first cathodic reduction peak potential. Oxygen was removed with high purity argon. A three-electrode circuit was used with the Ag^{+}/Ag electrode as reference and coiled platinum wire as the counter electrode. The solution was mixed with a magnetic stirrer.

3. RESULTS AND DISCUSSION

3.1. Voltammetric Behaviors

Cyclic voltammograms for 1.0×10^{-3} M solution of benzoxazoles are presented in Fig. (**2**). As shown, nitro-substituted benzoxazoles (B2 and B3) display virtually the same electrochemical behavior. Two well-defined cathodic peaks at about -1.20 V and -1.75 V, and three anodic peaks at about -1.35 V, -1.10 V and -0.80 V were observed. The parent molecule B1 was electro-inactive within the potential range scanned as the straight, flat voltammogram shown in (Fig. **2a**). Apparently, electrochemical reduction of the benzoxazoles concerned is not reversible in the potential range 0.00-(-1.90) V range. The first cathodic peak at about -1.20 V is expected to correspond to the one-electron reduction of the nitro group to the radical anion. The peak potential is noticeably more negative compared to the literature findings

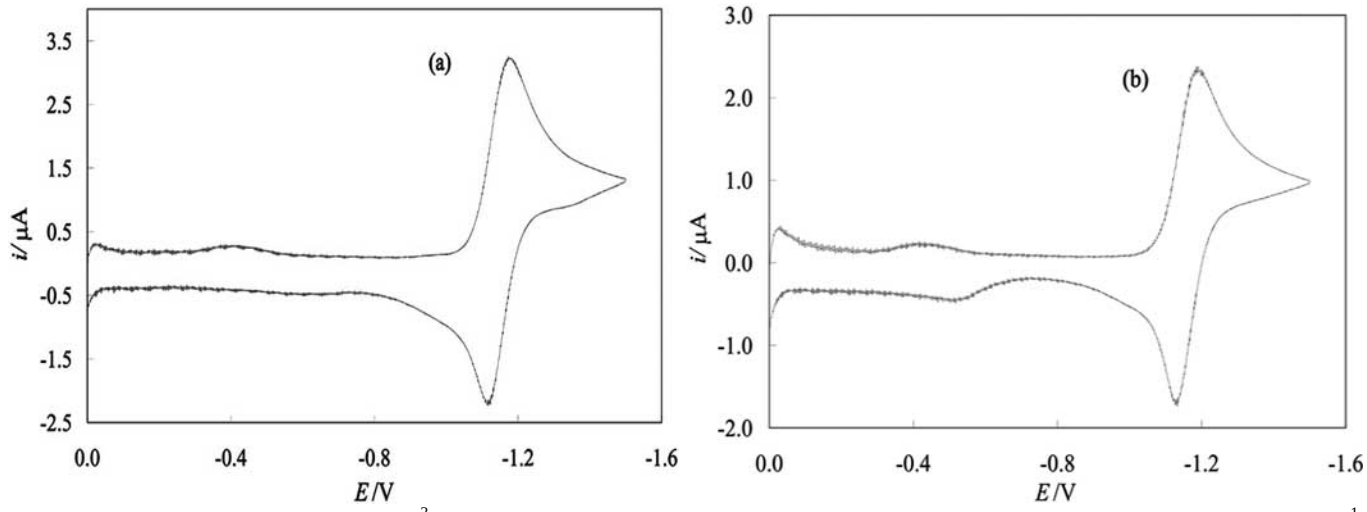

Fig. (3). Cyclic voltammograms of 1.0×10^{-3} M (a) B2 and (b) B3 in DMSO containing 0.1 M TBATFB at HMDE at a scan rate of 0.25 Vs^{-1}, switching potential: -1.50 V (*vs.* Ag^{+}/Ag electrode).

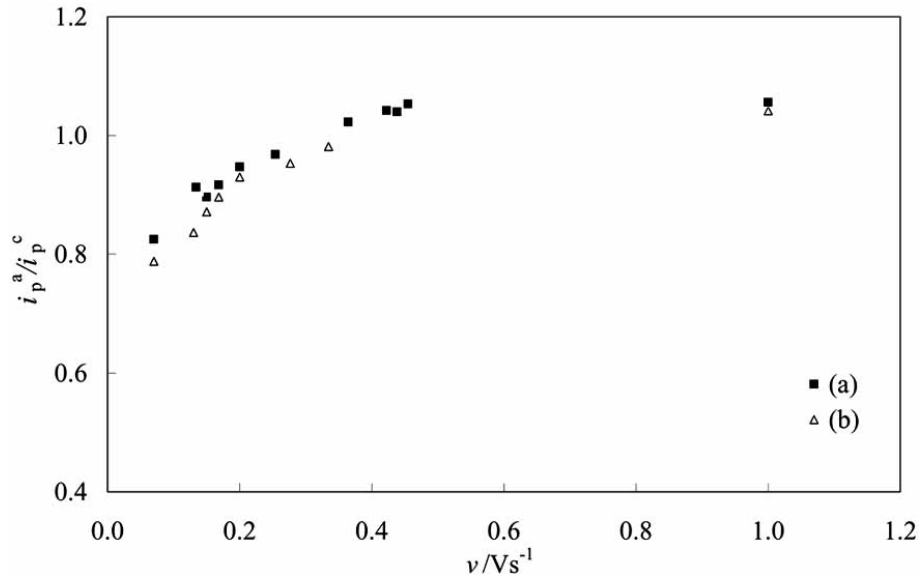

Fig. (4). Variation of i_p^a/i_p^c ratio with v of 1.0×10^{-3} M (a) B2 and (b) B3 in DMSO containing 0.1 M TBATFB.

on related nitro compounds [13, 16, 27, 28]. The difference is most probably due to the fact that the literature data were obtained in DMF or aqueous DMF whereas ours in DMSO.

Changing the switching potential to -1.50 V leads to a great simplification in the voltammogram (Fig. **3**). Obviously, the complexity of the voltammogram in Fig. (**2**) is related to the second reduction step at -1.75 V and possibly the chemical (sequence of) reaction(s) thereof.

The first step of the reduction is quasi-reversible, because, ΔE_p (E_p^a-E_p^c) approaches 0.059 V and the i_p^a/i_p^c ratio tends to approach to unity as the scan rate increases (Fig. **4**). The literature on the similar structures [12, 14, 18, 24] reports that the first step reduction of nitro aromatics in aprotic media proceeds *via* a reversible one-electron reduction process with the formation of the respective anion radical. In our case, the slight departure from reversibility may be due to the possibility of the formation of resonance forms of the anionic radical. Using the Nicholson-Shain criteria (i_p^c *vs* $v^{1/2}$), diffusional control of the first cathodic currents could be proved by the proportionality of the peak current with the square root of scan rate (Fig. **5**).

The second cathodic peak at -1.75 V is irreversible, corresponding to the reduction of the nitro radical anion to the nitroso dianion derivative as has been previously reported for other nitroaromatic compounds in aprotic media [16, 24-26].

For the first cathodic peak, the log i_p^c *vs.* log v plots are given in Fig. (**6**). The slopes of these graphs fall in the range 0.469±0.006 for B2 and 0.469±0.009 for B3. These results indicate that the adsorption phenomenon is not dominant at this step. Furthermore, tests to search for weak adsorption (*i.e*, examination of the appearance of the plots of $i_p/Cv^{1/2}$ *vs*. v; i_p/Cv *vs*. v and i_p/C *vs.* C) were applied to benzoxazole derivatives and no weak adsorption effects were observed in these tests [29].

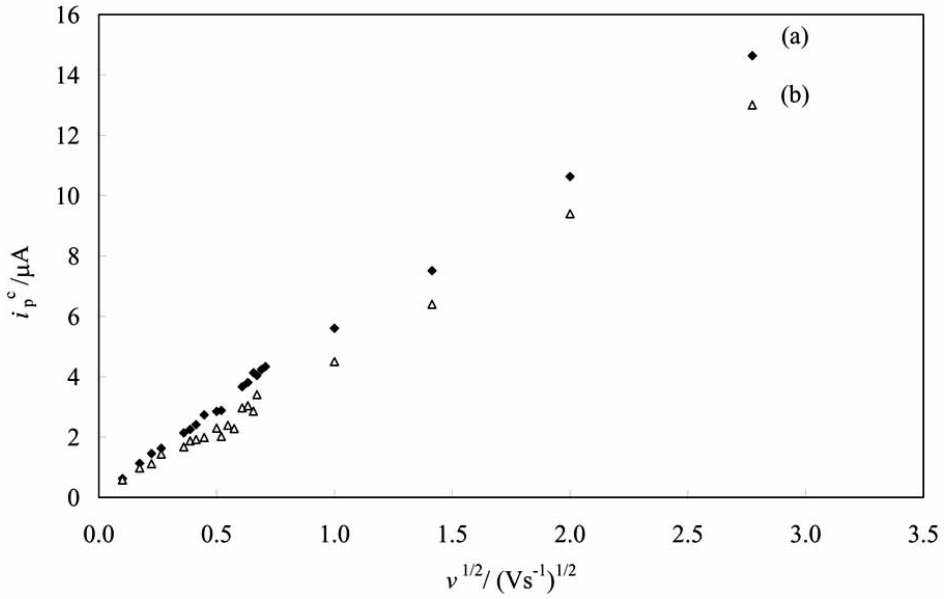

Fig. (5). Variation of cathodic peak currents with $v^{1/2}$ of 1.0×10^{-3} M (a) B2 and (b) B3 in DMSO containing 0.1 M TBATFB.

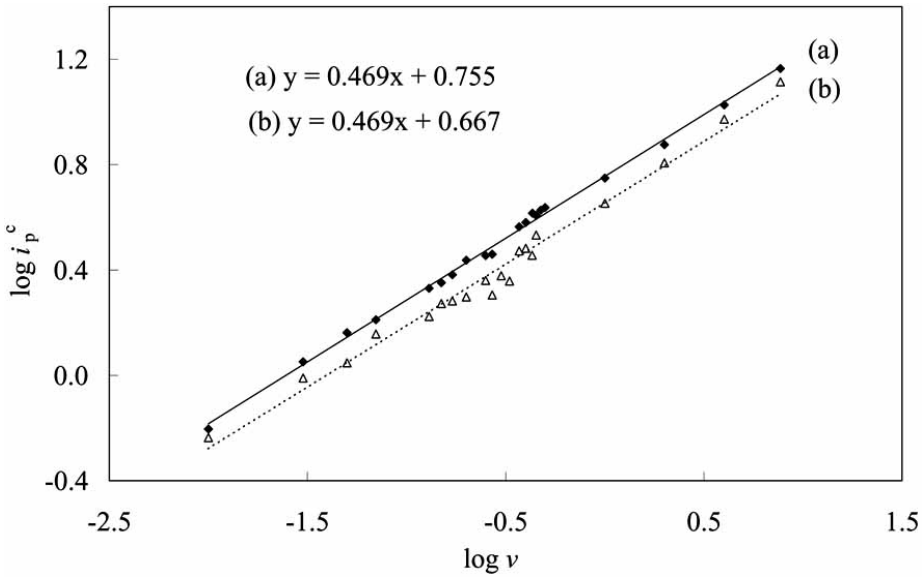

Fig. (6). log i_p^c-log v plots of 1.0×10^{-3} M (a) B2 and (b) B3 in DMSO containing 0.1 M TBATFB.

3.2. Chronoamperometry and Constant Potential Coulometry

Given the potential applied to an electrode falling into the diffusion-controlled region, the current is given by Cottrell equation:

$$i = \frac{nFACD^{1/2}}{\partial^{1/2}t^{1/2}} \qquad \text{eq. (1)}$$

Where,

n = number of electrons

F = Faraday constant, 96500 coulombs/mole

A = Area of the (planar) electrode, cm^2

C = Concentration, molarity (mole/cm^3)

D = Diffusion coefficient, cm^2/s

t = Time, s

This equation serves as one of the basis for the determination of diffusion coefficients. However, it is only applicable for those cases where the electrode reactions are not preceded or followed by an adsorption [30]. As we have shown that the electrochemical reduction peak at -1.20 V corresponds to a process where no adsorption is involved, we determined the diffusion coefficient by using the equation above and the results are summarized in Table **1**. Constant potential coulometry was performed at -1.50 V for both, B2 and B3. The data in Table **1** indicate that the first reduction peak corresponds to a one electron-per molecule. The results

Table 1. Diffusion Coefficients, Number of Electrons Transferred and Standard Rate Constants for Heterogeneous Electron Transfer (k_s) in DMSO (1.0×10^{-3} M B2 and B3 containing 0.1 M TBATFB)[a]

Compound	Diffusion Coefficients (D), cm^2s^{-1}	Number of Electron Transferred Peak I	Standard Rate Constants (k_s), cms^{-1}
B2	$(4.20 \pm 0.92)\times10^{-6}$	0.96±0.04	$(1.04 \pm 0.03)\times10^{-3}$
B3	$(1.25 \pm 0.12)\times10^{-6}$	0.98±0.02	$(3.53 \pm 0.27)\times10^{-4}$

[a] : standard deviation for 4 results

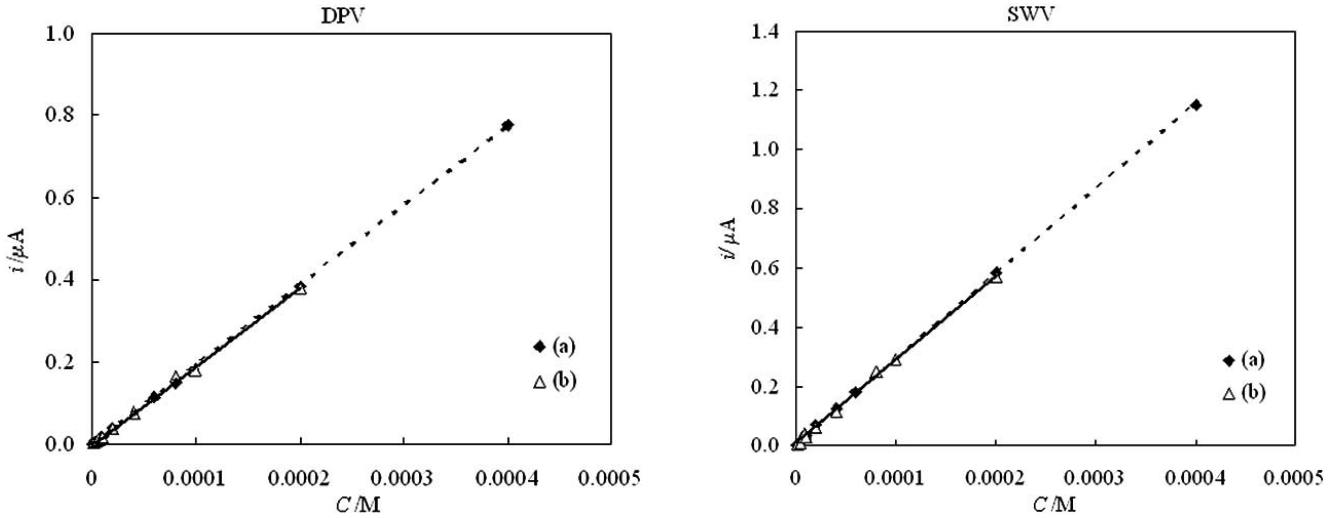

Fig. (7). Calibration curves for (a) B2 and (b) B3 obtained by DPV and SWV methods.

show that a stable free radical is generated for the first reduction peak of compounds.

3.3. Klingler-Kochi Method for Determination of the Heterogeneous Electron-Transfer Standard Rate Constants

In general, as the scan rate is increased, E_p^a, E_p^c and the peak width values, $E_{p/2}$, all change and so does the value of k_s. The k_s *vs.* $v^{1/2}$ plot tend to take the form of a plateau at high scan rates. In our case, this plateau started to appear after the scan rate exceeded ~2.0 Vs^{-1}. The average k_s values that are independent of v are tabulated in Table **1**. These k_s values are another indication that the system is quasi-reversible, because the condition $2.0\times10^{-5}v^{1/2}<k_s<0.3v^{1/2}$ is fulfilled here [31].

3.4. Development of Voltammetric Methods for the Determination of Nitro-Benzoxazoles

The first cathodic peak is obviously suitable for use as the bases of a quantitative analytical technique for the determination of benzoxazoles, because it is well resolved and diffusion controlled. This peak is also adequate for the precise and accurate measurement of current. Hence, all subsequent work was based on the measurement of the current at this peak potential.

The peak current corresponding to the first cathodic peak at about -1.20 V was correlated to the concentration of the nitro-benzoxazoles. For the measurement of the peak current, two alternative techniques, DPV and SWV were employed.

The peak currents obtained by DPV and SWV increased linearly with increasing benzoxazole concentration. Under chosen experimental parameters described in experimental section, linear calibration plots were obtained for benzoxazoles for both techniques (Fig **7**). The characteristics of the calibration plots are summarized in Table **2**. As can be seen from Fig. (**7**), Table **2**, for the DPV technique, linear working ranges for B2 and B3 were found to be (6.0×10^{-7} -4.0×10^{-4}) M and (1.0×10^{-6}-2.0×10^{-4}) M, respectively. The corresponding ranges for these compounds found by SWV were (6.0×10^{-7}-4.0×10^{-4}) M and (1.0×10^{-6}-2.0×10^{-4}) M. The detection limits for B2 obtained from DPV and SWV were calculated to be 1.33×10^{-7} M and 1.76×10^{-7} M, respectively. The detection limits with B3 were almost the same.

The detection (LOD) and quantification (LOQ) limit of the procedures are also shown in Table **2**. The lower detection limits were calculated as the blank response plus, three times the blank standard deviation divided by the slope of calibration curve.

3.5. Proposed Mechanism

The nitro group is one of the strongest of the common electron-withdrawing groups and is one of the most adept species at accepting one electron to form the corresponding radical anion. For example, nitrobenzene is readily reduced electrochemically to corresponding radical anion and then to a dianion in DMF. The first reversible reduction potential for nitrobenzene in DMSO is -1.51 V. Introduction of an electron-withdrawing group into the para position of nitrobenzene shifts the potential to a more positive position by stabilizing the radical anion being formed [32].

Table 2. Regression Data of the Calibration Lines for Quantitative Determination of B2 and B3 in DMSO Using DPV and SWV

	DPV		SWV	
	B2	**B3**	**B2**	**B3**
Measured potential (V)	1.12	1.13	1.17	1.18
Linearity range (M)	$6.0\times10^{-7} - 4.0\times10^{-4}$	$1.0\times10^{-6} - 2.0\times10^{-4}$	$6.0\times10^{-7} - 4.0\times10^{-4}$	$1.0\times10^{-6} - 2.0\times10^{-4}$
Slope ($\mu A\ M^{-1}$)	1.94×10^{3}	1.91×10^{3}	2.88×10^{3}	2.85×10^{3}
Intercept (μA)	9.7×10^{-4}	3.43×10^{-4}	3.79×10^{-3}	6.60×10^{-3}
Correl. Coeff.	1.000	0.999	1.000	0.999
SE of slope	4.92	24.53	13.57	44.04
SE of intercept	6.3×10^{-4}	1.79×10^{-3}	1.78×10^{-3}	3.37×10^{-3}
LOD	1.33×10^{-7}	1.35×10^{-7}	1.76×10^{-7}	1.78×10^{-7}
LOQ	4.44×10^{-7}	4.51×10^{-7}	5.88×10^{-7}	5.93×10^{-7}

SE: Standard Error

Our electrochemical studies of nitro-substituted benzoxazoles show that the radical anions are generated on the cyclic voltammetric time scale (sweep rate 0.1 Vs^{-1}) to give quasi-reversible reduction potentials, whereas the parent benzoxazole is not electroactive at all (Fig. **2**). The first quasi-reversible reduction peak, I, corresponds to one-electron step, which corresponds to the $ArNO_2/ArNO_2^{\bullet -}$ couple, according to equation (2).

$$ArNO_2 + e^- \rightleftharpoons ArNO_2^{\bullet -} \qquad \text{eq. (2)}$$

The second cathodic peak II is observed at -1.75 V. This peak is irreversible, corresponding to the three-electron reduction of the nitro radical anion to form the protonated nitroso dianion, as was previously described for other nitro aromatic compounds, according to equation (3) [14, 16]. The protons involved may originate from the solvent.

$$ArNO_2^{\bullet -} + 3e^- + 3H^+ \rightarrow ArNHO^- + H_2O \qquad \text{eq. (3)}$$

Furthermore, in the anodic sweep an oxidation peak (III) at -1.4 V (Fig. **2-III**) appears. This peak is obviously related to the formation of the nitroso dianion. In effect, upon making a voltammogram with a switching potential less cathodic than the peak II, the anodic peak III was not observed (Fig. **3**). This implies that the oxidable species (peak III) must have been generated in the reduction sweep (peak II). Consequently, it is possible to conclude that the oxidation peak III must be due to the oxidation of the protonated nitroso anion according to the following equation (4):

$$ArNHO^- \rightarrow ArNO + 2\,e^- + H^+ \qquad \text{eq. (4)}$$

Other oxidation peaks at more anodic potentials were observed. They were not given any attention so far, as we concentrated more on the first cathodic reduction, that is, the diffusion controlled $ArNO_2/ArNO_2^{\bullet -}$ peak.

Our findings are in accordance with the literature data considering electroreduction of nitroimidazoles and other nitro-compounds in aprotic media [14, 16, 24, 25].

4. CONCLUSION

Our voltammetric results show that B2 and B3, novel potentially antimicrobial agents, are electrochemically reduced through the formation of a stable nitro radical anion in a similar way as that of the electrochemical reduction of the well-known bactericidal drug nitroimidazoles in aprotic media.

In addition, we believe that for the compounds that act *via* free radicals, e.g., nitroimidazoles derivatives, the voltammetric determination of simple parameters, such as the reduction potential and standard rate constants, may be of value in carrying out an *in vitro* first step screening to select a bioactive compound, avoiding more expensive and tedious procedures.

This work shows that the quantitative determinations of B2 and B3 can be done by using voltammetric techniques such as DPV and SWV because of their reduction process corresponding to the nitro moiety over the HMDE. The described methods are direct methods for the determination of B2 and B3 and do not include any extraction process. Electroanalytical method is a considerable timesaver and the overall cost of analysis is lower when compared with the chromatographic methods. This study shows the possibility of monitoring these compounds that make the method useful for pharmacokinetic and pharmacodynamic purposes.

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