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Original scientific paper

Voltammetric and theoretical studies of the electrochemical behavior of cephalosporins at a mercury electrode

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Abstract: The adsorption and electroreduction behavior of cefpodoxime proxetil, cefotaxime, desacetylcefotaxime, cefetamet, ceftriaxone, ceftazidime, and cefuroxime axetil at a mercury electrode surface were studied using cyclic (CV), differential pulse (DPV) and adsorptive stripping differential pulse (AdSDPV) voltammetry. The quantitative structure property relationship (QSPR) study of the seven cephalosporins adsorption at the mercury electrode was based on density functional theory DFT-B3LYP/6-31G(d,p) calculations of molecular orbitals, partial charges and electron densities of the analytes. The DFT-parameters and QSPR model explain well the process of adsorption of the examined cephalosporins. The QSPR study defined that cephalosporins with lower electron density on the nitrogen atom of the N–O bond, higher number of hydrogen bond-accepting groups, and higher principal moment of inertia should express high adsorption on the mercury electrode.

Keywords: cephalosporins; AdSDPV; CV; DFT; QSPR; computational electrochemistry.

INTRODUCTION

Cephalosporins are semi-synthetic β-lactam antibiotics similar to penicillins, but with a broader spectrum of antibacterial properties and a higher resistance to β-lactamase.[1]

These compounds contain a β-lactam/dihydrothiazine moiety bearing different substituents at the C3 and C7 position. Methoxyimino cephalosporins are reducible at a mercury electrode and therefore present electrochemically a very important class of antibiotics. This characteristic enables the application of electroanalytical techniques for the sensitive determination of methoxyimino cephalosporins. These cephalosporins were extensively studied at a mercury elec-

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trode, the mechanism of methoxyimino reduction at the mercury electrode was established and voltammetric methods based on the adsorptive accumulation of cephalosporins at the mercury electrode were developed.[2–6] Regardless of the high sensitivity of the determination in pharmaceutical formulations, this method still could not be used for the determination of cephalosporins in a biological matrix. Apart from the reduction at mercury electrode, methoxyimino cephalosporins may be reduced or oxidized at different solid electrodes that may be specially modified and activated.[7–12] These determinations appeared to be less sensitive than at a mercury electrode.[7–12] Since the process of the reduction of methoxyimino cephalosporins is associated with adsorption at the electrode surface, adsorptive stripping voltammetry was successfully applied for their quantitative determination as a highly selective and precise electroanalytical technique.[13–15]

The application of adsorptive stripping method enabled the determination of low concentrations of cephalosporins *in vivo* from biological samples, such as urine, serum or cerebrospinal fluid.[13–15] The mechanism of reduction of the methoxyimino cephalosporins, such as cefpodoxime proxetil (CPDX-PR), cefotaxime (CTX), desacetylcefotaxime (DCTX) and cefetamet (CET), at a mercury electrode was established and reported in previous papers.[16–20] The Methoxyimino group in cephalosporin molecules undergoes reduction at mercury electrodes yielding well-defined polarographic waves and voltammetric peaks, over a wide pH interval from 2 to 12.[16–20]

Based on previous findings,[16–20] the voltammetric study is now extended to include structurally closely related cephalosporins, *i.e.*, ceftriaxone (CRO), ceftazidime (CAZ) and cefuroxime axetil (CXM).

In this work, adsorptive techniques were applied for a study of the electroreduction behavior and for the quantitative determination of ceftriaxone, ceftazidime, and cefuroxime axetil. The experimental results of the group of seven methoxyimino cephalosporins were further used in a quantum chemical study. The theoretical study was used to describe the adsorption mechanism at the mercury electrode surface and to predict the electrochemical adsorption at mercury electrode of related cephalosporins.

To the best of our knowledge, there is no scientific report either about the study of the electrochemical behavior of cephalosporins or a quantum chemical study of their electrochemical adsorption mechanism on a mercury electrode.

EXPERIMENTAL

Reagents and chemicals

Cephalosporins (CEF) were from Sigma and all chemicals were of analytical grade quality. Britton–Robinson (BR) universal buffer was prepared from stock solutions of 0.04 mol dm^{-3} boric, orthophosphoric and acetic acids with the appropriate volumes of 0.2 mol dm^{-3} NaOH.

Apparatus

The voltammetric measurements were performed with an Amel 433-A computerized polarographic analyzer. A three-electrode system was employed with a hanging mercury dropping electrode (HMDE), an Ag/AgCl reference electrode and a Pt-auxiliary electrode. All potentials in the paper are expressed *vs*. Ag/AgCl. Adsorptive stripping differential pulse voltammetry (AdSDPV) was performed under the following conditions: scan speed 200 mV s^{-1}, pulse amplitude 100 mV, pulse width 20 ms, from 0 to –1.6 V. After recording the base-line, when a fresh mercury drop has been formed, voltammograms were recorded after a certain time of adsorptive accumulation at selected accumulation potential and selected pH, in a stirred solution (300 rpm). The accumulation period in a stirred solution was followed by a 10 s settling period to allow for quiescence of the solution and uniform distribution of the deposited substance on the surface of the mercury drop. When the differential pulse voltammetry (DPV) mode was used, the following parameters were applied: pulse repetition 100 ms, pulse amplitude 25 mV and pulse width 20 mV. The cyclic voltammograms (CV) were recorded at a scan rate ranging from 5 to 100 mV s^{-1}.

A Radiometer pH meter, PHM 220, with a combined pH electrode Radiometer GK2401B, was used and appropriate standard buffer solutions.

Solutions preparations

A stock solution (So) of 1×10^{-4} mol dm^{-3} of CEF was prepared by dissolving an accurate mass of CEF in redistilled water, and stored in freezer. More dilute solutions were prepared daily from the stock solution.

Procedures

A 15 mL aliquot of the corresponding supporting electrolyte solution (BR buffer only) or 13.5 mL aliquot of the corresponding supporting electrolyte solution (BR buffer) and 1.5 mL of S_0 was placed in the voltammetric cell, and deaerated for 10 min with high purity nitrogen and voltammograms were recorded.

Computational methods

The experimentally determined slope ($\Delta i_p/\Delta v$) and the computed molecular parameters of the examined cephalosporins were used to build QSPR models and to examine electrochemical adsorption and electroreduction mechanism of the cephalosporins.

Calculation of the pK_a values and a selection of the dominant molecules/ions species at the experimental pH 2.0–3.5 (Fig. 1), were performed for all the analyzed compounds using the Marvin 5.5.1.0 program.[21] The minimum energy conformations of the analyzed compounds were obtained by the CS Gaussian 98 program[22,23] using the B3LYP/3-21G basis set.[24-26]

The molecular refractivity (*MR*), the partition coefficient (*C*log *P*), the distribution coefficient (log *D* at pH 1.5, 2.5, and 4.0), the radius, the principal moment of inertia (*PMI*), the Connolly accessible area (*SAS*), the Connolly molecular area (*MS*), the molecular surface area (*MSA*), the polar surface area (*PSA*), the hydrogen bond donors (*HBD*) and the hydrogen bond acceptors (*HBA*) were computed for the optimized molecular models using the MarvinSketch 5.1.5.0[21] and the Chem3D Ultra 7.0.0[22] programs.

The CS Gaussian 98 program[23] using the B3LYP hybrid functional that included the 6-31G basis set (B3LYP/6-31G(d,p))[24-26] was applied for the computation of the molecular parameters, *i.e*., the energies of the highest occupied molecular orbital (*HOMO*) and the lowest unoccupied molecular orbital (LUMO), the chemical potential (μ), electronegativity (χ), hardness (η), global softness (S), electrophilicity index (ω) and the dipole moment.

The calculated molecular descriptors were used for the development of the QSPR model using partial least square (*PLS*) regression.[27]

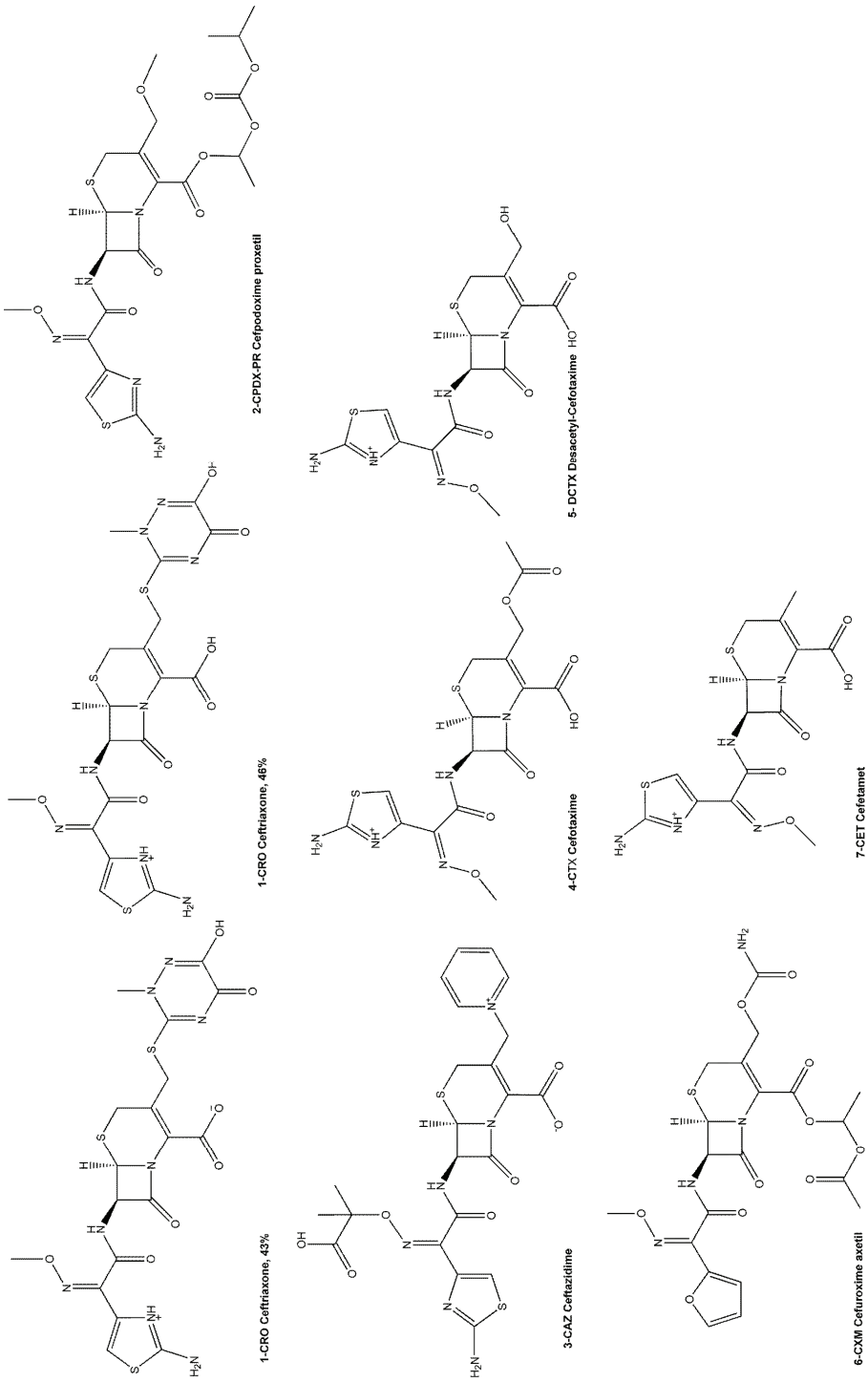


Fig. 1. Dominant forms of the cephalosporins at the analytical pH 2.0–3.5.

The QSPR study was realized using the soft independent modeling of class analogy SIMCA P+ 12.0 program,[28] for the PLS regression analysis. In QSPR modeling, a summary of the importance of every variable (X_k) for both **Y** and **X** matrices is described by the variable importance in the projection (VIP_k) parameter. The *X* variables with a *VIP* value larger than 1 are the most relevant for explaining the regression model, while the *X* variables with a *VIP* value below 1 have a smaller influence on the regression model.[27]

Validations of the *PLS* regression models were performed by the leave-one-out cross-validation (LOO-CV) method. The predictive power of the model is determined by the Q^2 value, which is the cross-validated version of R^2, and the root mean square error of prediction (*RMSEP*). The model was fitted to the data leaving one data point out. The elaborated PLS model then predicts the left-out data point. This procedure was repeated until all data points had been left out, which results in a number of parallel models. The difference between the observed and the predicted values in the left-out data point ($e_{(i)}$) were calculated for each model and used for the calculation of the prediction error (*RMSEP*).

In this setting, the predicted sum of squares (*PRESS*), *RMSEP* and $Q^2(Y)$ were defined as:

$$PRESS = \sum_{i=1}^{n} e_{(i)}^2 \quad (1)$$

$$RMSEP = \sqrt{(PRESS / n)} \quad (2)$$

$$Q^2 = 1 - (PRESS / SSTo) \quad (3)$$

where *SSTo* is the variation, sum of squares (total).

Models with $Q^2 \geq 0.5$ could be considered as having good predictive capabilities.[27]

The quality of the PLSR models was estimated using such parameters as *RMSEP*, Q^2, and the correlation coefficients observed *vs.* predicted (r^2 (Obs *vs.* Pred)).[27]

RESULTS AND DISCUSSION

The mechanism of the reduction of methoxyimino group involves two steps.[29–31] First, the nitrogen of the N–OCH_3 group is protonated (1), then the N–O bond is cleaved (2), yielding an imine that was then protonated (3) and reduced to the corresponding amine (4):

$$R_2C=NOCH_3 + H^+ \rightleftharpoons R_2C=NH^+OCH_3 \quad (1)$$

$$R_2C=NH^+OCH_3 + 2e + H^+ \longrightarrow R_2C=NH + CH_3OH \quad (2)$$

$$R_2C=NH + H^+ \rightleftharpoons R_2C=NH_2^+ \quad (3)$$

$$R_2C=NH_2^+ + 2e + 2H^+ \longrightarrow R_2CHNH_2 \quad (4)$$

The specificity of this reduction is evidenced by the appearance of only one well-defined voltammetric peak (I) in acid and neutral media, while in slightly alkaline medium, splitting of this peak occurs, and two peaks are obtained (II and III). Peak I represents the overall reduction of the oxime group that involves transfer of four electrons yielding an amine. As the rate of protonation of oxime decreases with increasing pH, the reduction peak decreases, and above certain pH value, the reduction occurs in two steps corresponding to oxime reduction to the imine, and imine reduction to amine, respectively. This separation into two two-

-electron processes is caused by differences in position and rate of establishment of acid–base equilibrium resulting in the protonation of the oxime and imino group,[32] *i.e.* their pK_a values.

In more alkaline solutions, at pH > 10, a new peak (IV) appeared at a more negative potential, $E \approx -1.5$ V (Fig. 2) due to the reduction of the unprotonated form. In addition, all the cephalosporins underwent a two-electron reduction of the unsaturated C=C bond of the dihydrothiazine ring. This reduction occurred in an acid medium at potentials very close to that of hydrogen ion reduction and therefore was not convenient for analytical investigations.

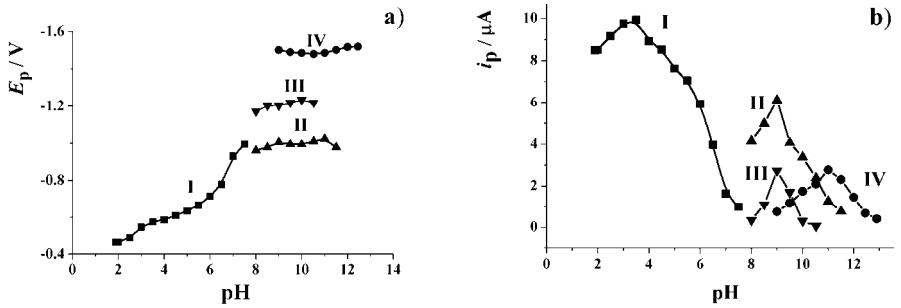


Fig. 2. Graphically presented pH influence on the DPV peak: a) potential and b) current of 1×10^{-5} mol dm^{-3} CPDX-PR in BR buffer.[18]

A plot of the obtained peak potentials as a function of pH (Fig. 2a) shows several linear segments with varying dE_p/dpH slopes, which indicates a varying number of protons transferred before the potential determining electron transfer. The slopes, dE_p/dpH, obtained by curve fitting were as follows: 0.058 V pH^{-1} at pH 2–6, 0.189 V pH^{-1} at pH 6–7.5 for peak I; 0.026 V pH^{-1} at pH 8–10 for peak II; 0.029 V pH^{-1} at pH 8–10 for peak III and ≈0 V pH^{-1} at pH > 9 for peak IV. The slope of 58 mV obtained for peak I at pH < 6 suggested the same number of electrons and protons involved in the electrode process, while the slope of 26–29 mV obtained for peaks II and III suggested fewer protons involved, (protons:electrons = 1:2). Decrease in the slope at pH > 8 indicates the pH region in which the pre-protonation becomes too slow relative to diffusion. The peak potential of peak IV is pH-independent, which is in accordance to theory in the case of the reduction of unprotonated species.

According to the peak current–pH dependence (Fig. 2b), it is evident that all peaks show a maxima at a certain pH value. The maximum of the i_p *vs.* pH curve indicates pronounced adsorption at the given pH. All the investigated cephalosporins showed DPV current maximum of peak I at a pH of around 3.

The mechanism of the reaction of methoxyiminocephalosporins at a mercury electrode[16–20] confirmed that the reduction of cephalosporins was mostly complicated by the effects of adsorption at the electrode surface. The conjugated

acids of these compounds were adsorbed at the electrode surface at potentials between 0.0 and 0.2 V, and desorbed between –1.0 and –1.2 V. Previous polarographic experiments proved that the reduced form was less strongly adsorbed than the oxidized one,[33] while the unprotonated form of cephalosporins, which was reduced at pH ≥ 10, showed no adsorption.[5,32,33] These experiments confirmed that the adsorption prevails in an acid medium.[5,32,33] The symmetrical shape of the voltammetric peaks of cefpodoxime, cefotaxime, desacetylcefotaxime and cefetamet, as well as the pronounced maxima of the curves presenting the current intensity *vs.* pH, indicated strong adsorption of these compounds at the mercury surface. The linear dependence of the voltammetric peak current on the scan rate, i_p *vs.* v, is also characteristic for adsorption-controlled processes (Fig. 3), and a higher slope was obtained when the adsorption was more pronounced.

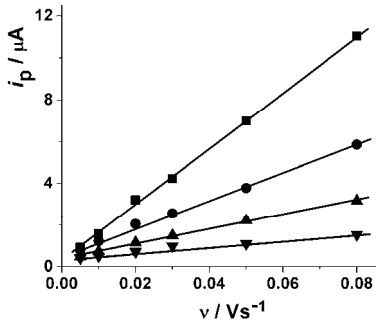


Fig. 3. Effect of the scan rate on the peak current for 1×10^{-5} mol dm^{-3} ceftriaxone (■), cefpodoxime proxetil (●), ceftazidime (▲) and cefuroxime axetil (▼) in BR buffer solutions.

Thus, the electrochemical adsorption of CRO, CPDX-PR, CAZ, CTX, DCTX, CXM and CET on the mercury electrode (Table I) was monitored by measuring the slopes ($\Delta i_p/\Delta v$).

TABLE I. Experimentally obtained slopes ($\Delta i_p/\Delta v$) for the investigated cephalosporins

Compound	pH	Slope ($\Delta i_p/\Delta v$) / μA V^{-1} s
Ceftriaxone (+/–, +)	3.0	134.07
Cefpodoxime proxetil	3.5	65.80[18]
Ceftazidime	3.0	35.56
Cefotaxime	2.8	17.40[16,19]
Desacetylcefotaxime	2.8	16.30[16]
Cefuroxime axetil	3.0	14.43
Cefetamet	2.0	13.70[17]

In addition, the regression equations for log $i_p = f(\log v)$ were calculated for all the investigated cephalosporins. Some of them are listed below:

– ceftriaxone (pH 3.0): log i_p = 0.898log v + 2.016 (r = 0.9988)
– cefpodoxime proxetil (pH 3.5): log i_p = 0.706log v + 1.510 (r = 0.9970)
– ceftazidime (pH 3.0): log i_p = 0.682log v + 1.232 (r = 0.9986)
– cefuroxime axetil (pH 2.8): log i_p = 0.561log v + 0.742 (r = 0.9961).

The corresponding slopes (higher than the theoretical value of 0.5 for a diffusion controlled process but lower than 1.0 for a process controlled only by adsorption) confirmed the influence of adsorption in acid solutions at mercury surface. According to the obtained slopes, the most pronounced adsorption was observed for ceftriaxone, and it decreased in the same order as already established with the $\Delta i_p/\Delta v$ values.

The differences observed between the investigated compounds are the consequence of specific adsorption and different orientation of these molecules at the mercury surface. It was established that the adsorption was more pronounced when the C7 substituent was more bulky. Since all these compounds possess a 2-aminothiazole ring at C7, it could be assumed that this ring plays a great role in adsorption on the mercury surface. The presence of the NH_3^+ group of the aminothiazole ring in an acid medium creates electrostatic forces with the mercury surface in the negative potential range and thus contributes to the adsorption. Finally, electron donor atoms, such as nitrogen and oxygen, in the side chain, increase the electron density of the thiazole ring and enhance the adsorption of methoxyimino cephalosporins.

Although the substituent in C2 and C3 position shows less contribution to the adsorption than the C7 substituent, the presence of different structures causes the differences in the adsorption characteristics. Therefore, the more complex structures of CRO, CPDX-PR, CAZ and CTX compared to those of DCTX, CXM and CET could generally explain the more strongly pronounced adsorption of the molecules in the first group.

Further, a quantum chemical and QSPR study of CRO, CPDX-PR, CAZ, CTX, DCTX, CXM and CET adsorption at the mercury electrode was performed to investigate the adsorption mechanism of the cephalosporins and to create a model for the prediction of the electrochemical adsorption for related compounds.

In the QSPR study, the experimentally determined slope ($\Delta i_p/\Delta v$), obtained using the CV technique on a mercury electrode, were used as dependent variables, while the computed molecular parameters (*MR*, log *D*, *SAS*, *MS*, *MSA*, *PSA*, *HBD*, *HBA*, *HOMO*, *LUMO*, chemical potential (μ), electronegativity (χ), hardness (η), global softness (S), electrophilicity index (ω) and dipole moment) of the examined compounds were used as independent variables. The density functional theory (DFT)-based reactivity descriptors (*HOMO*, *LUMO*, μ, χ, η, S and ω) were successfully used in many previous studies[34–43] for the interpretation of various reaction mechanisms.

Descriptors with the highest *VIP* and coefficient values were selected for building the QSPR model (Fig. 4A). The optimal combination of the most relevant descriptors (HBA, electron density on the nitrogen of the N–O bond ($ED_{(N)}$), PMI_Y, *HBA–HBD*, *PSA*, *MR*, *C*log *P*, diameter, and ovality for building

the QSPR models was chosen based on the R^2, Q^2 and *RMSEP* values of the obtained PLS models.

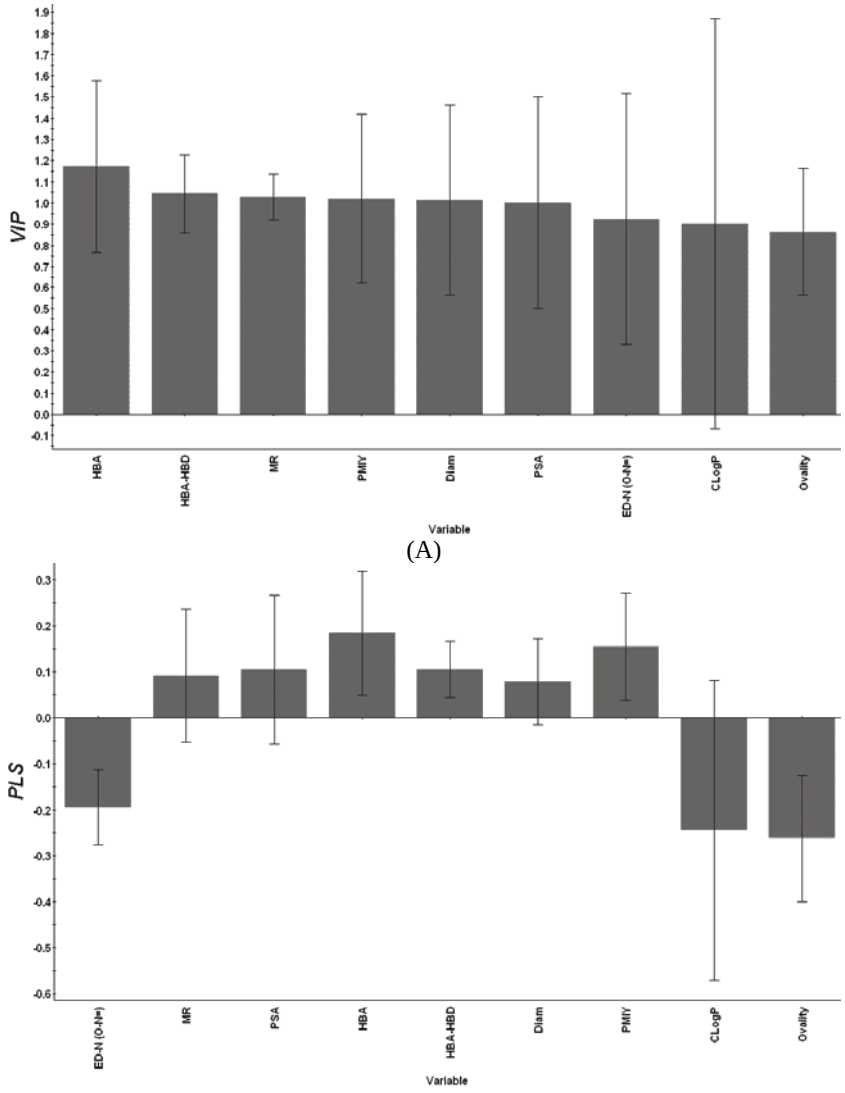


Fig. 4. A) *VIP* plot and B) coefficient plot of the developed QSPR model.

The coefficient plot (Fig. 4B) of the developed QSPR model indicated a negative correlation between the $ED_{(N)}$, *C*log *P* and ovality parameters and adsorption on the surface of a mercury electrode (Table II). Therefore, the cephalosporins with lower electron density on the nitrogen atom of the N–O bond

TABLE II. Molecular descriptors of electrochemical adsorption of the cephalosporins on a mercury electrode (slope, $\Delta i_p/\Delta v$), selected in the QSPR study. Observed and QSPR-predicted electrochemical adsorption on a mercury electrode (slope, $\Delta i_p/\Delta v$)

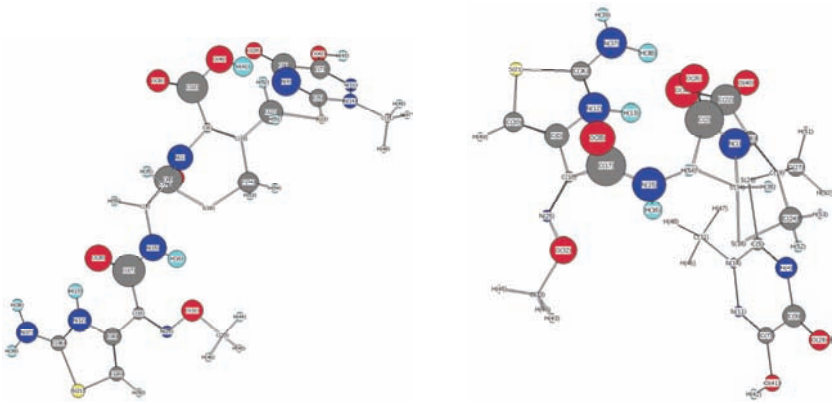
Compound	*HBA*	$ED_{(N)}$, B3LYP-(6-31(d,p))	PMI_Y	*HBA–HBD*	*PSA*	*MR*	*C*log *P*	Diameter	Ovality	Slope, $\Delta i_p/\Delta v$ μA V^{-1} s	Predicted slope, $\Delta i_p/\Delta v$ μA V^{-1}
Ceftriaxone (+/–, +)	16.76	5.36609	12996.80	11.52	213.72	145.60	–1.278550	18	1.55442	134.07	123.61
Cefpodoxime proxetil	13.62	5.37192	13530.30	10.24	180.97	131.36	0.800662	18	1.58462	65.80[18]	63.3864
Ceftazidime	14.23	5.38056	9143.53	9.46	192.83	143.88	0.426563	17	1.59622	35.56	57.8674
Cefotaxime	12.56	5.46491	8521.44	8.12	175.12	116.30	0.144262	15	1.62029	17.40[16,19]	14.6256
Desacetyl--cefotaxime	11.59	5.46569	6983.57	6.18	169.05	107.15	–0.773237	13	1.54477	16.30[16]	26.9867
Cefuroxime axetil	12.00	5.44607	10327.80	9.00	189.06	117.03	0.654200	15	1.67265	14.43	6.22526
Cefetamet	10.13	5.39467	6356.62	5.26	148.82	105.37	0.862763	12	1.54172	13.70[17]	4.55847
R^2	0.926									*RMSEP*	11.248
Q^2	0.725									r^2, Obs *vs.* Pred	0.962

lower lipophilicity should express high adsorption on a mercury electrode. The coefficient plot (Fig. 4B) also indicated a positive correlation between the *MR*, *PSA*, *HBA*, *HBA-HBD*, PMI_Y and diameter parameters and adsorption on the surface of a mercury electrode and hence, cephalosporins with higher *PSA*, *MR*, diameter and PMI_Y values and a higher number of hydrogen bond accepting groups should have a high adsorption on a mercury electrode.

The QSPR-model with the two significant components, $R^2 = 0.926$ and $Q^2 = 0.725$, with the lowest *RMSEP* (11.248) and the highest r^2 value (Obs *vs*. Pred; 0.962), was selected for further study (Table II). The obtained statistical parameters of the QSPR model indicated to a good prognostic capacity of the developed QSPR model.

Prediction of the slope ($\Delta i_p/\Delta v$) using the developed PLS-QSPR-model, could be applied to the other related cephalosporins.

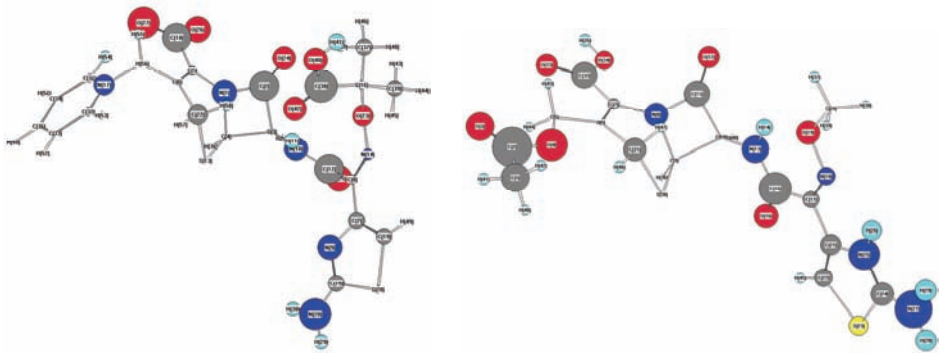
Molecular models of cephalosporins (Fig. 5) confirmed essential influence of electron densities and charge of nitrogen for their adsorption on the mercury electrode surface.



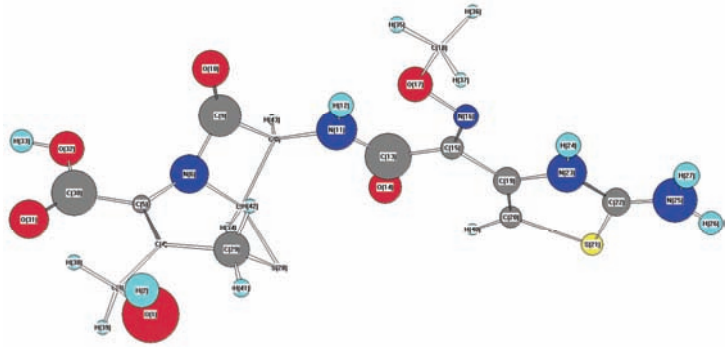
(A) (B)

(C)

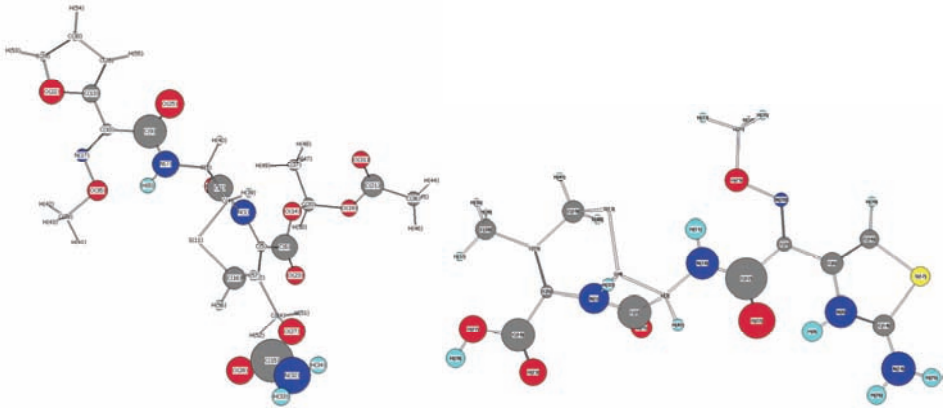
Fig. 5. Molecular models of: A) the ceftriaxone cation, B) the ceftriaxone zwitterion and C) cefpodoxime proxetil, based on the partial atomic charge values.



(D) (E)



(F)



(G) (H)

Fig. 5. (Continued) Molecular models of: D) ceftazidime, E) cefotaxime, F) desacetylcefotaxime, G) cefuroxime-axetil and H) cefetamet, based on the partial atomic charge values.

CONCLUSIONS

A previous voltammetric study of the electroreduction behavior and adsorption of methoxyimino cephalosporins (cefpodoxime proxetil, cefotaxime, desacetylcefotaxime and cefetamet) on a mercury electrode surface has been ext-

ended to structurally related cephalosporins (ceftriaxone, ceftazidime, and cefuroxime axetile). The density functional theory and QSPR studies were used to explain the adsorption mechanism at a mercury electrode surface and to predict the electrochemical adsorption at a mercury electrode of the related cephalosporins. The QSPR study selected the *HBA*, the electron density on the nitrogen of the N–O bond ($ED_{(N)}$), PMI_Y, *HBA–HBD*, *PSA*, *MR*, *C*log *P*, diameter and ovality parameters as the most significant molecular determinants for the electrochemical adsorption of cephalosporins on a mercury electrode.

The developed QSPR model indicated a negative correlation between the $ED_{(N)}$, *C* log *P*, and ovality parameters and adsorption, and a positive correlation between the *MR*, *PSA*, *HBA*, *HBA-HBD*, PMI_Y and diameter parameters and adsorption on the surface of a mercury electrode. Therefore, cephalosporins with lower electron density on the nitrogen atom of the N–O bond, lower lipophilicity, a higher principal moment of inertia and higher number of hydrogen bond accepting groups should express high adsorption on a mercury electrode. Prediction of the electrochemical adsorption using the developed QSPR model could be a very helpful tool for use in future cephalosporins studies. The presented study is first reported theoretical investigation of the electrochemical behaviors of cephalosporins.

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И З В О Д

ВОЛТАМЕТРИЈСКО И ТЕОРИЈСКО ПРОУЧАВАЊЕ ПОНАШАЊА ЦЕФАЛОСПОРИНА НА ЖИВИНОЈ ЕЛЕКТРОДИ

КАТАРИНА НИКОЛИЋ, МАРА М. АЛЕКСИЋ, ВЕРА КАПЕТАНОВИЋ и ДАНИЦА АГБАБА

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Применом цикличне (CV), диференцијално-пулсне (DPV) и адсорптивне "*stripping*" диференцијално-пулсне (AdSDPV) волтаметрије испитано је електрохемијско понашање и адсорпција цефподоксим-проксетила, цефотаксима, дезацетил-цефотаксима, цефетамета, цефтриаксона, цефтазидима и цефуроксим-аксетила на површини живине електроде. Студија квантитативних односа структуре и особина (QSPR) је коришћена за испитивање адсорпције седам цефалоспорина на живиној електроди. Применом теорије функционала густине DFT-B3LYP/6-31G(d,p) су израчунате енергије молекулских орбитала, парцијално наелектрисање и електронске густине испитиваних аналита, које су употребљене као молекулски параметри у QSPR студији. Помоћу изабраних DFT-параметара и QSPR модела је објашњен процес адсорпције испитиваних цефалоспорина. Резултати QSPR анализе показали су да већу адсорпцију на живи показују цефалоспорини са нижим наелектрисањем на сумпору тиазинског дела молекула, мањом електронском густином на атому азота N–O везе, већим бројем група које граде водоничне везе и већим главним моментом инерције.

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