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*Original Scientific Paper*

# Electrochemical Behaviour of the Antibiotic Drug Novobiocin Sodium on a Mercury Electrode

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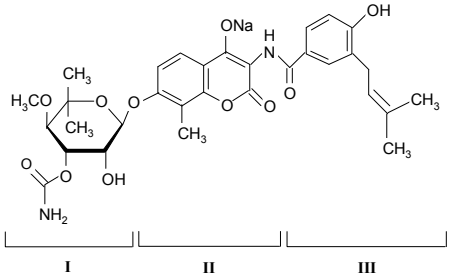
*Abstract.* In this paper, electrochemical and adsorption behaviors of the antibiotic drug novobiocin sodium in 0.04 mol $dm^{-3}$ Britton-Robinson buffers (pH = 2–12) at a hanging mercury drop electrode have been studied by means of cyclic voltammetry, square-wave voltammetry and square-wave adsorptive stripping voltammetry techniques. In 0.04 mol $dm^{-3}$ Britton-Robinson buffers, novobiocin sodium has developed an irreversible cathodic wave over the pH range 5–12. The variation of the potential and/or current of reduction signal with pH of the supporting electrolyte and instrumental variables such as scan rate, frequency, pulse height and deposition time have been studied. Novobiocin exhibits an adsorption characteristic due to its adsorption phenomena. It has been also found that the adsorption of novobiocin on the electrode surface depends predominantly on the pH of the supporting electrolyte. Since the electrode reaction mechanism of novobiocin sodium has been firstly discussed, a mechanism is proposed for the reduction process. At the mercury electrode, the reduction of novobiocin sodium has been probably carried out by means of the attack of hydroxyl ion to the coumarin moiety in the molecular structure and then the consumption of two electrons.

*Keywords:* antibiotic, novobiocin sodium, voltammetry

## INTRODUCTION

Novobiocin, produced by the actinomycete *Streptomyces niveus*, is an amino coumarin antibiotic and exhibits potent activity against gram-positive bacteria.[1–5] The coumarin-containing antibacterial agents block the negative supercoiling of relaxed DNA by inhibiting ATP hydrolysis in the B subunit of DNA gyrase.[6–10] Novobiocin contains a deoxysugar moiety named noviose (**I**), substituted coumarin (**II**) and 4-hydroxybenzoic acid (**III**) (Scheme 1). Noviose binds to the 7' position of the coumarin and it gives the biological activity to this compound.[11,12] Coumarin is found in many plants naturally and is distributed in many household products.[13] Coumarins have several biological functions.[14] Consequently, novobiocin has garnered the attention of researchers as a drug used in the treatment of bacterial illnesses. Novobiocin and its derivatives have also been investigated as potential anticancer drugs.[15–19]

Although a number of studies on the determination, utility and effect of novobiocin have been found in the literature,[20–25] there is only one report published on the electrochemistry. Wang and Mahmoud[26] have reported the sensitive determination of trace amounts of novobiocin in 0.05 M phosphate buffer, pH = 7.4 by adsorptive stripping voltammetry. However, their paper has not included detailed knowledge about the adsorption behaviour, electrochemical activity and the reduction mechanism of novobiocin sodium at the mercury electrode. In this paper, the voltammetric and adsorption behaviors of novobiocin sodium and its reduction mechanism at mercury electrode have been comprehensively discussed by using cyclic voltammetry, square-wave voltammetry and square-wave adsorptive stripping voltammetry techniques.




**Scheme 1.** The molecular structure of novobiocin sodium.

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## EXPERIMENTAL

### Apparatus

Voltammetric measurements were carried out using an EG&G PAR 384B Polarographic Analyzer. An EG&G PARC 303A stand was used in the hanging mercury drop electrode (HMDE) mode. The three-electrode system was completed by means of an $Ag|AgCl|KCl_{sat.}$ reference electrode and a platinum wire as a counter electrode. An EG&G PAR 305 magnetic stirrer was used to provide the convective transport during accumulation. The recording of current-potential curves was obtained by means of a Houston Instrument DMP–40 plotter connected to the polarograph. All pH measurements were made with a Jenway 3010 pH-meter.

### Reagents

Novobiocin sodium salt was obtained from Fluka. All other chemicals were of analytical grade and were obtained from Merck. A stock solution of $1.0\times10^{-3}$ mol dm$^{-3}$ novobiocin sodium salt was prepared daily by dissolution in triple-distilled and deionized water and was further diluted with the same solvent to appropriate concentration. 0.04 mol dm$^{-3}$ Britton-Robinson buffers (pH=2–12) were prepared from boric acid, phosphoric acid and acetic acid and adjusted to the desired pH values with sodium hydroxide.

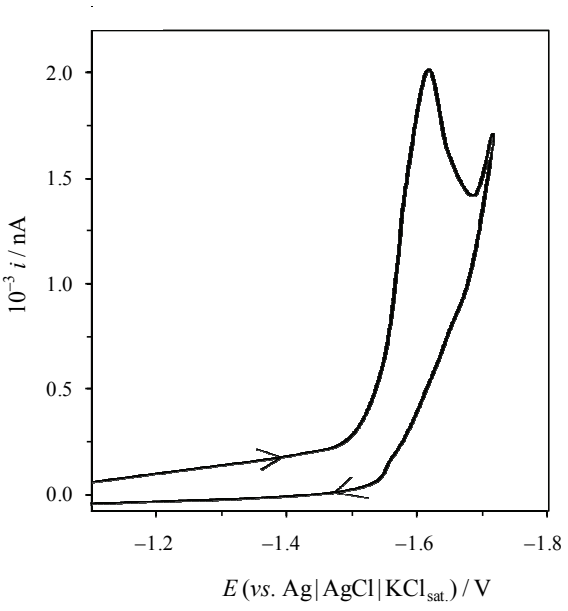



**Figure 1.** Cyclic voltamogram for $9.9\times10^{-6}$ mol dm$^{-3}$ novobiocin sodium in 0.04 mol dm$^{-3}$ Britton-Robinson buffer at pH=5. Experimental conditions: scan rate ($\nu$) = 500 mV s$^{-1}$, equilibrium time = 5 s, drop size medium.

### Procedure

10 mL of 0.04 mol dm$^{-3}$ Britton-Robinson buffer solution was placed in the voltammetric cell. The solution was deoxygenated with pure nitrogen gas for 5 min. The nitrogen gas was then kept over the solution and blank voltamograms were obtained. Certain volume of novobiocin sodium stock solution was added to the buffer solution by using micropipette. The mixture was purged for a further 10 s. After an equilibrium time of 5 s was allowed for the solution to become quiescent, the voltamograms were recorded. Each voltamogram was recorded using a new mercury drop. For square-wave adsorptive stripping voltammetry experiments, preconcentration of novobiocin sodium onto the HMDE was performed at various deposition times (30–240 s) while stirring the solution at 400 rpm with a magnetic stirrer. All data were obtained at room temperature.

## RESULTS AND DISCUSSION

### Cyclic Voltammetry (CV)

The cyclic voltamograms of novobiocin sodium show one irreversible peak in the 0.04 mol dm$^{-3}$ Britton-Robinson buffer solution at pH=5–12. Figure 1 displays a cyclic voltamogram of $9.9\times10^{-6}$ mol dm$^{-3}$ novobiocin sodium in 0.04 mol dm$^{-3}$ Britton-Robinson buffer at pH=5 on a HMDE. A well-defined cathodic peak, corresponding to the reduction of novobiocin is observed at –1.628 V. The reduction process of novobiocin sodium has not been accompanied by an anodic wave, which indicates that the electrode reaction is irreversible. The half-wave potential of coumarin in phosphate buffer, pH=7.4 has been reported at –1.50 V (*vs.* Saturated Calomel Electrode).[27] Therefore, the reduction peak at –1.628 V can be attributed to the reducible coumarin group in the novobiocin molecule.

The effect of pH on the cyclic voltammetric response of novobiocin sodium has been examined in 0.04 mol dm$^{-3}$ Britton-Robinson buffer at pH=2–12. The reduction of novobiocin at HMDE has been found to be pH-dependent. In the interval of $2\leq pH<5$, the reduction peak for novobiocin sodium has not been seen since its reduction peak has been probably obscured by the hydrogen evolution. On the other hand, as from the pH=5 the reduction peak of novobiocin sodium has been begun to appear and it could be seen up to pH=12. Figure 2 displays pH dependence of peak current ($i_p$) and peak potential ($E_p$) of novobiocin. As can be seen in Figure 2a, there is a linear relationship between $E_p$ and pH values. This linear relation can be expressed by the equation:

$$E_p/\mathrm{V} = 0.0431\ \mathrm{pH} - 1.8254 \quad (r = 0.9950) \qquad (1)$$

As a result, the $E_p$ shifts to more positive potential values with increasing pH (thus, decreasing the concentration of protons in the electrolyte solution). The similar results have been also obtained between the half-wave potential and pH for a 5α-reductase enzyme inhibitor finasteride[28] and a macrolide antibiotic josamycin.[29] This observation is a very rare case for the organic compounds. The CV measurements clearly show that protons cannot be included in the reduction process. In the literature, it has been previously reported that coumarins convert to coumarinic acid salts by means of the attack of hydroxyl ions.[30] The similar case has been also reported for the electrochemical behaviour of coumarin.[31]

In Figure 2b, it is seen that $i_p$ tends to increase with decreasing pH value. The reason for this behavior may be concluded that the amount of electroactive species is also increased by the acid-catalysed hydrolysis of novobiocin sodium at the acidic medium (Scheme 2).

The dependence of $E_p$ on the logarithm of the scan rate (log $v$) has been examined at pH=5, pH=7 and pH=10 (Figure 3). At all three pH values, the reduction peak has moved to more negative potentials when the scan rate has increased, confirming the irreversible nature of the reduction reaction.[32]

For an irreversible electrode reaction, the relationship between the peak potential and scan rate can be expressed as:[33]

$$E_p = E^\circ + (2.303\ RT/\alpha nF) \log (RTk_f^\circ/\alpha nF) - (2.303\ RT/\alpha nF) \log v \qquad (2)$$

where $\alpha$ is the charge transfer coefficient, $n$ is the number of electrons involved in the charge transfer step, $k_f^\circ$ is the standard rate constant of the surface reaction and the other symbols have their usual meaning.

The graph of $E_p$ *vs.* $\log v$ gives a straight line for each of these pH values. The $\alpha n$ values are calculated from the slope according to the Eq. (2). Regression equations and $\alpha n$ values are listed in Table 1. The number of electrons exchanged by the molecule has been assumed to be $n=2$. Therefore, the values of the charge transfer coefficients for pH=5, 7 and 10 have been determined to be 0.995, 0.635 and 0.895, respectively.

By the analogy to the polarographic reduction of organic compounds,[34] the reduction of novobiocin sodium can be generally represented as:

$$\mathrm{Ox} + n\mathrm{e}^- + z\mathrm{OH}^- \rightarrow \mathrm{Red} \qquad (3)$$

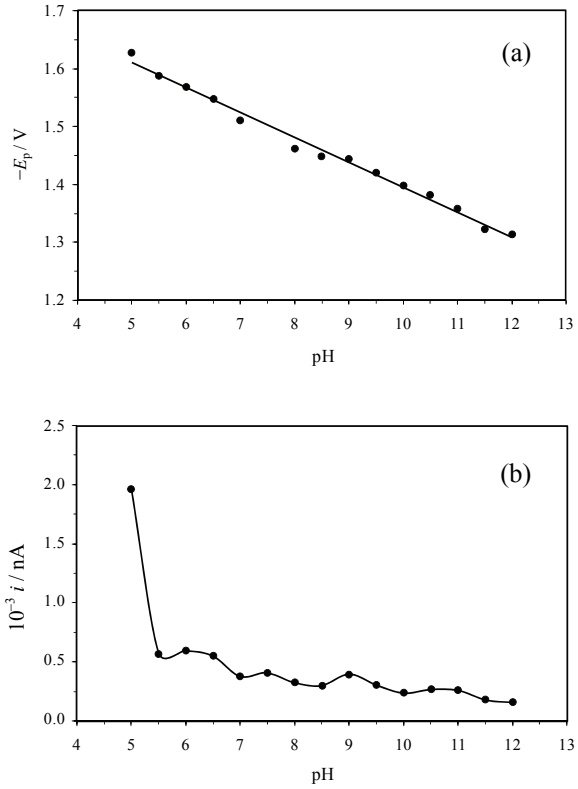
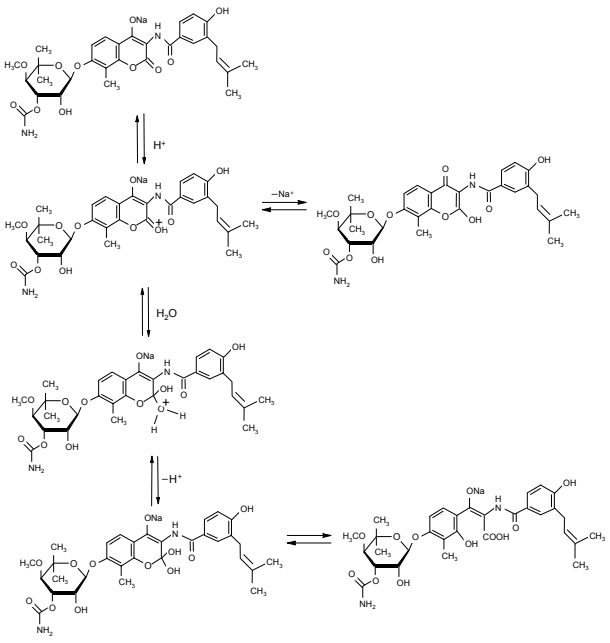



**Figure 2.** pH dependence of peak potential (a) and peak current (b) in CV.



**Scheme 2.** The probable acid-catalyzed hydrolysis of novobiocin sodium.

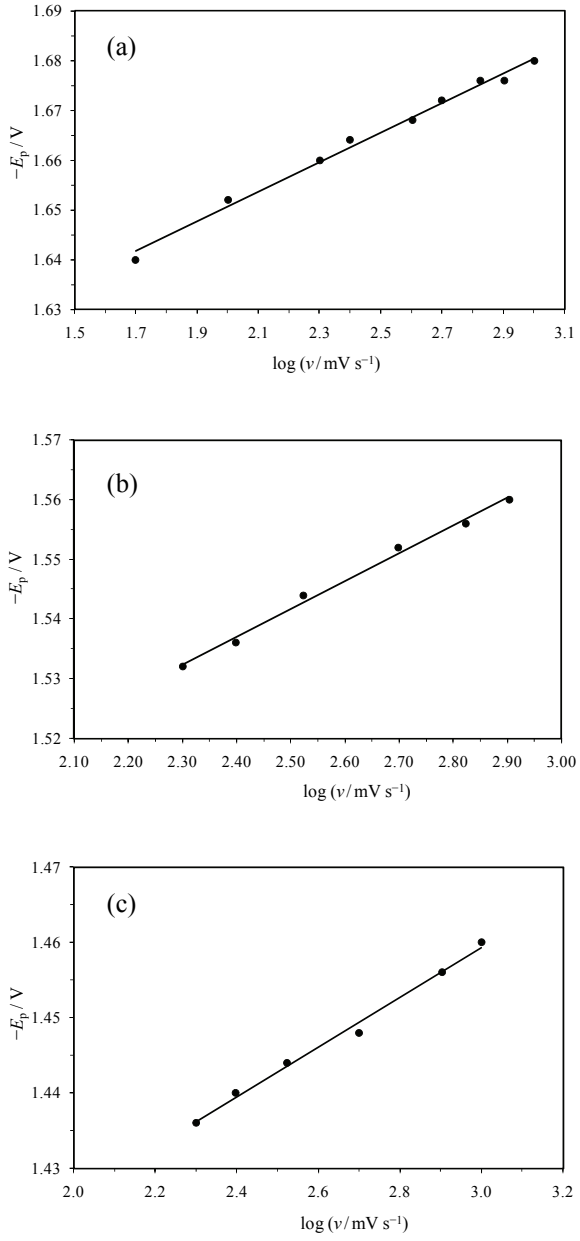



**Figure 3.** Semilogarithmic dependence of the peak potential, $E_p$, on the logarithm of the potential scan rate (log $v$). $9.9\times10^{-6}$ mol dm$^{-3}$ novobiocin sodium + 0.04 mol dm$^{-3}$ Britton-Robinson buffers at pH = 5 (a), pH = 7 (b), and pH = 10 (c).

For the thermodynamically irreversible this process, the relationship between half-wave potential ($E_{1/2}$) and pOH:

$$E_{1/2} = E_{1,\text{const.}} - (2.303\, zRT/\alpha nF)\ \text{pOH} \qquad (4)$$

By the addition of pOH = 14 – pH, this equation can be modified as:

$$E_{1/2} = E_{2,\text{const.}} + (2.303\, zRT/\alpha nF)\ \text{pH} \qquad (5)$$

At 25 °C, the number of hydroxyl ions $z(OH^-)$ consumed in the rate-determining step can be obtained from the following equation:

$$\Delta E_{1/2} / \Delta\text{pH} = 0.059\, z(OH^-) / \alpha n \qquad (6)$$

At the Eq. 6, with using peak potential ($E_p$) instead of half-wave potential ($E_{1/2}$), the calculated $z(OH^-)$ numbers for different pH values have been given in Table 1. As can be seen in Table 1, the $z(OH^-)$ value has been found to be *ca.* 1 (1.45 for pH = 5, 0.93 for pH = 7 and 1.31 for pH = 10) indicating that one hydroxyl ion was consumed in the rate determining step. So, it can be said that the overall reduction process of novobiocin sodium includes the addition of hydroxyl ion to the drug molecule.

For the pH = 5, pH = 7 and pH = 10, the adsorption- or diffusion- controlled character of reduction process of novobiocin sodium on the HMDE in 0.04 mol dm$^{-3}$ Britton-Robinson buffer has been studied by means of the effect of the scan rate upon peak current (Figure 4). In acidic medium, the peak current ($i_p$) increases linearly with increasing square root of scan rate ($v^{1/2}$) (Figure 4a). This result points out to the diffusion-controlled process. On the other hand, in neutral and basic medium, novobiocin has showed an adsorptive nature, since $i_p$ *vs.* $v$ graphs gave a straight line (Figures 4b and c).

In addition, $i_p / v^{1/2}$ *vs.* $v$ graph also confirms the above results. Figure 5 shows the relationship between the current function and scan rate for three pHs medium. At pH = 7 and pH = 10, the current function

**Table 1.** Effect of scan rate and pH on cathodic peak potential of novobiocin sodium in CV

| pH | Equation | Correlation coefficient ($r$) | $\alpha n$ | $\Delta E_p / \Delta$pH | $z(OH^-)$ |
|---|---|---|---|---|---|
| 5 | $E_p$ / V = – 0.0297 log ($v$/mV s$^{-1}$) – 1.5913 | 0.9959 | 1.99 | 0.0431 | 1.45 |
| 7 | $E_p$ / V = – 0.0466 log ($v$/mV s$^{-1}$) – 1.4251 | 0.9964 | 1.27 | 0.0431 | 0.93 |
| 10 | $E_p$ / V = – 0.0331 log ($v$/mV s$^{-1}$) – 1.3601 | 0.9966 | 1.79 | 0.0431 | 1.31 |

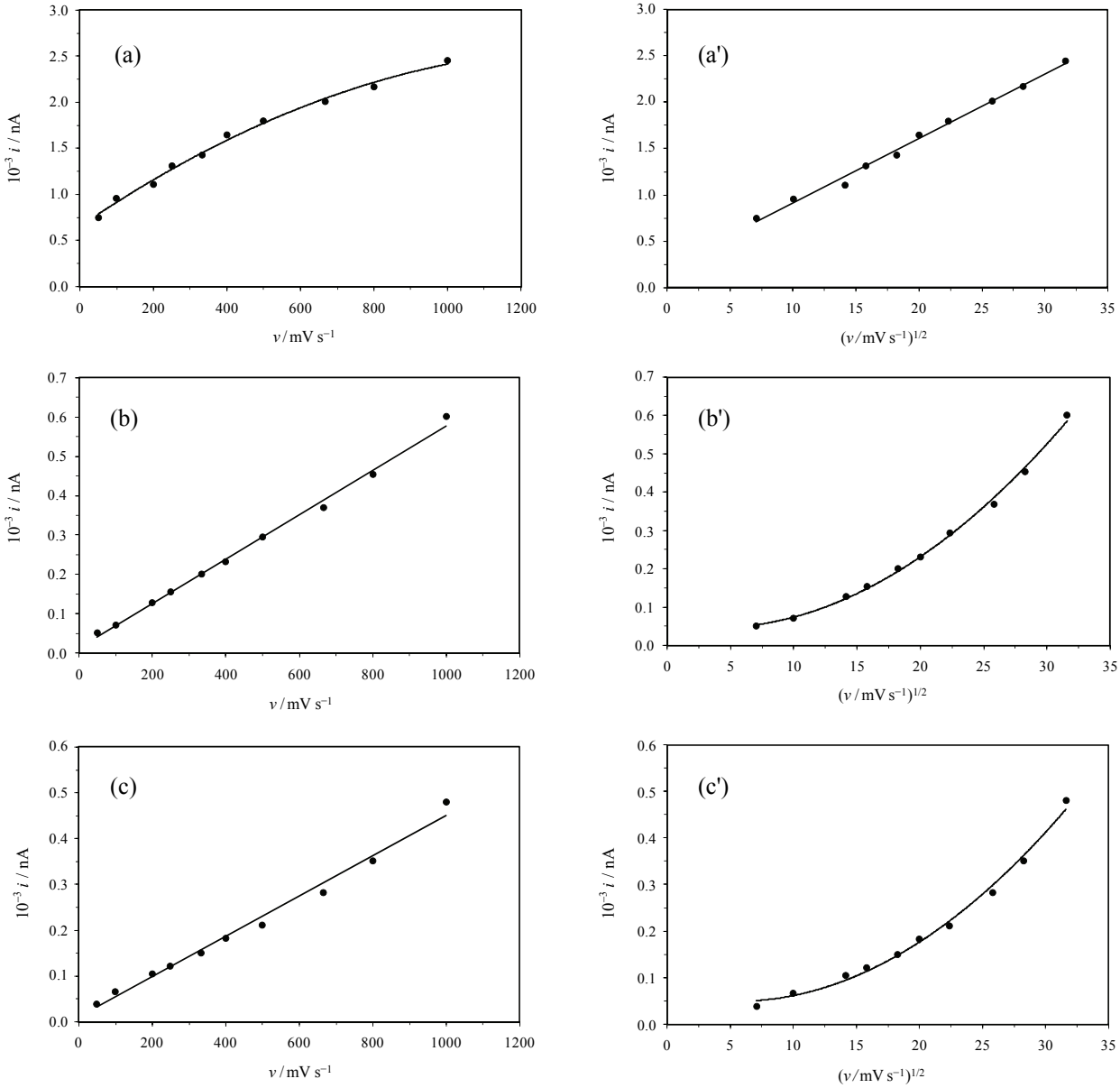



**Figure 4.** $i_p$ *vs.* $v$ (a, b, c) and $i_p$ *vs.* $v^{1/2}$ (a', b', c') graphs of $9.9 \times 10^{-6}$ mol dm$^{-3}$ novobiocin sodium at three different pH values: pH = 5 (a, a'), pH = 7 (b, b'), and pH = 10 (c, c').

($i_p / v^{1/2}$) linearly depends on the scan rate, indicates the adsorptive nature of novobiocin sodium. The literature-result[35] shows that the current function of the adsorption peak has increased with increasing scan rate. However, at pH = 5, the current function decreases with increasing scan rate. This behavior points out to CE mechanism.[36] The behaviour of current function observed at pH = 5 has been also obtained for catalytic waves in the literature.[37] Nevertheless, in pH = 7 and 10, the process is still of CE type, but the rate of C step is high and its effect to the overall electrochemical behaviour is insignificant. In these media, the adsorption effects of the process become evident. Generally speaking, the mechanism is complicated by a preceding chemical reaction and adsorption of the reactant.[38–40]

## Square-wave Voltammetry (SWV)

The nature of the electrochemical process has been also studied by square-wave voltammetry (SWV). Figure 6 displays a square-wave voltamogram of $9.9 \times 10^{-6}$ mol dm$^{-3}$ novobiocin sodium in 0.04 mol dm$^{-3}$ Britton-Robinson buffer at pH = 5 on a HMDE.

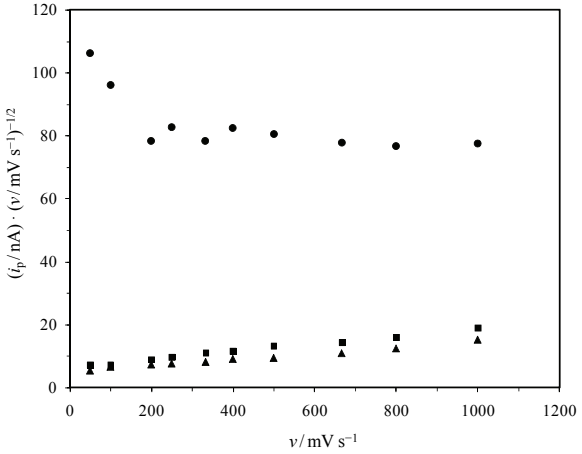



**Figure 5.** The $i_p / v^{1/2}$ *vs.* $v$ graph of novobiocin sodium. pH = 5 (●), pH = 7 (■) and pH = 10 (▲). Except for scan rate, other experimental conditions are same as described in Figure 1.

The effect of pH on the SWV response of novobiocin has been also examined in 0.04 mol dm$^{-3}$ Britton-Robinson buffer at pH = 2 – 12. SWV experiments have given the similar results to CV experiments. In Figure 7, pH dependence of peak current and peak potential of novobiocin is shown. Like in CV, it is seen that $i_p$ values have a tendency to decrease with increasing pH and $E_p$ values showed linear positive shift upon increasing pH. The relation between $E_p$ and pH can be expressed by the equation:

$$E_p/\text{V} = 0.0425\ \text{pH} - 1.807 \quad (r = 0.9950) \qquad (7)$$

As confirmed by SWV and CV measurements, it is probable that hydroxide group is involved in the reduction process rather than protons. Most probably, $OH^-$ ions are involved in the overall mechanism, by participating in the preceding chemical step and attacking the coumarin moiety before the electron transfer becomes possible. Thus, in pH = 5, the preceding chemical reaction is rather slow revealing the CE nature of the overall mechanism.

In square-wave experiments, the frequency is an important parameter. The dependence of peak potential on the logarithm of the frequency has been examined at pH = 5, 7 and 10 (Figure 8). The plot of $E_p$ *vs.* log$f$ for each pH shows one straight line (Figure 8) and the regression equations have been given in Table 2.

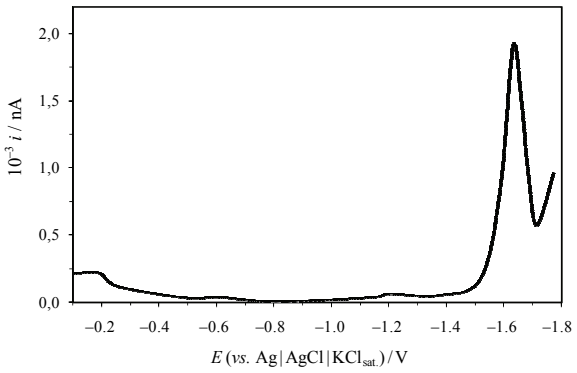



**Figure 6.** Square–wave voltamogram for $9.9 \times 10^{-6}$ mol dm$^{-3}$ novobiocin sodium in 0.04 mol dm$^{-3}$ Britton-Robinson buffer at pH = 5. Experimental conditions: scan rate ($\nu$) = 200 mV s$^{-1}$, frequency ($f$) = 100 Hz, pulse height ($\Delta E_a$) = 0.020 V, scan increment ($\Delta E_s$) = 2 mV, equilibrium time = 5 s, drop size medium.

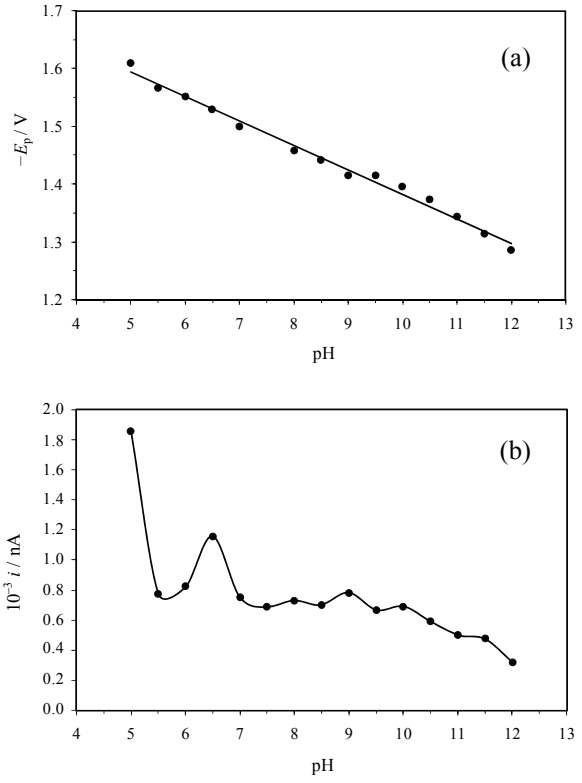



**Figure 7.** pH dependence of peak potential, $E_p$ (a) and peak current, $i_p$ (b) in SWV.

**Table 2.** Effect of frequency and pH on cathodic peak potential of novobiocin sodium in SWV

| pH | Equation | Correlation coefficient ($r$) | $\alpha n$ | $\Delta E_p / \Delta$pH | $z(OH^-)$ |
|---|---|---|---|---|---|
| 5 | $E_p/\text{V} = -0.031 \log(f/\text{Hz}) - 1.586$ | 0.9960 | 1.91 | 0.0425 | 1.38 |
| 7 | $E_p/\text{V} = -0.053 \log(f/\text{Hz}) - 1.440$ | 0.9984 | 1.12 | 0.0425 | 0.80 |
| 10 | $E_p/\text{V} = -0.030 \log(f/\text{Hz}) - 1.369$ | 0.9978 | 1.97 | 0.0425 | 1.41 |

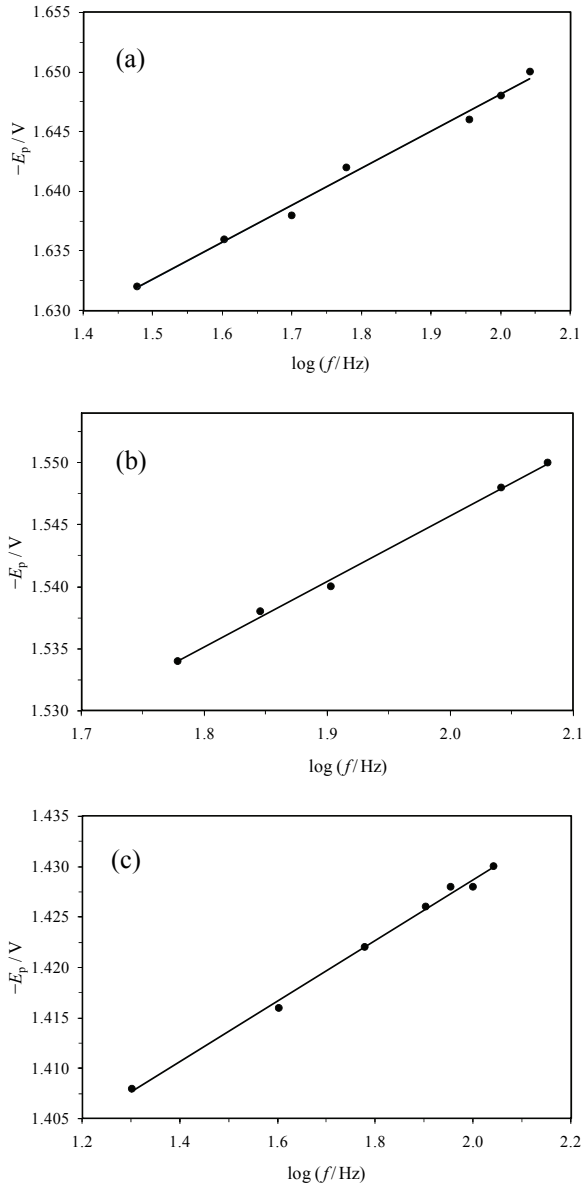



**Figure 8.** The dependence of $E_p$ with log $f$. $9.9\times10^{-6}$ mol dm$^{-3}$ novobiocin sodium + 0.04 mol dm$^{-3}$ Britton-Robinson buffer at pH = 5 (a), pH = 7 (b), and pH = 10 (c).

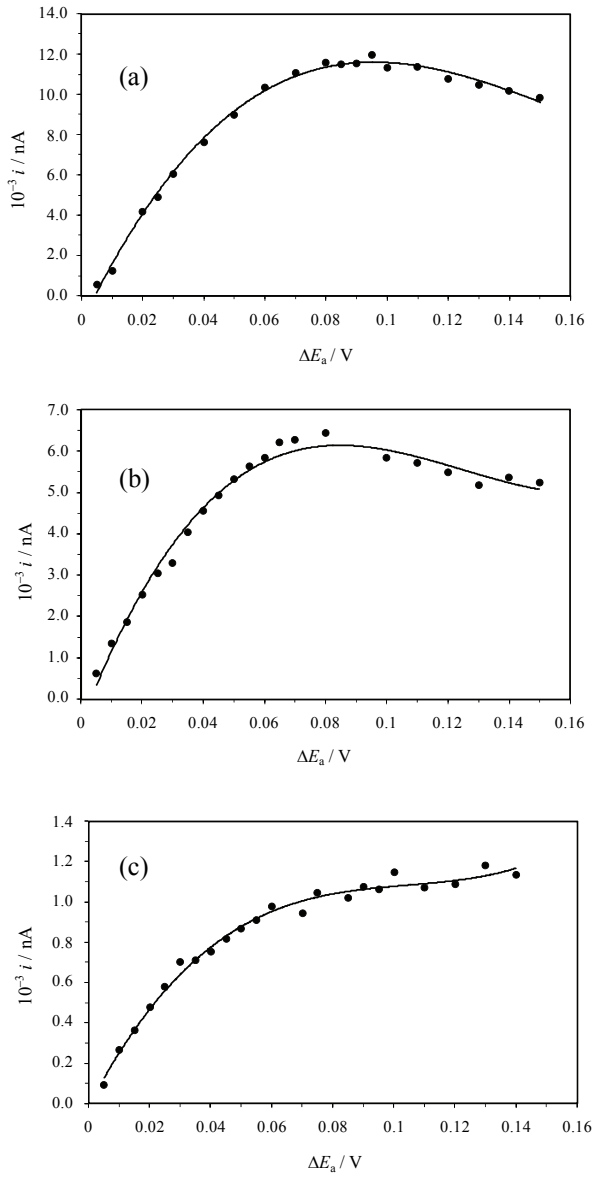



**Figure 9.** Dependence of the peak current $i_p$, with the square-wave pulse height $\Delta E_a$, at: pH = 6 (a), pH = 7 (b), and pH = 10 (c) for experiments carried out under the following conditions: $c$(novobiocin) = $9.9\times10^{-6}$ mol dm$^{-3}$ with scan increment ($\Delta E_s$) = 2 mV and frequency ($f$) = 100 Hz.

For irreversible systems, the relationship between the peak potential and the frequency can be expressed as:[41]

$$\Delta E_p / \Delta \log f = -2.3\, RT/\alpha nF \qquad (8)$$

For different pHs, the values have been determined from slopes of the $E_p$ *vs*. log $f$ graphs (Table 2). Like in CV, the $z(OH^-)$ values, calculated from the slope of the $E_p$-pH plot, are shown for different pHs in Table 2. As can be seen in Tables 1 and 2, the values of $\alpha n$ and $z(OH^-)$ obtained by square-wave voltammetry and cyclic voltammetry are in agreement with each other.

The pulse height ($\Delta E_a$) is another parameter that strongly influences the peak current in SWV. Figure 9 shows this effect obtained from the experimental data for $9.9\times10^{-6}$ mol dm$^{-3}$ novobiocin sodium salt solution. The peak current at pH = 6 and 7 has a linear relationship with pulse height for the range of 5–50 mV whereas at pH = 10 this linear relationship has been observed in the range of 5–30 mV (Figure 10).

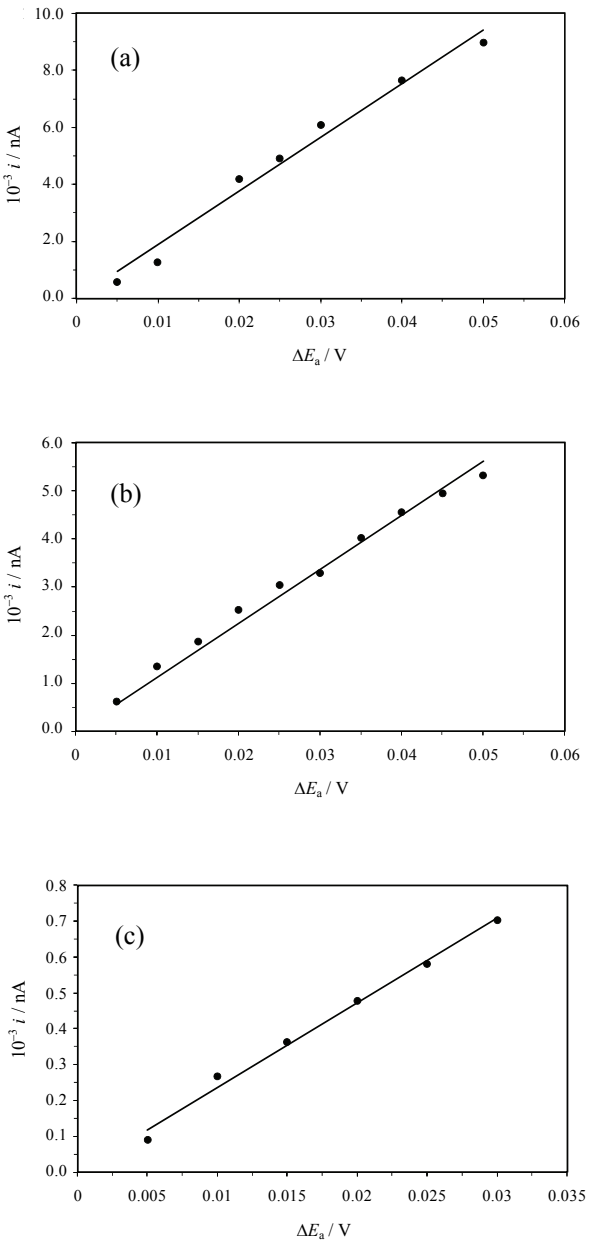



**Figure 10.** The linear relationship between $i_p$ and $\Delta E_a$ at: pH = 6 (a), pH = 7 (b), and pH = 10 (c).

So, Figure 10 allows the calculation of the surface concentration ($\Gamma$) of the adsorbed novobiocin sodium according to the following equation:[42, 43]

$$\partial i_p/\partial \Delta E_a = 500\, A\, \alpha\, n^2\, F\, f\, \Delta E_s\, \Gamma \qquad (9)$$

where $A$ is the electrode area, $\Delta E_a$ is the pulse amplitude (height), $f$ is frequency and $\Delta E_s$ is the scan increment. The calculated $\Gamma$ values for pH = 6, 7 and 10 are $5.3 \times 10^{-10}$, $4.3 \times 10^{-10}$ and $5.1 \times 10^{-11}$ mol cm$^{-2}$, respectively.

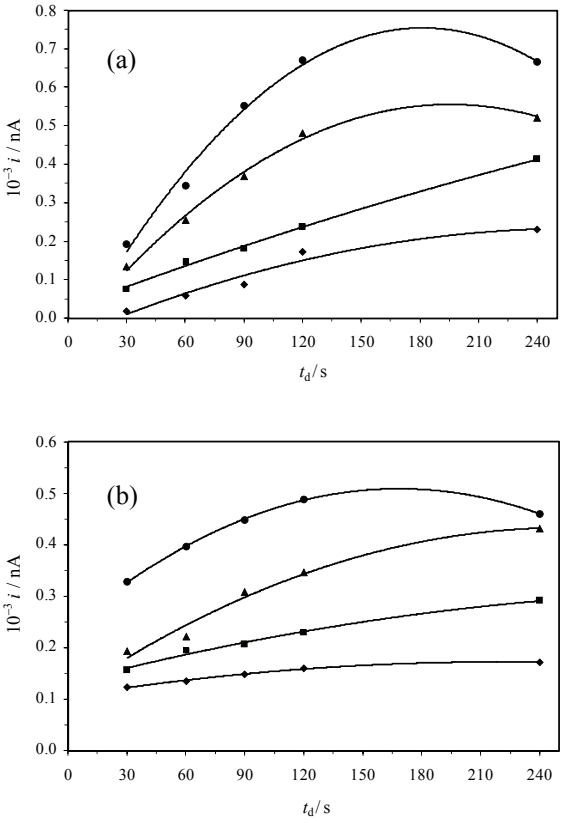



**Figure 11.** Effect of deposition time ($t_d$) on the peak current ($i_p$) for: $4.98\times10^{-8}$ mol dm$^{-3}$ (♦), $9.9\times10^{-8}$ mol dm$^{-3}$ (■), $1.96\times10^{-7}$ mol dm$^{-3}$ (▲), and $4.3\times10^{-7}$ mol dm$^{-3}$ (●) novobiocin sodium in 0.04 mol dm$^{-3}$ Britton-Robinson buffer at pH = 7 (a), and pH = 10 (b).

## Square-wave Adsorptive Stripping Voltammetry (SW-AdSV)

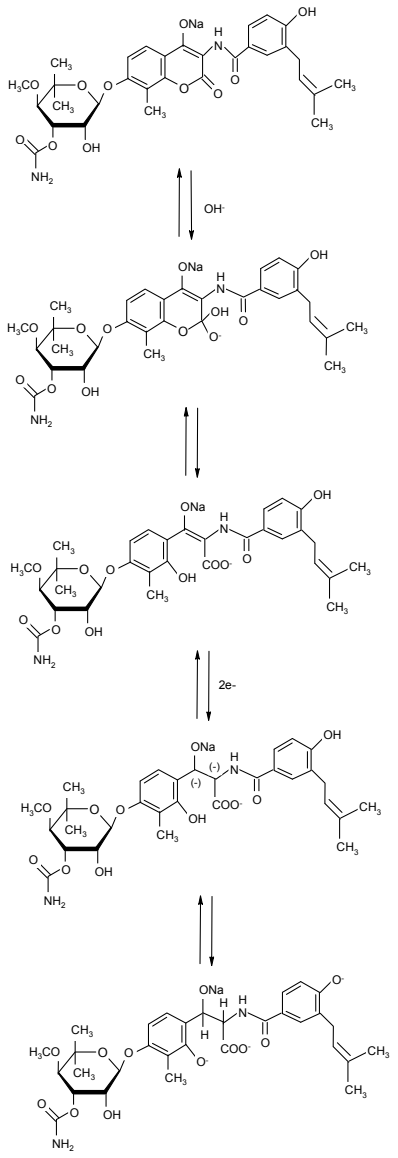
At pH = 5, 7 and 10, the effect of depositon time ($t_d$) on peak current ($i_p$) obtained at various concentrations of novobiocin ($4.98 \times 10^{-8}$ mol dm$^{-3}$, $9.9 \times 10^{-8}$ mol dm$^{-3}$, $1.96 \times 10^{-7}$ mol dm$^{-3}$ and $4.3 \times 10^{-7}$ mol dm$^{-3}$) in 0.04 mol dm$^{-3}$ Britton-Robinson buffer onto HMDE has been evaluated. At pH = 5, there has not been any reduction peak observed owing to the low novobiocin sodium concentration. As can be seen in Figure 11, the $i_p$-$t_d$ plot at pH = 7 is similar to that of pH = 10.

As expected, the deposition time plays an important role on the extent of preconcentration. For the low concentrations (*ie*. $4.98\times10^{-8}$ mol dm$^{-3}$ and $9.9\times10^{-8}$ mol dm$^{-3}$), the peak current linearly increases with the increasing deposition time. On the other hand, at the fixed deposition time the growth of the adsorbed novobiocin layer is faster as the bulk solution concentration of novobiocin increases. In such a way that at fixed deposition time, peak current increases with increasing novobiocin sodium concentration for pH = 7 and 10 (Figure 11).

As shown in Figure 11, in the both graphs, for the highest novobiocin concentration ($4.3 \times 10^{-7}$ mol dm$^{-3}$) the peak current increases at first, and to a plateau region, and then begins to decrease. A decrease of the peak current has been observed with deposition times probably owing to an inhibition of the voltammetric process occuring after saturation of mercury drop[44] or the increasing repulsive interactions between the adsorbed novobiocin molocules on mercury.[45]

### Mechanism of the Electrode Reaction

Depending on the coumarin group, the ring-opening with the attack of hydroxyl ion and then the taking of two electrons are involved in the reduction of novobiocin sodium and the following overall course can be proposed for the reduction (Scheme 3):




**Scheme 3.** The proposed electrochemical reduction mechanism for novobiocin sodium.

## CONCLUSION

From these experimental studies, it has been concluded that the attack of hydroxyl ion to coumarin moiety of novobiocin sodium is responsible from the voltammetric response of the molecule. The drug is reduced at HMDE using an irreversible two-electron process. Also, it has an adsorption property on the mercury electrode surface. These results will be useful to understand the redox behaviour and surface activity of novobiocin sodium.

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# SAŽETAK

## Elektrokemijsko ponašanje antibiotskog lijeka novobiocin-natrija na živinoj elektrodi

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U ovom radu proučavana su elektrokemijska i adsorpcijska ponašanja antibiotskog lijeka novobiocin-natrij u Britton-Robinson puferima koncentracije 0,04 mol $dm^{-3}$ (pH = 2–12) uporabom živine elektrode s visećom kapi korištenjem tehnika cikličke voltammetrije, pravokutnovalne voltammetrije i pravokutnovalne adsorpcijske voltammetrije otapanja. U Britton-Robinson puferima koncentracije 0,04 mol $dm^{-3}$ novobiocin-natrij razvio je ireverzibilni katodni val unutar pH vrijednosti 5–12. Proučavana je varijacija potencijala i/ili struje redukcijskog signala s promjenom pH, kao i s promjenom instrumentnih varijabli (brzina snimanja, frekvencija, visina pulsa, i vremena taloženja). Osim toga pronađeno je da adsorpcija novobiocina na površini elektrode ovisi pretežno o pH. Pošto je na početku razmatran reakcijski mehanizam na elektrodi, predložen je mehanizam redukcije na živinoj elektrodi. Redukcija novobiocin-natrija odvija se vjerojatno napadom hidroksilnog iona na kumarinski dio molekule uz utrošak 2 elektrona.