Full Paper

Wiley Online Library

ELECTROANALYSIS

DOI: 10.1002/elan.201900698

Theoretical Analysis of a Surface Catalytic Mechanism Associated with Reversible Chemical Reaction Under Conditions of Cyclic Staircase Voltammetry

Sofija Petkovska[a] and Rubin Gulaboski*[a]

Abstract: In this work, we present theoretical results in cyclic staircase voltammetry of a surface catalytic mechanism that features reversible chemical step, the so-called "surface catalytic EC_{rev}' mechanism". We consider specific surface regenerative mechanism, in which both of the electro-inactive substrates are present in large excess in electrochemical cell from the beginning of the experiment. The chemical reversibility brings at this mechanism more complexity in respect to the features of well-elaborated surface catalytic EC' mechanism coupled with chemically irreversible regenerative reaction. As we present plenty of simulated cyclic voltammograms, we also propose methods to get insight to kinetics and thermodynamics parameters relevant to chemical regenerative step. The elaboreted results can be important in analysing the kinetics and thermodynamics of many drug-drug and drug-DNA interactions, for example. In addition, with the results elaborated in this work we can access relevant information about the chemistry of important lipophilic enzymes studied in protein-film voltammetry set up.

Keywords: surface catalytic EC_{rev}' mechanism · catalytic rate constant · drug-DNA interactions · kinetics of drug-drug interactions · protein-film voltammetry

Introduction

Cyclic voltammetry is seen as an inevitable instrumental technique in almost every electrochemical laboratory. This is because it provides means to get insight into important chemical and mechanistic aspects of many organic and inorganic substances [1–4]. One of the biggest achievements of voltammetry is its ability for direct probing of redox enzymes and proteins [5–8]. The method enabling this is called "protein-film voltammetry" (PFV). Getting insight into thermodynamics and kinetics of complex enzymatic reactions is possible to be achieved with PFV, whose experimental set up is quite simple [5–7]. It is worth to note that theoretical models relevant to protein-film voltammetry [5–7] are equivalent to those of so-called "surface electrode mechanisms" [1,4]. Indeed, a good theoretical basis is needed to understand many phenomena when given redox enzymes or surface-active redox compounds are voltammetrically analyzed [4,5]. Among the surface redox systems studied with voltammetric techniques, those coupled with chemical reactions are of outmost importance [1,4,9–27]. This is because voltammetric studies on such systems can provide valuable information about their chemical features [1,4–7]. In all surface mechanisms complicated with chemical reactions, the surface catalytic (regenerative) mechanism EC' (or, more precisely, the surface EC_{irr}' mechanism, where "*irr*" stands for irreversible) is most comprehensively studied under voltammetric conditions [1–4,22–27]. Voltammetric theories developed on this mechanism provide simple approaches to get access into kinetics and thermodynamics of electron transfer and the chemical reactivity of many compounds [4,25–27]. The catalytic EC' mechanism is physiologically relevant, since it is a valuable model to evaluate relevant chemical parameters related to many important enzyme-substrate systems [6–8]. Moreover, the surface EC' mechanism is also suitable to studying the kinetics of many drug-drug [1,2,9,28,29] and drug-DNA interactions [28–36]. In this electrode mechanism, a chemical and irreversible reaction between electrochemically created product Red(ads) with a defined substrate Y (that is present in excess) regenerates the initial reactant Ox(ads). Many relevant studies of surface EC' mechanism under voltammetric conditions are elaborated in [1,3,4,22–36]. In our recent theoretical studies [23–25], we reported on several novel aspects of the surface EC' mechanism under conditions of square-wave voltammetry [24,25] and cyclic voltammetry [23]. In the current paper we present theoretically a more complex surface EC' mechanism, assuming regenerative steps that feature chemical reversibility. The abbreviation of this particular mechanism is a *surface catalytic reversible EC_{rev}' mechanism* (or simply *surface catalytic EC_{rev}'* mechanism). In is worth to mention that this particular mechanism is relevant to study the kinetics and thermody-

[a] S. Petkovska, R. Gulaboski
Faculty of Medical Sciences, „Goce Delcev" University, Stip, Macedonia
E-mail: rubin.gulaboski@ugd.edu.mk

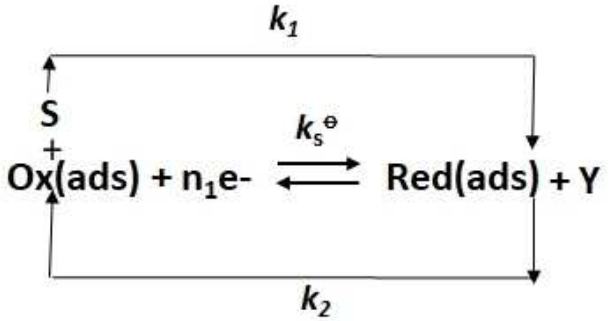
Supporting information for this article is available on the WWW under https://doi.org/10.1002/elan.201900698

namics of interactions between lipophilic (electrochemically active) drugs and physiologically relevant molecules, as the DNA molecules for example. As in most of the drug-DNA redox interactions a certain degree of chemical reversibility exists [28], a theoretical model considering chemical reversibility of regenerative step describes more closely the chemical reactivity of such systems [28,33–36]. We use the cyclic staircase voltammetry, because it is most familiar electrochemical technique among the experimentalists [1–3,6–8].

Mathematical Model

We elaborate in our model a kinetically controlled surface electrode mechanism: Ox(ads)+ne-↔Red(ads). In this "simple" surface electrode reaction, we additionally assume that the initial reactant Ox(ads) undergoes a chemical reaction with substrate "S" (present in large excess) while creating product R(ads). Moreover, the product R(ads) (generated electrochemically and chemically) undergoes a follow-up chemical reaction with "Y" species present also in large excess as dissolved species in solution. As a result of chemical reaction between R(ads) and Y, initial electroactive reactant Ox(ads) is regenerated (and the substrate "S", too). We suppose that "Y" and "S" are "electrochemically inactive" i.e. they do not show electrochemical activity in the frame of the applied potentials. We also assume that substrates "S" and "Y" are both present in large excess in electrochemical cell from the beginning of the experiment, and they do not react between them. We suppose that both electrochemically active forms of species Ox and Red are strongly adsorbed ("ads") to the surface of working electrode. The model is solved in absence of any interactions between all adsorbed species. We also suppose that there is no mass transport that takes place by diffusion from the bulk of solution. A schematic description of this specific surface electrode mechanism is as follows:

Initially, we have only the species of redox adsorbate Ox present in the electrochemical cell. Thereafter, we add large amount of substrates "S" and "Y" in the voltammetric cell (commonly several millimolar in concentration). It is worth to mention that substrates "S" and "Y" should not react chemically between them. Molar concentration of "S" and "Y" species in the bulk of solution is supposed to be higher than the total surface concentration Γ^*(Ox). Consequently, the chemical steps in Scheme 1 are supposed to be of pseudo-first order. k_s° is a rate constant of electron transfer (potential-dependent), while k_1 and k_2 are the rate constants of respective chemical steps. For an excess molar concentration of species S and Y present in voltammetric cell, we can define the following chemical (catalytic) rate parameter: $\varepsilon=(k_1+k_2)$, where k_1 (s^{-1}) and k_2 (s^{-1}) are rate constants defined as: $k_1=k_f' c(S)$ and $k_2=k_b' c(Y)$. k_f' and k_b' are real chemical rate constant ($mol^{-1}\,cm^3\,s^{-1}$), while c(S) and c(Y) are molar concentration of substrates "S" and "Y", respectively. Mathematically, this mechanism can be described by following equations:



Scheme 1. Simple representation of the relevant steps of a surface catalytic EC_{rev}' mechanism

$$[\mathrm{d}\,\Gamma\,(\mathrm{Ox})/\mathrm{d}t] = -I/(nFA) + k_2\,I(\mathrm{Red}) - k_1\,I(\mathrm{Ox}) \quad (1)$$

$$[\mathrm{d}\,\Gamma\,(\mathrm{Red})/\mathrm{d}t] = I/(nFA) - k_2\,I(\mathrm{Red}) + k_1\,I(\mathrm{Ox}) \quad (2)$$

Differential equations (1) and (2) are solved under following conditions:

(a) $t = 0;\ \Gamma(\mathrm{Ox}) + \Gamma\,(\mathrm{Red}) = \Gamma^*(\mathrm{Ox});\ [k_2/k_1] = K\mathrm{eq}$

(b) $t > 0;\ \Gamma\,(\mathrm{Ox}) + \Gamma\,(\mathrm{Red}) = \Gamma^*(\mathrm{Ox})$; and $[k_2/k_1] = K\mathrm{eq}$

However, for $t>0$, when potential is applied, changes of Γ (Ox) and Γ (Red) at working electrode surface produce flow of electrical current. In that scenario, by applying the Butler-Volmer equation, we get:

(c) $t > 0;\ I/(nFA) = k_s^\circ\,\exp(-\alpha\Phi)\,[\Gamma\,(\mathrm{Ox}) - \exp(\Phi)\,\Gamma\,(\mathrm{Red})]$

Γ^*(Ox) ($mol\,cm^{-2}$) is the initial surface concentration of starting electrochemically active material Ox at working electrode surface. By A we define the active area of working electrode (cm^2), F is the Faraday constant (96485 C/mol), while n is number of exchanged electrons between the working electrode and redox adsorbates Ox (ads) and Red(ads) in an elementary act of electrochemical reaction. α is the electron transfer coefficient, while Φ is the dimensionless potential defined as $\Phi=nF(E-E^\circ_{Ox/Red})/(RT)$. In the last equation, E is the potential applied, while $E^\circ_{Ox/Red}$ is the standard (or more precisely, the formal) redox potential of couple Ox(ads)/Red(ads). R is the universal gas constant (8.314 $J\,mol^{-1}\,K^{-1}$), and T is the thermodynamic temperature. Analytical solution of differential equations (1) and (2) has been obtained by numerical integration method described in [37]. The recurrent formulas for calculation theoretical cyclic voltammograms are given in the Supplementary Material of this work. In the simulations, we assumed that the electron transfer coefficient of cathodic and anodic step of the electrode reaction are both equal, and their values

were set to $\alpha=0.5$. Moreover, we set the number of exchanged electrons to $n=2$, and temperature $T=298$ K in all simulations. All cyclic voltammograms are recorded by a scan starting from positive potentials (+0.35 V) and running toward the switching potential having negative values. The theoretical calculations have been performed by using the MATHCAD 14 software. We give in the Supplementary Material entire MATHCAD working sheet of considered surface catalytic EC_{rev}' mechanism.

Parameters of which simulated cyclic voltammograms are affected

We define the dimensionless current of simulated cyclic staircase voltammograms as $\Psi=I\tau/[(nFA\,\Gamma^{*}(\mathrm{Ox}))]$. In the last equation, τ is the duration time of potential steps in cyclic staircase voltammetry. Calculated cyclic staircase voltammograms of surface catalytic EC_{rev}' mechanism depend on several parameters. The dimensionless electrode kinetic parameter $K_{ET}=k_s^{\circ}\tau$ reflects the effect of kinetics of electron transfer (via k_s°) relative to the time-duration of step potential τ. In addition, the features of simulated cyclic voltammograms depend on equilibrium constant of chemical steps Keq, and by dimensionless chemical catalytic rate parameter $K_{catalytic}$. The dimensionless parameter $K_{catalytic}$ is defined as $K_{catalytic}=\varepsilon\tau$. In the last equation, ε is a chemical parameter linked to the rate of regenerative chemical reaction. ε is defined as $\varepsilon=(k_1+k_2)$, where k_1 and k_2 are the rate constants of direct and backward steps of the chemical reaction, respectively. As previously explained, for an excess molar concentration of species "S" and "Y" in voltammetric cell, k_1 and k_2 are linked to their bulk concentrations as follows: $k_1=k_f'\,c(\mathrm{S})$ and $k_2=k_b'\,c(\mathrm{Y})$. k_f' and k_b' are real chemical rate constant ($\mathrm{mol^{-1}\,cm^3\,s^{-1}}$), while $c(\mathrm{S})$ and $c(\mathrm{Y})$ are molar concentration of substrates "S" and "Y", respectively. Consequently, the value of $K_{catalytic}$ can be altered by modifying the molar concentrations of S or Y.

In all theoretical calculations, we used following parameters of applied potential: duration of potential steps $\tau=0.001$ s, and the height of step potential $dE=4$ mV. Entire MATHCAD working simulation sheet of this mechanism is given in the Supplementary of this work. We explored the MATHCAD 14 commercial package to calculate the cyclic staircase voltammograms. We assigned the forward (reduction) currents with red colour. The backward (reoxidation) currents are presented with blue colour.

Results and discussion

At the beginning of this section, we should explain some important aspects of this specific surface catalytic model. Although we suppose to have a chemical equilibrium even from the beginning of the experiment between Ox (ads) and Red(ads) (in absence of applied potential), the total concentration of all adsorbed electroactive species at working electrode surface remains constant. Indeed, the chemical equilibrium between Ox(ads) and Red(ads) governed by Keq (in absence of applied potential) will affect the initial magnitudes of current-potential curves (cyclic voltammograms). However, when we apply a potential on working electrode, and once the electrochemical electrode reaction starts, only in that situation (i.e. during the time-frame of current measurement at step potentials in CSV), we "sense" and we detect the additional contribution of chemical reaction to the features of recorded voltammograms. In Figure 1 we present a series of cyclic voltammograms that are calculated at six values of kinetics of electrode reaction (K_{ET}), for an equilibrium constant Keq=10, and for a small value of $K_{catalytic}$ ($K_{catalytic}=0.00001$). Obviously, at small rates of chemical reaction, the mutual conversion between Ox and Red takes place in accordance with the applied potential. As a consequence, we obtain cyclic voltammograms having features that are almost identical as those of a simple surface systems $\mathrm{Ox_{(ads)}}+n\mathrm{e^-}\leftrightarrow\mathrm{Red_{(ads)}}$ (Figure 1). As the peak-to-peak separation changes from 20 mV (for $K_{ET}=50$) to 300 mV (for $K_{ET}=0.01$), the ratio between cathodic and anodic peak currents is near to 1 for almost all K_{ET} values. Noticeably, under conditions in Figure 1, we see that peak currents of backward (oxidation) components are slightly higher than those of forward peaks. This effect is slightly more pronounced at smaller values of K_{ET} (Figure 1c–f). A cause of this effect is found in a very specific feature of this mechanism. As Ox(ads) gets regenerated via chemical reaction of Red(ads) and "Y", its additional transformation to Red(ads) takes place simultaneously in two parallel ways: (a) via electrochemical and (b) via chemical ($\mathrm{Ox_{(ads)}}+\mathrm{S}$) way. Indeed, this phenomenon will contribute some more Red(ads) to be created under simulation conditions of Figure 1c–f. This is why the peak currents of backward components get slightly higher than forward ones for Keq=10, and $K_{catalytic}=0.00001$. If the equilibrium constant of chemical step is large (i.e. Keq >1000), then catalytic rate parameter $K_{catalytic}$ produces the same features as in cyclic voltammograms of "simple" surface regenerative EC_{irr}' mechanism coupled with irreversible chemical step (see Figure 2). Under such conditions, an increase of catalytic rate parameter leads to decrease of the backward current component and concomitant increase of the forward current component (Figure 2a–c). This effect is followed by rising of the limiting current measured at the end of cyclic voltammograms. If $K_{catalytic}>0.5$, a sigmoidal (steady-state) curve is observed (Figure 2d–f), with limiting currents being function of $K_{catalytic}$ only [23]. At very high rates of chemical reaction, we observe identical sigmoidal shapes of both current components, implying that the same electrochemical reaction happens in both scan directions. This scenario happens when the rate of "backward" catalytic chemical step Red(ads)+Y→Ox (ads)+S gets much faster than the rate of electron transfer step Red(ads) – ne-→Ox(ads). Additional phenomenon we observe at high catalytic rates is the shifting of half-wave potential ($E_{mid,p}$) of steady-state voltammo-

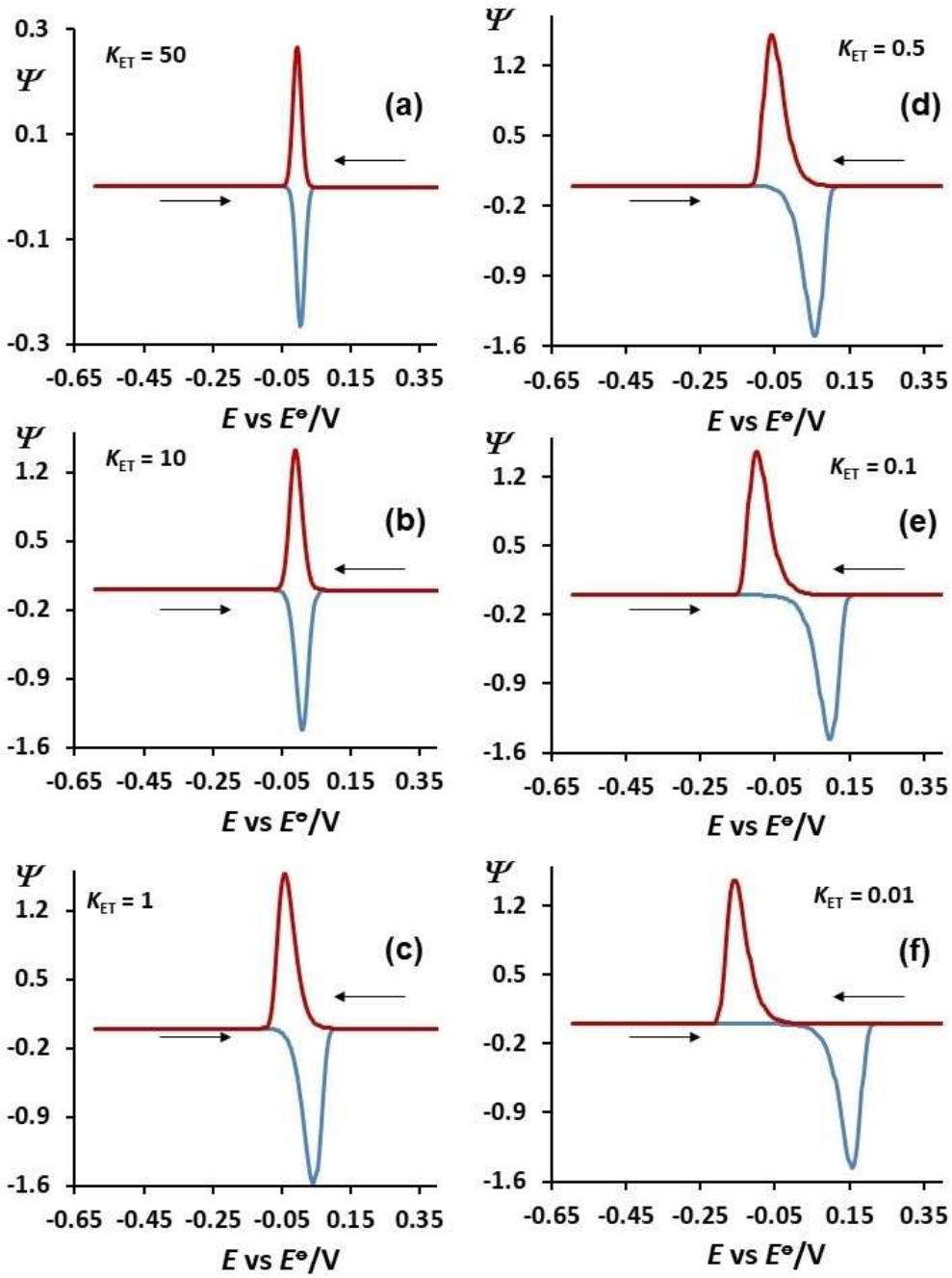


Fig. 1. Cyclic voltammograms calculated as a function of kinetics of electrode step K_{ET}. Voltammograms are simulated for an equilibrium constant of regenerative reaction Keq = 10, and for small rate of regenerative reaction ($K_{catalytic}$ = 0.00001). The other parameters used in simulations are: temperature T = 298 K; number of electrons ne^- = 2; electron transfer coefficient α = 0.5, potential step dE = 4 mV, time increment τ = 0.001 s. K_{ET} values of dimensionless electrode parameter are given in the charts. Starting potential was + 0.35 V.

grams toward more negative potentials by increasing of $K_{catalytic}$ (Figure 2d–f). Figures 1 and 2 are the two limiting situations of elaborated surface catalytic EC_{rev}' mechanism, whose voltammetric features are reported in the literature [1–3]. When the value of equilibrium constant Keq < 100, then we observe several specific effects caused by kinetics and thermodynamics parameters (related to chemical reaction) to the features of calculated cyclic voltammograms. These effects are elaborated in the next two chapters.

Effect of the equilibrium constant of catalytic reaction to the features of calculated cyclic voltammograms

For a given value of K_{ET} and for defined values of catalytic rate parameter $K_{catalytic}$, the features of theoretical

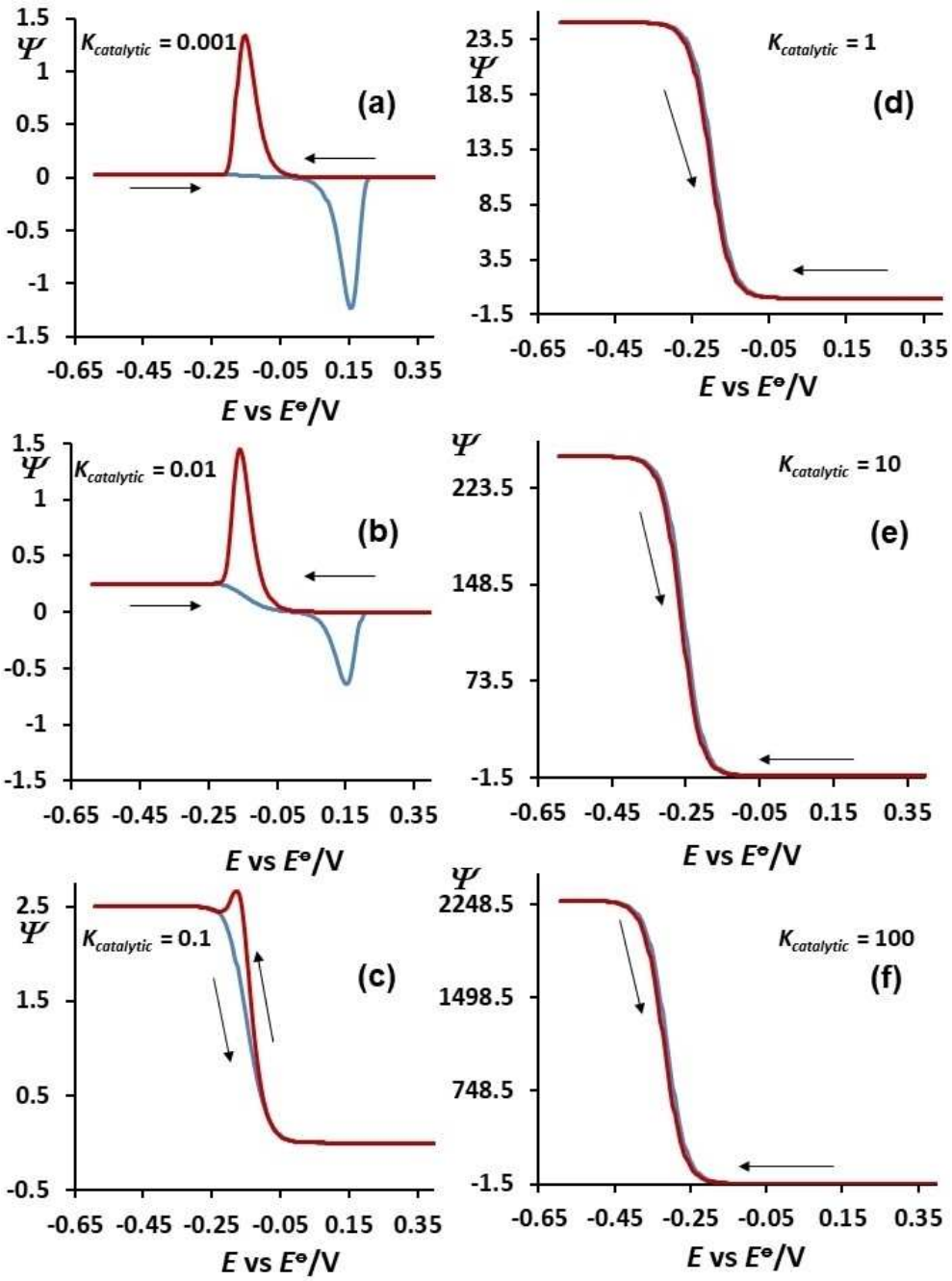


Fig. 2. Influence of catalytic reaction rate to the features of theoretical cyclic voltammograms of a surface catalytic EC_{rev}' mechanism, simulated for $K_{ET}=0.1$ and Keq = 1000. The other parameters in simulation model were identical as those in Figure 1.

cyclic voltammograms of surface EC_{rev}' mechanism depend on the magnitude of equilibrium constant Keq. In Figure 3 we present a series of cyclic voltammograms simulated for $K_{ET}=10$, for $K_{catalytic}=0.0447$ (moderate rate of catalytic reaction), and for six different values of equilibrium constant Keq. Remarkably, all relevant parameters of calculated cyclic voltammograms, i.e. the heights of cathodic and anodic peaks, the separation between cathodic and anodic peaks at potential scale, as well as the "limiting currents" (which are the current magnitudes corresponding to the plateau in the after-peaks potential regions at negative potentials) are affected by Keq. Under such simulation conditions, the ratio of the peak currents of cathodic *vs* anodic peaks varies from 1.20 (for Keq of 100) to 1.55 (for Keq of 0.01). Moreover, a decrease of Keq value from 100 to 0.01 is associated by shifting of the cathodic peak for 45 mV in negative direction, and of the anodic peak for 45 mV in positive direction. In Figure 4 we present the peak-to-peak separation ($|\Delta E_p|$) dependence as a function of log

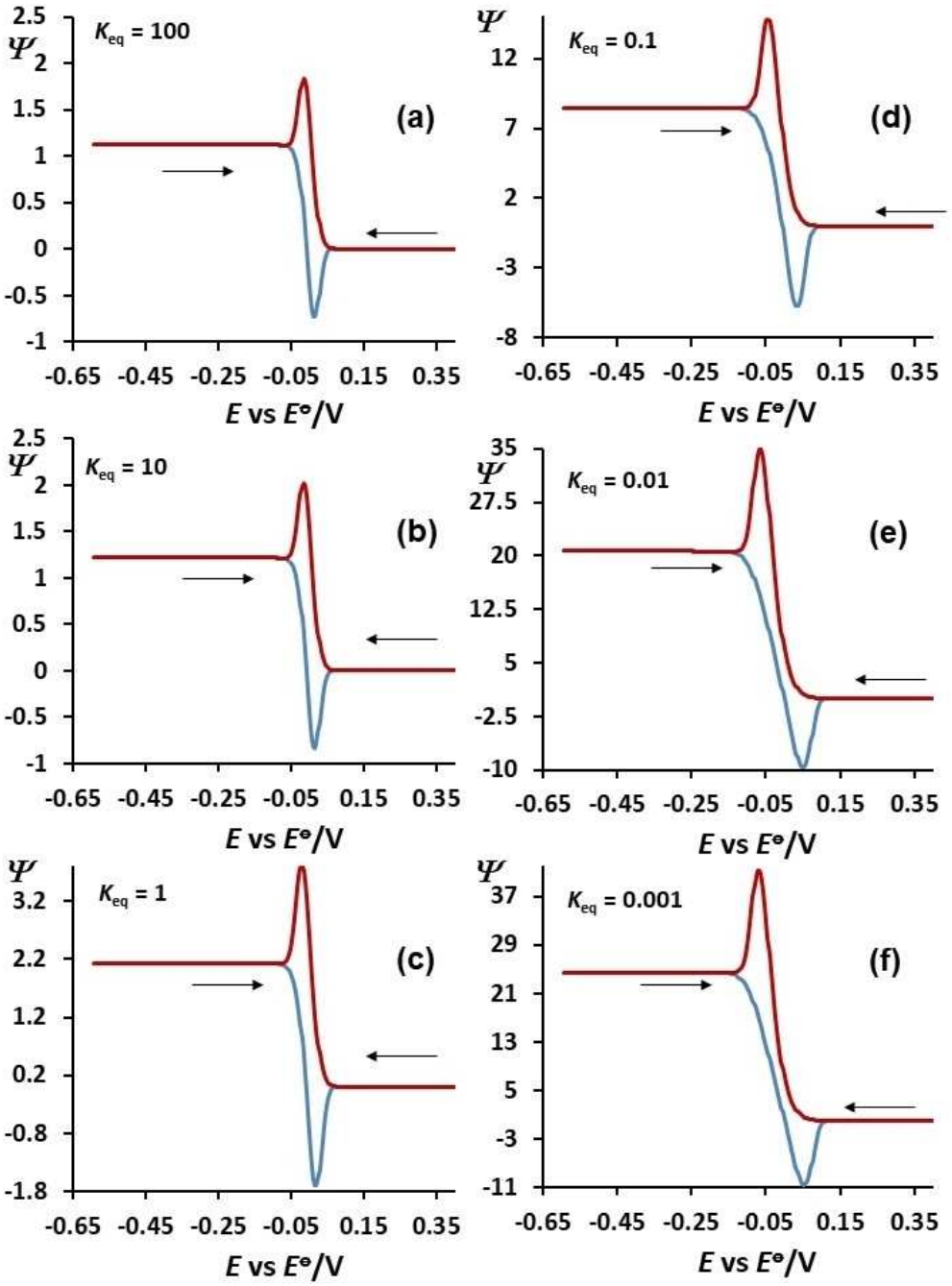


Fig. 3. Effect of equilibrium constant of chemical reaction to the characteristics of theoretical cyclic voltammograms, simulated for $K_{ET}=10$ and $K_{catalytic}=0.0447$. The other parameters in simulation model were identical as in Figure 1.

(*K*eq). The curves are estimated for $K_{catalytic}=0.0447$, and for three different values of K_{ET}. The sigmoidal dependences portrayed at Figure 4 are typical for the EC reaction mechanisms [1,2,4]. Linear dependence between ΔE_p and log(*K*eq) exists (roughly) in the region $-2.0<\log(Keq)<1$. As the slopes of linear parts at all curves of dependences ΔE_p *vs.* log(*K*eq) at Figure 4 are identical [−45 mV/log(*K*eq)], the intercepts depend on K_{ET}. Consequently, the dependences ΔE_p *vs.* log(*K*eq), as those corresponding to linear parts of curves in Figure 4, can be explored for calculating the value of *K*eq, providing that *n*, α and k_s° are known. To get access to *n*, α and k_s° related to simple surface reaction $Ox(ads)+ne^-\leftrightarrow Red(ads)$ (i.e. in absence of "S" and "Y"), we advise readers to following works [1–3].

As reported in [1–3,23], the magnitude of "limiting current" ($\Psi_{limiting}$) of cyclic voltammograms in EC' mechanisms is relevant parameter that can be used for analytical purposes, and for kinetic estimations, too. We analyzed this parameter ($\Psi_{limiting}$) as a function of equilibrium

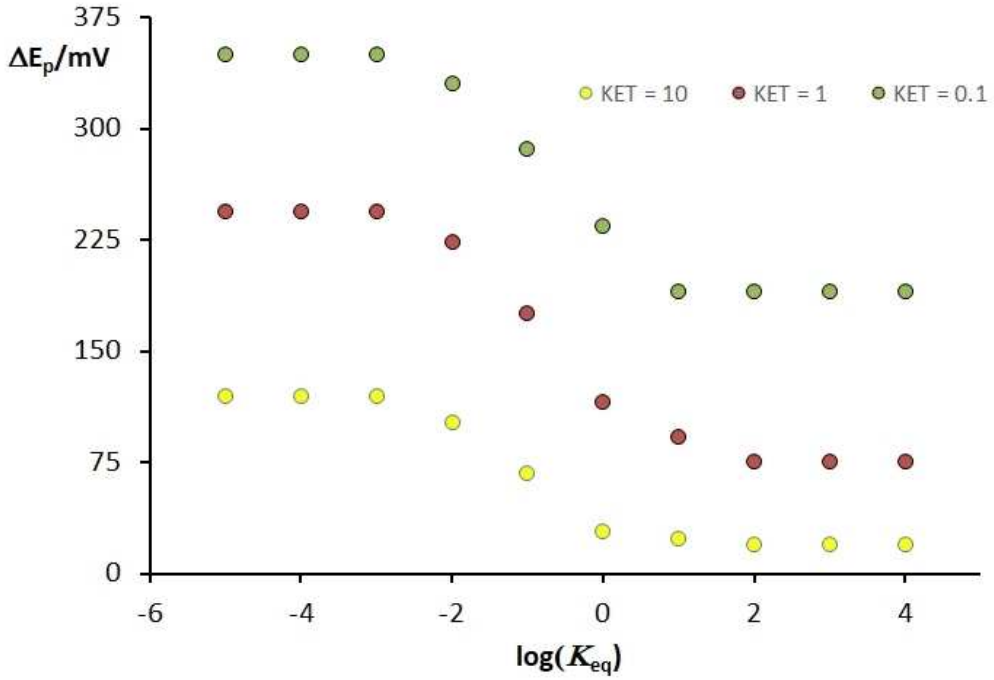


Fig. 4. Peak-to-peak separation $|\Delta E_p|$ of simulated cyclic voltammograms as a function of log(*K*eq). Curves are calculated for K_{ET} values of 0.1, 1 and 10, and for $K_{catalytic}$ of 0.0447. The other parameters used in simulation model were identical as in Figure 1.

constant, measured at various rates of catalytic reaction. We present in Figure 5 the dependences of $\Psi_{limiting}$ *vs.* log (*K*eq). All curves in Figure 5 are calculated for $K_{ET}=10$, and for different values of catalytic parameter $K_{catalytic}$. For $K_{catalytic}<1$, sigmoidal-like dependences are observed between $\Psi_{limiting}$ and log(*K*eq). In a region of $-2<\log$

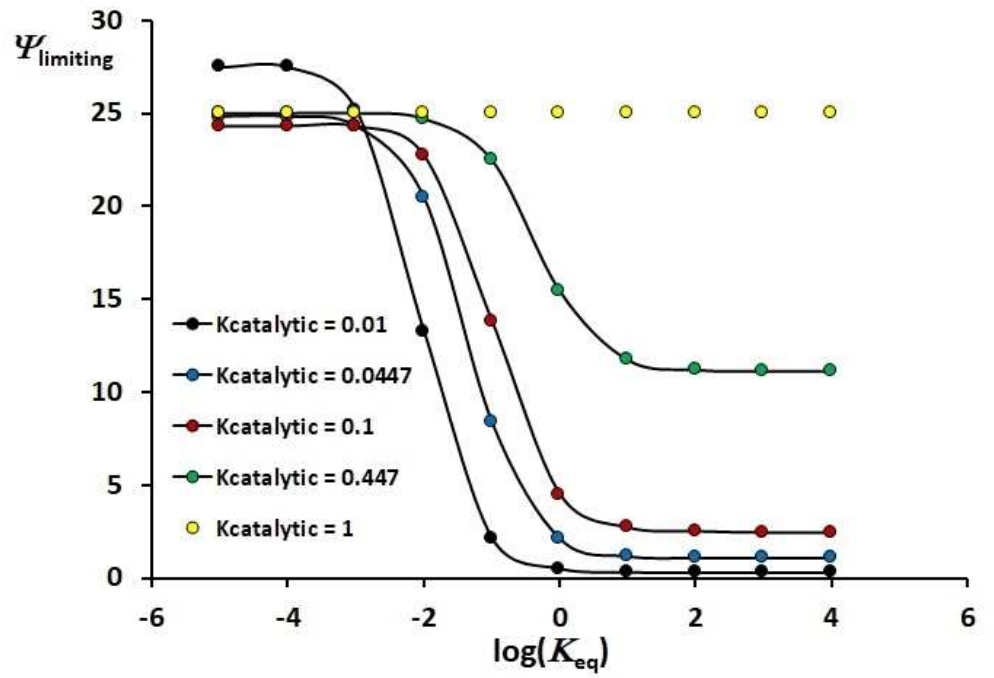


Fig. 5. Effect of *K*eq of chemical reaction to the magnitude of limiting currents $\Psi_{limiting}$ of calculated cyclic voltammograms. Curves are simulated for five different values of $K_{catalytic}$ (values are given in the chart) and for K_{ET} of 10. The other parameters in simulation model were identical as in Figure 1.

(Keq) < 0.5, a linear decrease of limiting currents by increasing of log(Keq) exists. For significant rates of catalytic reaction i.e. for $K_{catalytic} > 1$, we observe that the magnitude of limiting currents is independent on Keq (yellow circles in Figure 5). It is worth to mention that for a given value of $K_{catalytic}$, the rate of electron transfer (expressed via K_{ET}), does not influence the magnitude of limiting currents as a function of Keq (see Figure 6). Similar feature is already reported in [23], where it is shown that the magnitudes of limiting currents $\Psi_{limiting}$ of surface catalytic EC_{irr}' mechanism depend on the rate of regenerative reaction only.

Effect of the rate of regenerative chemical reaction to the features of calculated cyclic voltammograms

Most relevant parameter in voltammetric analysis of catalytic EC' mechanisms is the rate of regenerative (catalytic) chemical step. The rate of chemical reaction depends on concentration of regenerative agent, its nature (via the value of catalytic rate constant), on the temperature, pH, but also on the time scale of voltammetric measurements [1–4,21–26,29]. As demonstrated in [24], the rate of chemical regenerative reaction can influence also the rate of electron transfer step. It is worth to note that at EC' mechanisms, electrochemically active species get created as product, via electrode transformation of initial electroactive species at working electrode surface. The product species can further undergo a chemical reaction with given electrochemically inactive substrate. If such a chemical reaction can contribute in regeneration of initial electroactive species, the last will be capable to undergo additional electrochemical transformation at the working electrode. As presented in Figure 7, this scenario results in an overall irreversible electrochemical reaction, with the peak on the reverse scan diminished to an extent determined by the rate of the regenerative reaction. Since the catalytical species (the initial reactant in considered electrode mechanism) gets regenerated at working electrode surface, this effect will cause an increase of measured currents in forward direction (see cyclic voltammograms 7a–c). At large concentrations of substrate Y, the cyclic voltammograms can get a steady-state shape, featuring a plateau, instead of well-developed peaks (Figure 7d–e). This scenario happens if the kinetics of regenerative step Y + Red(ads) → Ox(ads) + S gets dominant over the rate of backward electrode reaction Red(ads) -ne- → Ox(ads). Under such conditions, entire amount of Red(ads) gets quick chemical transformation to the initial electroactive form Ox(ads). This phenomenon will cause the electrode reaction Ox(ads) + ne- → Red (ads) to take place multiple time at all applied potentials, and it will result in "steady-state" cyclic voltammograms (Figure 7d–f).

As reported in [1–3,23,31], the height of the plateau (i.e. the magnitude of limiting currents) of cyclic voltammograms of surface catalytic EC' mechanisms are function of molar concentration of substrate Y. In the surface catalytic EC_{rev}' mechanism elaborated in this work, entire scenario gets more complex due to the reversibility of the chemical step. Indeed, the ratio of rate constants of chemical regenerative reaction (portrayed via magnitude of equilibrium constant Keq) will affect the features of calculated cyclic voltammograms.

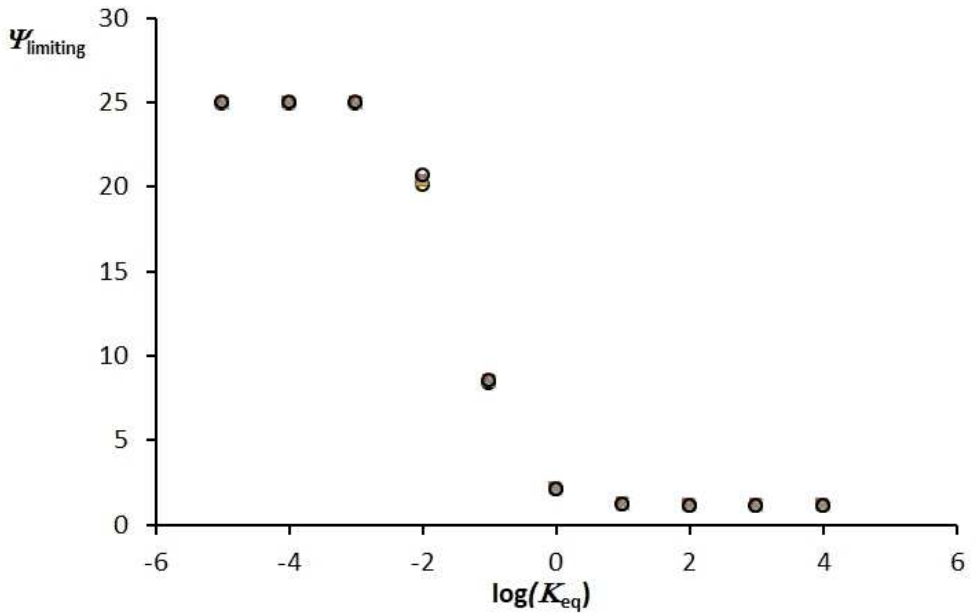


Fig. 6. Effect of equilibrium constant of the chemical reaction to the magnitude of limiting currents of calculated cyclic voltammograms. Curves are calculated for $K_{ET} = 0.001$; 0.01; 0.1; 1 and 10. $K_{catalytic}$ was se to 0.0447. Other parameters in simulation model were identical as in Figure 1.

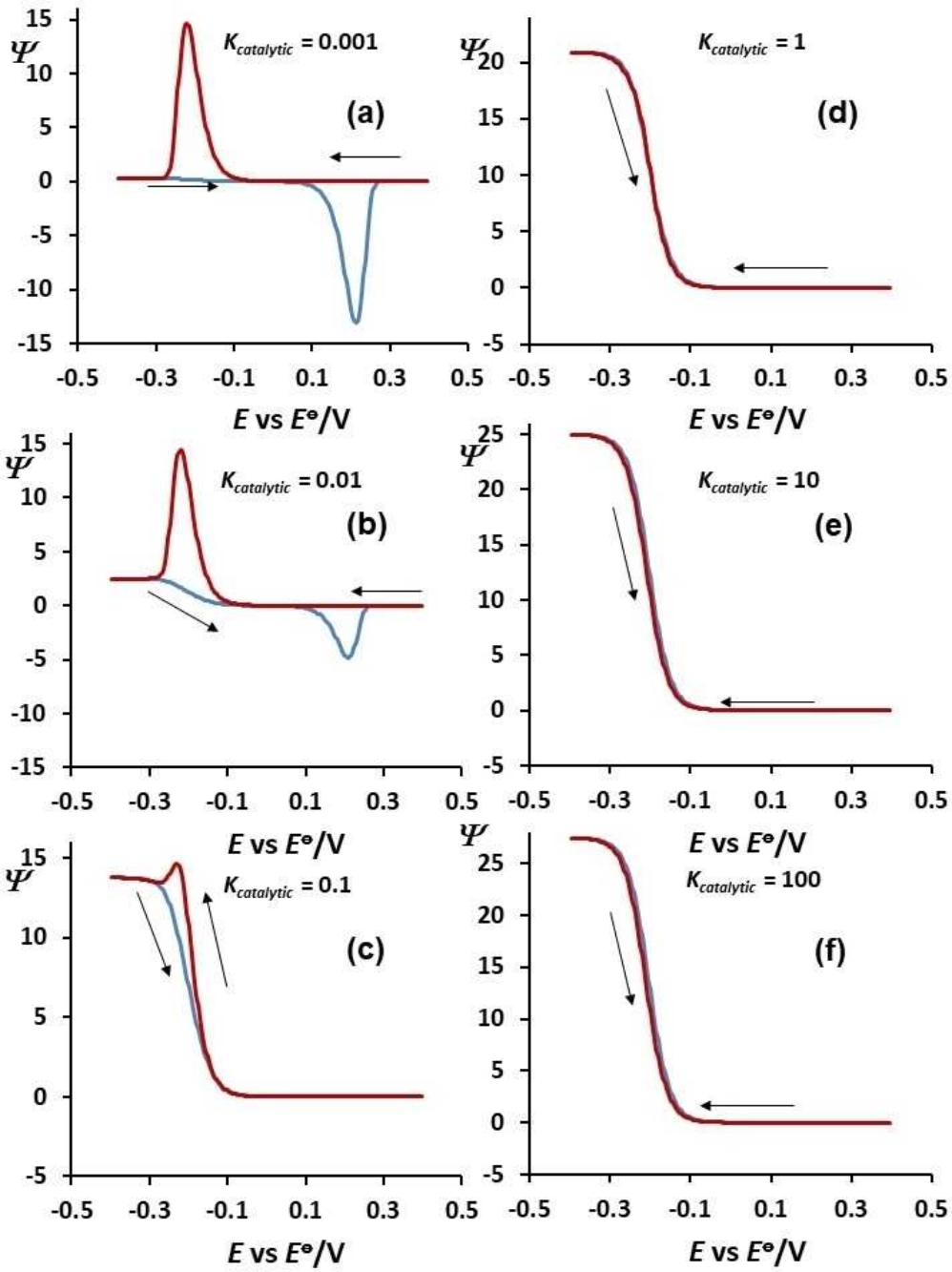


Fig. 7. Influence of chemical reaction rate to theoretical cyclic voltammograms of a surface catalytic EC_{rev}' mechanism. Voltammograms are simulated for six values of $K_{catalytic}$ (values are presented in the chart) for K_{ET} of 0.1, and Keq = 1. The other parameters used in simulation model were identical as in Figure 1.

In Figure 8 we present dependences of the mid-peak (or half-wave) potentials-$E_{mid,p}$ of calculated cyclic voltammograms as a function of the regenerative reaction rate. Note that $E_{mid,p}$ is defined as $E_{mid,p} = (E_{p,c} + E_{p,a})/2$ (in situation of existence of clearly measurable peaks at cyclic voltammograms), or it is the mid-point of the rising part between two plateaus at steady-state cyclic voltammograms measured at high rates of catalytic reaction. Curves in Figure 8 are calculated for several different values of Keq. For small and large values of equilibrium constant Keq (Figure 8A), we observe sigmoidal dependence between $E_{mid,p}$ and $\log(K_{catalytic})$. The linear parts of the curves in Figure 8A have identical slopes of −59 mV/log $(K_{catalytic})$ [slope = $-2.303RT(\alpha nF)$], independent on Keq. However, the intercepts of linear dependences between $E_{mid,p}$ and $\log(K_{catalytic})$ are function of electron transfer kinetics (Figure 8B). The equations corresponding to the linear segments of $E_{mid,p}$ *vs.* $\log(K_{catalytic})$ curves (as those

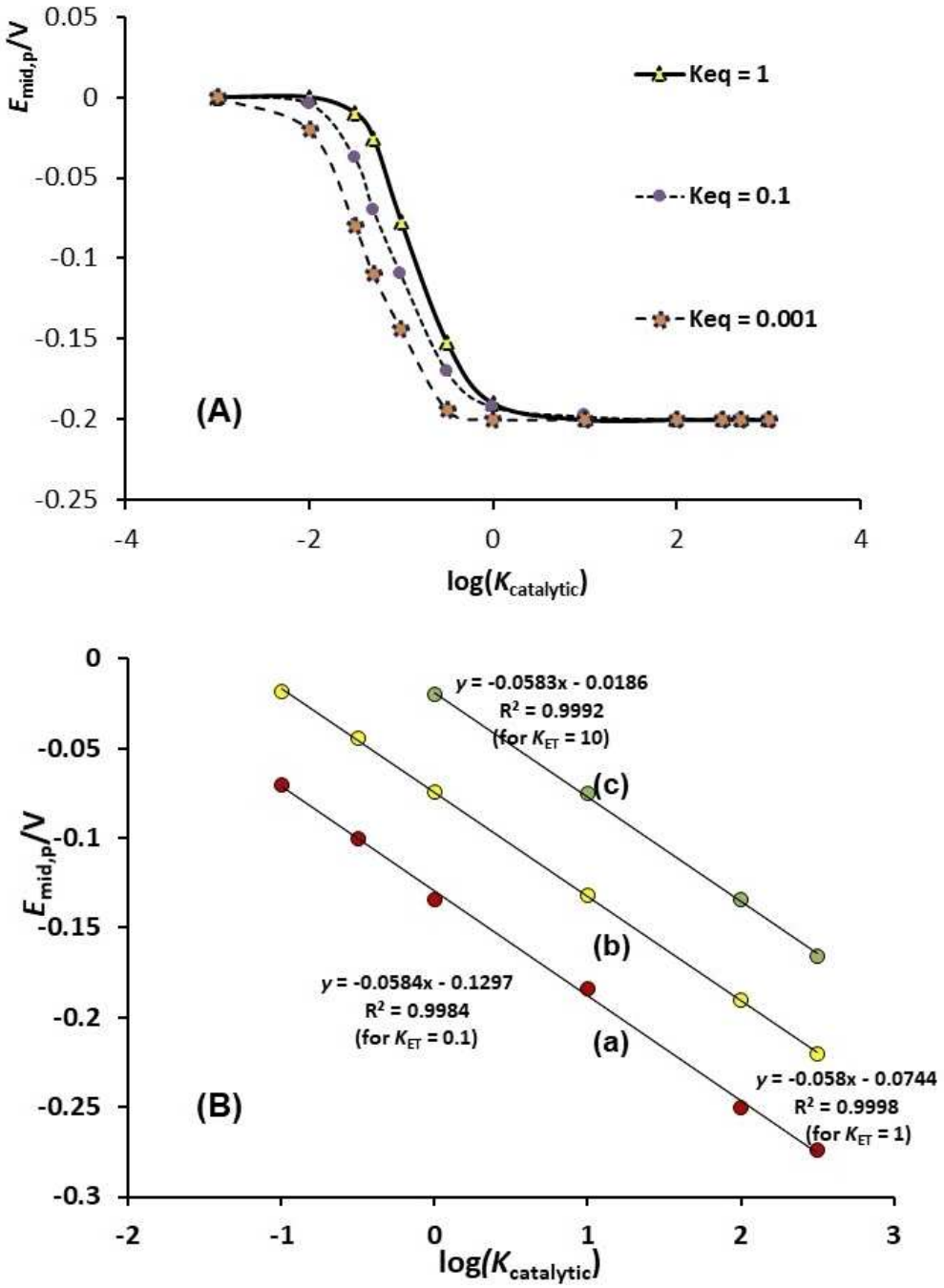


Fig. 8. Effect of rate of chemical reaction to the mid-peak potentials $E_{mid,p}$ of theoretical cyclic voltammograms. Curves are simulated for $K_{ET}=10$ and for several values of equilibrium constant Keq (panel A). Panel (B) shows only the linear segments of dependence $E_{mid,p}$ vs. log($K_{catalytic}$), estimated for Keq = 1000 and for K_{ET} of 0.1 (a), 1 (b) and 10 (c). Other parameters in simulation model were same as in Figure 1.

presented in Figure 8B) allow estimation of catalytic rate constant. For this, we need to know the value of rate constant of electron transfer (k_s°), the value of $E^\circ_{Ox/Red}$, as well as the values of n and α that should be previously determined for the simple surface system Ox(ads) + ne- ↔Red(ads).

The magnitudes of limiting currents of simulated cyclic voltammograms depend significantly on the rate of catalytic reaction. Shown in Figure 9 is dependence between $\Psi_{limiting}$ and log($K_{catalytic}$), evaluated from cyclic voltammograms calculated for several values of Keq and K_{ET} of 0.1. For Keq < 1000, we observe a sigmoidal dependence between $\Psi_{limiting}$ and log($K_{catalytic}$), with linear parts of the curves $\Psi_{limiting}$ *vs.* $K_{catalytic}$ having slopes that are function of Keq (see the inset Figure 9).

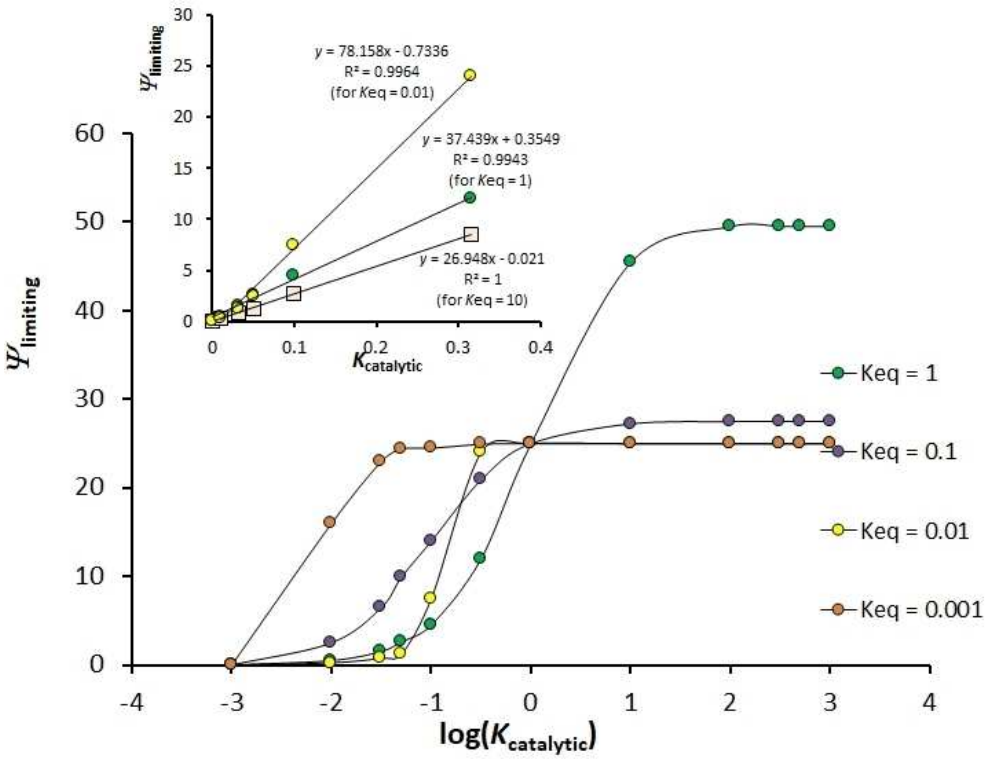


Fig. 9. Influence of dimensionless catalytic rate parameter $K_{catalytic}$ to the magnitudes of limiting currents of calculated cyclic voltammograms. Curves are simulated at four different values of *K*eq values (values of *K*eq are given in the chart) and for $K_{ET}=1$. The inset shows $\Psi_{limiting}$ *vs.* $K_{catalytic}$ linear dependences, calculated for three values of *K*eq, together with equations corresponding to linear regression lines. The other parameters used in simulation model were identical as in Figure 1.

However, for $Keq > 1000$, we observe a linear dependence between $\Psi_{limiting}$ and $K_{catalytic}$ in a wide range of $K_{catalytic}$ values (Figure 10), independent on K_{ET}. Identical linear dependence between $\Psi_{limiting}$ and $K_{catalytic}$ is already reported in [1–3,23], and it corresponds to the same feature reported for a simple surface EC_{irr}' mechanism. Large values of *K*eq will turn the surface EC_{rev}' into a simpler surface EC_{irr}' mechanism, whose features are well documented in the literature [1–3]. As described in [1,23], the slope of the linear dependence between $\Psi_{limiting}$ and $K_{catalytic}$ presented in Figure 10 can give access to the value of catalytic parameter ε at surface catalytic EC_{rev}' mechanism, if the value of equilibrium constant *K*eq >1000. As reported in [23], access to chemical catalytic parameter ε can be achieved by designing voltammetric experiment in which we modify the concentration of the substrate "Y"-*c*(Y) in voltammetric cell. Once a steady-state voltammograms are obtained, then by plotting the limiting current magnitudes $I_{limiting}$ as a function of the molar concentration of substrate *c*(Y), we should get a linear dependence similar to that presented in Figure 10. The slope of $I_{limiting}$ *vs.* *c*(Y) dependence is defined as: $\text{slope} = |(\varepsilon)[nFA\Gamma^*(\text{Ox})\tau^{-1}]|$. If the other parameters (and also *c*(S)) appearing in last equation are known, and if we perform experiments at constant scan rate (then we will know the value of τ), we can get access to the value of chemical parameter ε. This approach for estimation of ε does not require the parameters linked to the electron transfer step (k_s° and α) to be known.

Conclusions

Although surface catalytic EC' mechanism is the most comprehensively studied from all surface electrode mechanisms complicated with chemical reactions, a chemical reversibility of the catalytic step at this mechanism has not been considered so far. In this work we consider a special type of a surface EC' mechanism under conditions of cyclic staircase voltammetry, with regenerative step featuring chemical reversibility. At given rates of electron transfer reaction, the characteristics of simulated cyclic voltammograms of surface regenerative EC_{rev}' mechanism depend on catalytic reaction rate, but also on the magnitude of chemical equilibrium constant. We have demonstrated that this particular mechanism can be turned into a simpler one (i.e. to surface catalytic EC_{irr}'), if the value of chemical equilibrium constant is very large. In that case, one can explore methodology described in [23] to get access to the catalytic rate parameter relevant to regenerative chemical reaction. If $Keq < 100$, then we can explore the linear parts of peak-to-peak separation dependence as a function of log(*K*eq) (Figure 4) in order to get initial access to the value of *K*eq. Once the value of *K*eq is estimated, we can use the equations related to $E_{mid,}$

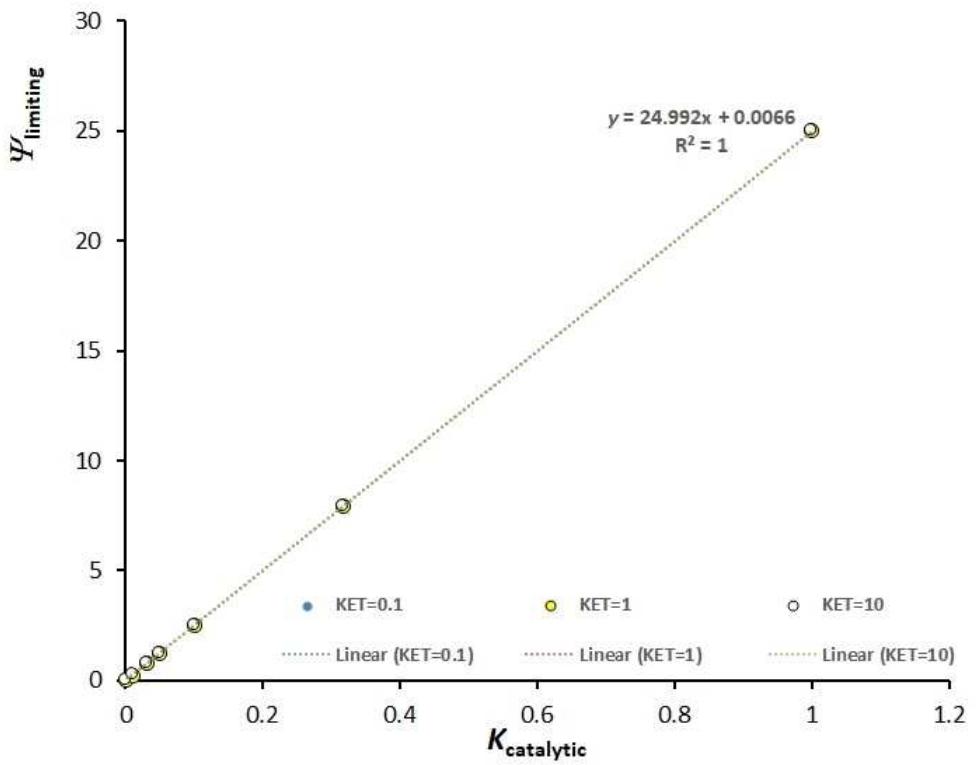


Fig. 10. Influence of rate of regenerative reaction ($K_{catalytic}$) to the magnitude of limiting currents of cyclic voltammograms. Voltammograms are simulated for Keq = 1000 and for K_{ET} values of 0.1; 1; and 10. The slope of the linear line allows estimation of catalytic parameter ε [1,23]. The other parameters used in simulation model were identical as those in Figure 1.

$_p$ *vs.* log($K_{catalytic}$) dependences of linear segments of curves presented in Figure 8 to evaluate the value of chemical (catalytic) rate parameter ε. To get access to both, the value of catalytic rate parameter ε, and to the value of equilibrium constant Keq, we need to know the standard rate constant of electron transfer ($k_s°$), the standard redox potential $E°_{Ox/Red}$, the number of exchanged electrons n, and the value of electron transfer coefficient α of simple Ox(ads) + ne- → Red(ads) reaction. For this, we advise the readers to explore methodologies reported in [1,2 and 3]. At this point, it is worth to mention one very specific moment of this electrode mechanism. As electrochemically generated Red(ads) reacts with "Y", we observe regeneration of Ox(ads) (and production of side product "S"). In the remaining time, at the same step potential, simultaneous electrochemical and chemical generation of Red(ads) happens during the current-measuring period. Indeed, a simultaneous parallel occurrence of two reactions $Ox_{(ads)} + ne- \leftrightarrow Red_{(ads)}$, and $Ox_{(ads)} + S \leftrightarrow Red_{(ads)} + Y$ creates differences between surface EC_{rev}' and the simple surface EC_{irr}' mechanism, if Keq < 100. These differences are clearly demonstrated in Figure 3, for example, where the effect of equilibrium constant to the current-potential features of calculated cyclic voltammograms is nicely visualized. We would like to point out that the time-duration of step potentials in cyclic staircase voltammetry affects simultaneously both, the electron transfer kinetics, and the kinetics of chemical regenerative reaction, too. Recall that the rate of regenerative reaction (expressed via the value of $K_{catalytic}$) can be also modified via changing the concentration of substrate "Y" in the voltammetric cell. Therefore, in order to reproduce the dependences as a function of catalytic reaction rate, we advise the readers to perform experiments in which the scan rate will be held constant, by modifying the concentration of "Y" in the voltammetric cell only. Experimental evidences of this particular mechanism are reported in [28,32–37].

Acknowledgments

Rubin Gulaboski and Sofija Petkovska wish to acknowledge the "Goce Delcev" University in Stip, Macedonia for the support.

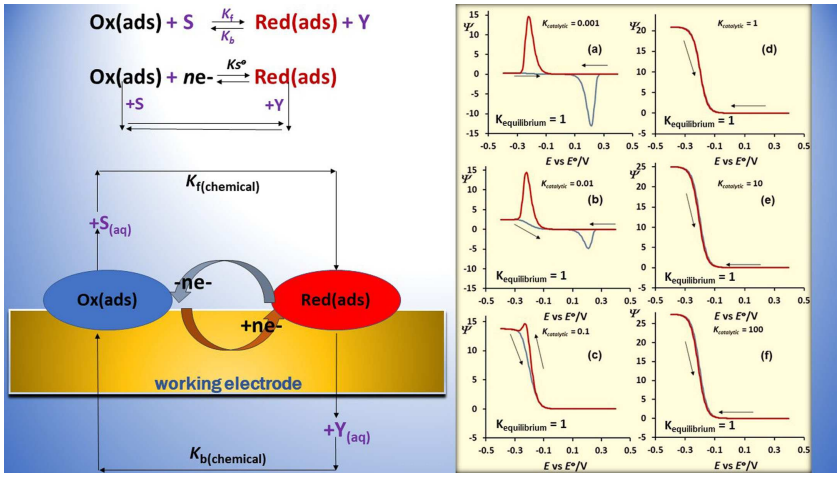
References

[1] R. G. Compton, C. E. Banks, Understanding voltammetry, 2nd Edition, Imperial College Press, London, UK, **2011**.
[2] A. J. Bard, L. R. Faulkner, *Electrochemical methods. Fundamentals and applications*, 3rd edition, John Wiley & Sons, Inc. **2004**.
[3] A. Molina, J. Gonzales, *Pulse voltammetry in physical electrochemistry and electroanalysis*, in *Monographs in elec-*

trochemistry (F. Scholz, ed.), Berlin Heidelber, Springer, **2016**.
[4] V. Mirceski, S. Komorsky-Lovric, M. Lovric, *Square-wave voltammetry*, *Theory and application*, Springer, Berlin, Germany, **2007**.
[5] R. Gulaboski, V. Mirceski, I. Bogeski, M. Hoth, *J. Solid State Electrochem.* **2012**, *16*, 2315.
[6] C. Léger, P. Bertrand, *Chem. Rev.* **2008**, *108*, 2379.
[7] F. A. Armstrong, *Voltammetry of Proteins.* In: A. J. Bard, M. Stratmann, G. S. Wilson (eds) *Encyclopedia of Electrochemistry*, vol. 9, Wiley VCH, Weinheim, **2002**.
[8] P. N. *Barlett, Bioelectrochemistry-Fundamentals, Experimental Techniques and Application*, Wiley, Chichester, **2008**.
[9] V. Mirceski, R. Gulaboski, M. Lovric, I. Bogeski, R. Kappl, M. Hoth, *Electroanalysis* **2013**, *25*, 2411.
[10] J. G. Osteryoung, J. J. O'Dea, *Square-Wave Voltammetry, Electroanalytical chemistry: a series of advances.* Marcel Dekker, Inc: New York, **1986**.
[11] E. Laborda. J. Gonzales, A. Molina, *Electrochem. Commun.* **2014**, *43*, 25.
[12] A. Molina, J. Gonzales, M. Henstridge, R. G. Compton, *Electrochim. Acta* **2011**, *56*, 4589.
[13] A. Molina, R. G. Compton, C. Serna, F. Martinez-Ortiz, E. Laborda, *Electrochim. Acta* **2009**, *54*, 2320.
[14] R. Gulaboski, *J. Solid State Electrochem.* **2009**, *13*, 1015.
[15] R. Gulaboski, L. Mihajlov, *Biophys. Chem.* **2011**, *155*, 1.
[16] P. Kokoskarova, V. Maksimova, M. Janeva, R. Gulaboski, *Electroanalysis*, **2019**, *31*, 1454.
[17] M. Lovric, "Square-wave voltammetry," in *Electroanalytical Methods*, F. Scholz, Ed. Springer, Berlin, Germany, 2nd edition, **2010**.
[18] R. Gulaboski, P. Kokoskarova, S. Mitrev, *Electrochim. Acta* **2012**, *69*, 86.
[19] E. Laborda, M. Henstridge, A. Molina F. Martinez-Ortiz, R. G. Compton, *J. Electroanal. Chem.* **2011**, *660*, 169.
[20] F. Garay, M. Lovric, *J. Electroanal. Chem.* **2002**, *518*, 91.
[21] R. Gulaboski, V. Mirceski, M. Lovric, I. Bogeski, *Electrochem. Commun.* **2005**, *7*, 515.
[22] V. Mirceski, R. Gulaboski, *Electroanalysis*, **2001**, *13*, 1326.
[23] R. Gulaboski, P. Kokoskarova, S. Petkovska, *Croat. Chem. Acta* **2018**, *91*, 377.
[24] R. Gulaboski, V. Mirceski, *Electrochim. Acta* **2015**, *167*, 219.
[25] R. Gulaboski, V. Mirceski, M. Lovric, *J. Solid State Electrochem.* **2019**, *23*, 2493.
[26] V. Mirceski, R. Gulaboski, *J. Solid State Electrochem.* **2003**, *7*, 157.
[27] V. Mirceski, R. Gulaboski, *Maced. J. Chem. Chem. Eng.* **2014**, *33,* 1.
[28] A. A. El Maali, *Bioelectrochemistry* **2004**, *64*, 99.
[29] A. Molina, J. M. Gomez-Gil, J. Gonzalez, E. Laborda, *J. Electroanal. Chem.* **2019**, *847*, 113097. doi.org/10.1016/j.jelechem.2019.04.057.
[30] J. M. Savéant, *Elements of Molecular and Biomolecular Electrochemistry: An Electrochemical Approach to Electron Transfer Chemistry*, Hoboken, NJ, Wiley, **2006**.
[31] I. Mohamed, *Anal. Chim. Acta* **2001**, *443*, 63.
[32] F. Arjmand, M. Aziz, S. Tabassum, *Curr. Anal. Chem.* **2011**, *7*, 71.
[33] G. M. Eckert, F. Gutmann, H. Keyzer, *Electrochemistry of drug interactions and incompatibilities* in *Modern Bioelectrochemistry* (F. Gutmann, H. Keyzer, eds.) **1986**, Springer, Boston.
[34] D. Huska, V. Adam, J. Hrabeta, M. Stiborova, T. Eckschlager, L. Trnkova, R. Kizek, *Electroanalysis* **2019**, *21*, 487.
[35] W. Sun, J. Han, K. Jiao, L. Lu, *Bioelectrochemistry* **2006**, *68*, 60.
[36] A. E. Nkodo, J. M. Garnier, B. Tinland,, *Electrophoresis*, **2001**, *22*, 2424.
[37] M. L. Olmstead, R. G. Hamilton, R. S. Nicholson, *Anal. Chem.* **1969**, *41*, 260.

Received: November 21, 2019
Accepted: December 11, 2019
Published online on ■■, ■■

FULL PAPER



*S. Petkovska, R. Gulaboski**