Voltammetric Investigation of Inclusion Complexes of the Selected Succinimides with β-Cyclodextrin and (2-Hydroxypropyl)-β-Cyclodextrin

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Abstract

The inclusion complexes of the selected, potentially biologically active, succinimides with β-cyclodextrin (βCD) and (2-hydroxypropyl)-β-cyclodextrin (HPβCD) were prepared. The formation of the inclusion complexes of the investigated monophenyl and diphenyl succinimide derivatives was confirmed using attenuated total reflection (ATR) study. Their electrochemical behavior was examined by cyclic voltammetry (CV) and square wave voltammetry (SWV) in 0.05 M $NaHCO_3$ on a gold electrode. The stability constants for compound **1** were determined by cyclic voltammetry and calculated as $K_{βCD}$ = 350.87 M^{-1} and $K_{HPβCD}$ = 250.67 M^{-1}. The SWV measurements reveal well defined peak at potential E_p = ~ 60 mV and the higher currents at E_p for both inclusion complex of the succinimides compared to the free compounds. The impact of chlorine atom in the phenyl moiety of succinimide derivatives on the activity in electrooxidation reaction is presented. Among the studied succinimides, according to SWV measurements, the most active is the monophenyl succinimide derivative (compound **1**) in complex with βCD. The difference of peak current of compound **1** + βCD compared to compound **1** + HPβCD and free compound is 6.3 and 35.2 $μA\ cm^{-2}$, respectively.

Keywords: Diphenylsuccinimide; threephenylsuccinimide; ATR analysis; inclusion complexes; voltammetry.

1. Introduction

Succinimides are derivatives of pyrrolidine-2,5-dione which can be modified by the introduction of various alkyl and/or aryl groups on nitrogen or carbon atoms. Some of the modifications can be illustrated by the structures presented in Fig. 1. Succinimide ring represents a renowned pharmacophore in the drug discovery since its derivatives possess anticonvulsant activity.[1–3] Substituted succinimides show anticholinesterase and antioxidant potentials,[4] posses antimicrobial,[5,6] antitumor,[7] analgesic[8] and antispasmodic[9] activity. Apart from their biological importance, they also find application in liquid crystal displays (LCD)[10] and in the production of water soluble reactive copolymers and polymers.[11,12] They are appropriate scaffolds for organic synthesis,[13] and in some cases, they are used as effective and recyclable catalysts.[14] Evaluation of pharmacokinetic properties and in vitro cytotoxic activity of *N*-phenyl substituted succinimides showed that all compounds were predicted for good permeability and solubility, oral absorption rate and moderate volume of distribution even for blood brain permeation, followed by acceptable observed toxicity.[15,16] Furthermore, quantum mechanical and experimental studies of *N*-phenyl succinimides were performed and detailed interpretation of spectral data were reported.[17,18] For 1-aryl-3-methylsuccinimides, it is shown that interactions with hydrogen bond donor solvents and non-specific interactions with solvents play an important role in the solvatochromic behavior of these compounds. Moreover, MEP (Molecular electrostatic potential) data revealed regions of possible intermolecular interactions of *N*-phenyl succinimides and according to the analysis, oxygen atoms are suitable sites for electrophilic attack as well as for hydrogen bonding interactions with environment.
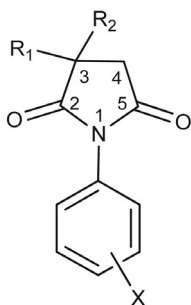
Figure 1. The structure of the investigated succinimides: (**1**) R_1=H, R_2=Ph, X=H; (**2**) R_1=Ph, R_2=Ph, X=H; (**3**) R_1=H, R_2=Ph, X=4-Cl; (**4**) R_1=Ph, R_2=Ph, X=4-Cl; (**5**) R_1=H, R_2=Ph, X=3-Cl; (**6**) R_1=Ph, R_2=Ph, X=3-Cl.

The synthesis and physico–chemical properties of the succinimides given in Fig. 1, classify as monophenyl succinimide derivatives (**1**, **3**, **5**) and 3,3-diphenyl succinimide derivatives (**2**, **4**, **6**) have been reported earlier.[19,20] Recently, the results obtained from cyclic and square wave voltammetry, on the gold electrode, combined with computational studies, revealed that these compounds are electrochemically active and oxidized by the mechanism involving the conversion of COCHPh or $-CH_2-$ group in free radical by the loss of one proton in one electron process.[21]

Succinimide electrochemistry has received modest attention so far. Previous electrochemical studies involve the electrochemical reduction of succinimides.[22,23] Voltammetric studies on Pt cathode in aqueous media reveal that the *N*-bromosuccinimide is a two-electron reduction process and succinimide anion is an intermediate in this reaction while succinimide and *N*-alkylated succinimide are the observed products.[22] The electrochemical reduction of succinimide examined on Pt cathode by cyclic voltammetry in aprotic media (acetonitrile) shows a single irreversible reduction peak. The product of these reaction is the succinimide anion in good yield and it was shown that this anion is stable in electrolysis medium.[23]

The aim of this work is to compare the already observed electrochemical activity of six selected succinimides with their activity in the form of inclusion complexes with cyclodextrines. Cyclodextrines (CD) are widely applied as non toxic encapsulated materials for a variety of guest molecules in order to improve their physico-chemical properties, such as aqueous solubility, physical chemical stability, and bioavailability of drug.[24–29] Due to the fact that the investigated succinimides are slightly soluble in water, their inclusion complexes are prepared in order to enhance their water solubility. Among the host molecules, β-cyclodextrins (β-cyclodextrin (βCD) and (2-hydroxypropyl)-β-cyclodextrin (HPβCD)), built up from seven glucopyranose units, are chosen since they are suitable for complexing molecules bearing phenyl groups such as investigated succinimides.

A number of nitrogen containing compounds have been electrochemicaly investigated, but to the best of our knowledge, the activity of succinimides (heterocyclic "pyrrolidine-2,5-dione" derivatives) in the form of inclusion complexes with cyclodextrines have not been subjected to the electrochemical studies. Since the impact of certain functional groups on the activity has been neglected in the literature, in this manuscript we provide the explanation about the influence of hydroxypropyl groups, chlorine atom or phenyl ring on the reactivity of investigated complexated compounds.

2. Experimental

2. 1. Material and Methods

All investigated compounds have been previously synthesized.[20] All used chemicals were p.a. grade (sodium hydrogen carbonate and sulphuric acid) obtained commercially from Sigma. 18 MΩ cm deionised water was obtained from a Milipore Waters Milli-Q purification unit.

ATR spectra of the investigated succinimides were collected on a Nicolet™ iS™ 10 FT-IR Spectrometer (Thermo Fisher SCIENTIFIC) with Smart iTR™ attenuated total reflectance sampling accessories.

2. 2. Preparation of Inclusion Complexes

The inclusion complexes of the investigated succinimides were prepared by mixing of the succinimides solution (0.15 mmol in 1 cm³ of methanol and then added to 100 cm³ of 0.05 M $NaHCO_3$) with cyclodextrines solution (0.15 mmol in 50 cm³ of 0.05 M $NaHCO_3$) to obtain 150 cm³ of 1:1 succinimide:cyclodextrine complex in 0.05 M $NaHCO_3$. The resulting mixture was shaken thoroughly and allowed to equilibrate at room temperature for 30 min before the addition to the electrochemical cell for electrochemical analysis.

2. 3. CV and SWV Measurements

Electrochemical studies were performed using three-electrode cell with an Au working electrode (surface area 7 mm²), an Au wire auxiliary electrode and a calomel reference electrode. The Au working electrode was polished with diamond paste, cleaned with a mixture of 18 MΩ water and sulfuric acid and further cleaned with 18 MΩ deionized water in an ultrasonic bath. Prior to each experiment working electrode was checked by cycling the potential scan between –0.40 and 1.1 V in basic solution (0.05 M $NaHCO_3$; pH = 8.4) at the scan rate of 50 mV s⁻¹ until the unchanged CV characteristics for Au electrode were obtained. After that the electrode was transfer to the electrochemical cell containing succinimides or complexated succinimides and CVs were performed.

For SWV measurements the accumulation of the succinimides and their inclusion complexes at the Au elec-

trode was carried out for 0.2 s at – 0.45 V. After that a square-wave voltammetric stripping initiated in the positive potential direction was performed. The following instrumental parameters were used to record the square-wave voltammograms: step size 5 mV, pulse size 75 mV, frequency 10 Hz, scan rate 50 mV s^{-1}. CV and SWV was carried out using PGZ 402 Volta Lab (Radiometer Analytical, Lyon, France).

3. Results and Discussion

In the first part of the work, inclusion complexes were prepared by dissolving corresponding succinimide and CD in 0.05 M NaHCO$_3$. The solutions were shaken for 15 min, and then evaporated under vacuum and dried. In order to study the formation of inclusion complexes, ATR analysis was performed. For illustration, Fig. 2A depicts ATR spectra of the relevant samples for the study of the inclusion complex of the compound **1** with HPβCD. The spectrum of HPβCD (b) displays characteristic bands at 3280 and 2926 cm^{-1} originating from O–H and C–H stretching vibrations, respectively and 1659 cm^{-1} as a result of H–O–H bending vibrations. The most prominent peaks at 1080 and 1021 cm^{-1} are ascribed to composition of the valence vibrations C–O–C, C–C–O and C–C–C. ATR spectra of **1** (c) show characteristic vibrations of carbonyl groups at 1775 and 1701 cm^{-1}. The spectrum of the physical mixture (d) represents the simple sum of the spectra of the succinimide molecule and HPβCD implying that this mixture do not provide inclusion of the guest molecule into the host molecule cavity. On the other hand, spectrum of inclusion complex (e) significantly differ from

all of the spectra (a-d). Bands at 1425 and 878 cm^{-1} of the inclusion complex appear from NaHCO$_3$, since the complexes are prepared in bicarbonate solution. The disappearance of the some corresponding peaks originating from succinimide ring and HPβCD is observed in this spectrum due to the restricted vibrations of the groups after the insertion of succinimde into HPβCD cavity. The decrease of the intensity and the shift from 1701 to 1685 cm^{-1} of the vibrations of the carbonyl group is observed in the spectrum of the inclusion complex as a result of the intermolecular hydrogen bonds between host and guest molecules. Furthermore, a broad band at 3280 cm^{-1} of HPβCD significantly decreased intensity and moved to 3458 cm^{-1} in complex clearly indicating the formation of inclusion complex. The same conclusions are derived for the inclusion complex of **1** with βCD (Fig. 2B).

In order to confirm the stoichiometry of the complex 1:1, CVs were recorded for different concentrations of sucinimide **1** while the HPβCD concentration remains unchanged, as it was proposed by [30]. From Fig. 3 it is clear that the oxidation peak corresponding to the succinimides is growing proportional to the amount added suggesting that the molar ratio is 1:1. In inset of Fig. 3 it is presented linearity of current density *vs.* concentration dependency recorded at 0.7 V with excellent regression coefficient R = 0.998.

For compound **1**, with the most pronounced electrochemical activity [21], the stability constants were determined by cyclic voltammetry and calculated by "electrochemical current method" for both inclusion complexes.[30,31] With the constant concentration of compound **1** and with different concentrations of both complexes the CVs were recorded as is presented in Fig. 4 and using
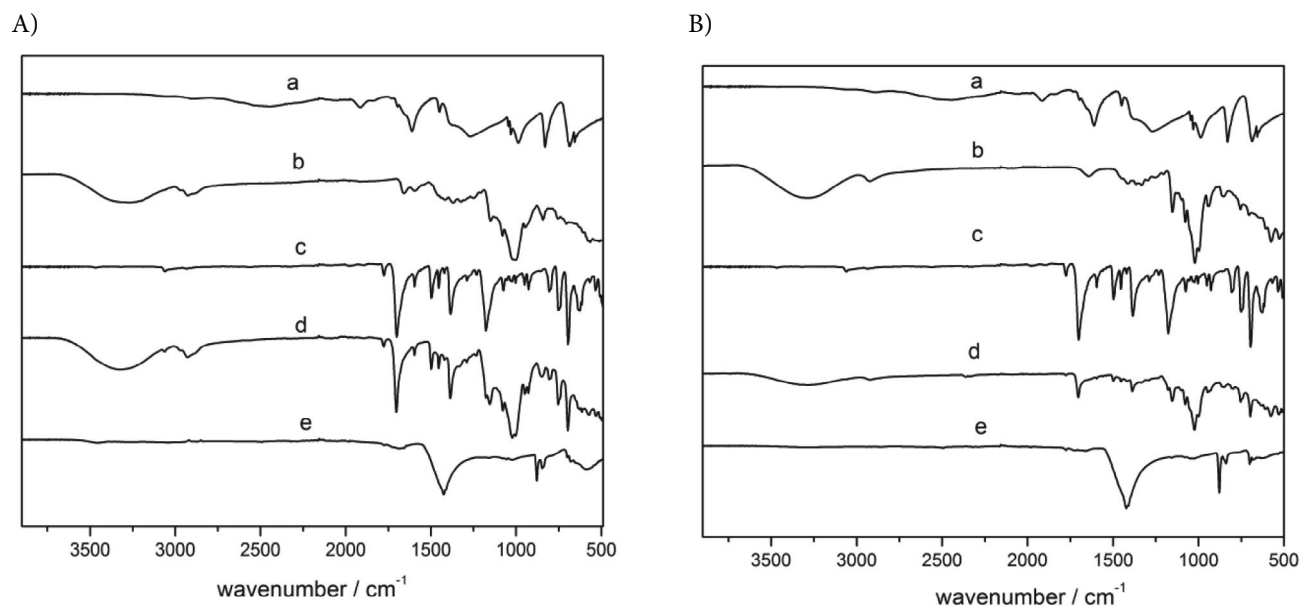
A)

B)

Figure 2. ATR spectra of the corresponding compounds in the formation of inclusion complex of **1** with HPβCD (A) and βCD (B): (a) NaHCO$_3$; (b) corresponding CD; (c) compound **1**; (d) physical mixture of the compound **1** and corresponding CD and (e) the inclusion complex of **1** with corresponding CD.
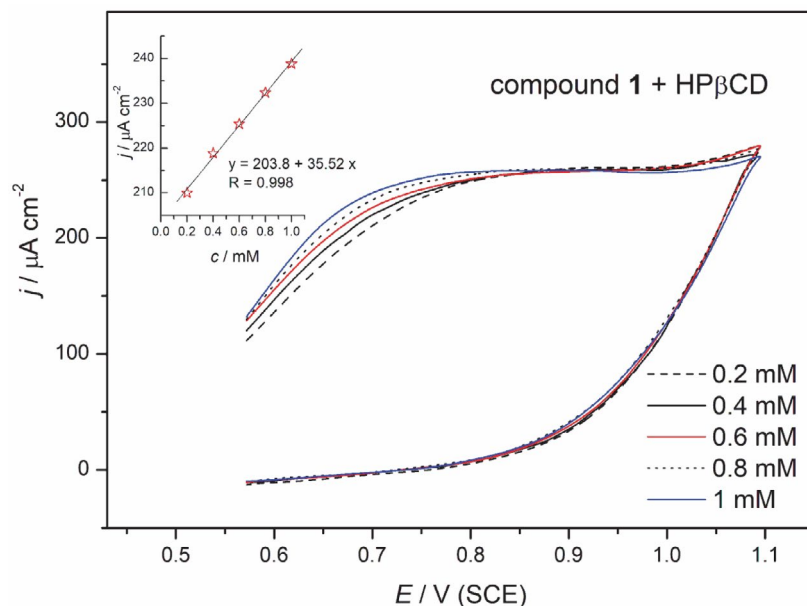
Figure 3. CVs of Au electrode in 0.05 M NaHCO₃ in the presence of compound **1** complexed with HPβCD (*c* = 1 mM). Concentrations of compound **1** are 0.2; 0.4; 0.6; 0.8 and 1 mM. *v* = 100 mV s⁻¹. Inset: current density *vs.* concentration dependency at 0.7 V.

equation from [30,31], the obtained stability constants are: $K_{\beta CD}$ = 350.87 M⁻¹ and $K_{HP\beta CD}$ = 250. 67 M⁻¹. Those calculated values are in accordance with the determined constants of cyclodextrin inclusion complexes for aromatic carbonyl compounds [31] and inclusion complexes with ascorbic acid, uric acid, acetaminophen and some xantine alkaloids.[30]

The electrochemical investigation consisted of voltammetric and kinetic studies of selected succinimides

performed by cyclic voltammetry is already published.[21] The cyclic voltammetry of the all examined inclusion complexes of succinimides show the same response as free compounds, with the higher current in the region of the oxide formation. In [21] is shown and pointed out that the anodic currents of investigated succinimides, appeared only in the region of the oxide formation at gold electrode, are more pronounced when SWV technique is applied. With the same succinimides inclusion complexes with
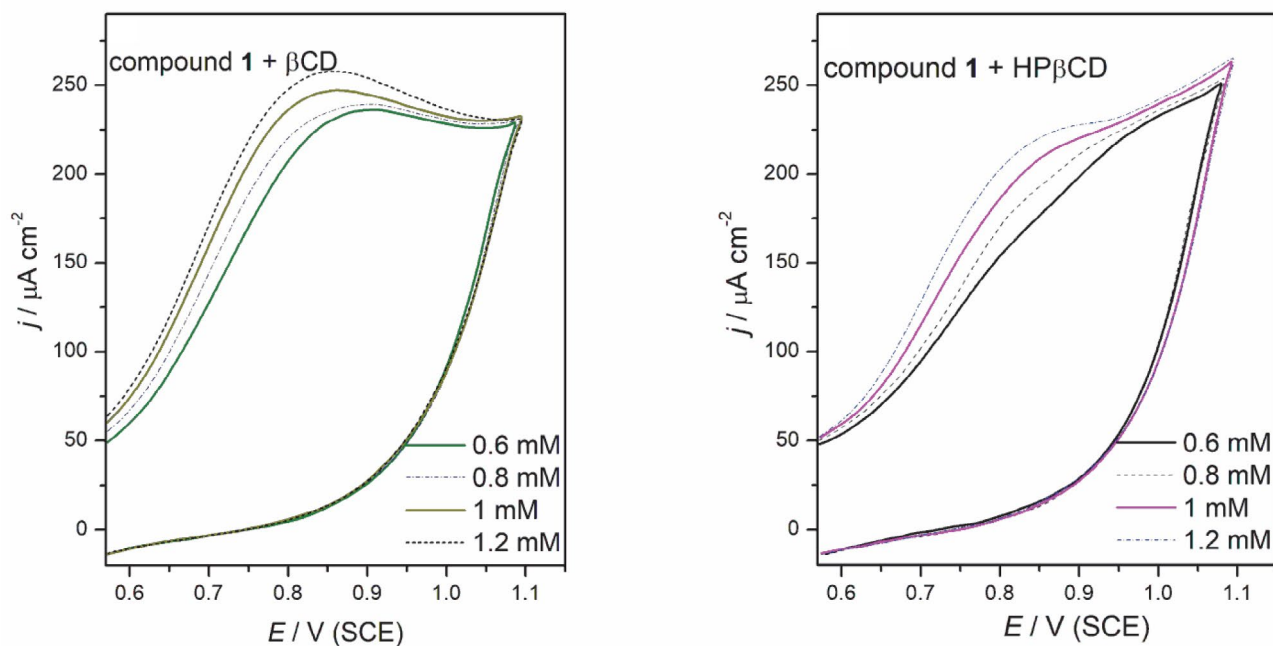

Figure 4. CVs of Au electrode in 0.05 M NaHCO₃ in the presence of compound **1** (*c* = 1 mM) complexated with βCD (A) and complexated with HPβCD (B). Concentrations of CDs are 0.6, 0.8, 1 and 1.2 mM. *v* = 100 mV s⁻¹.
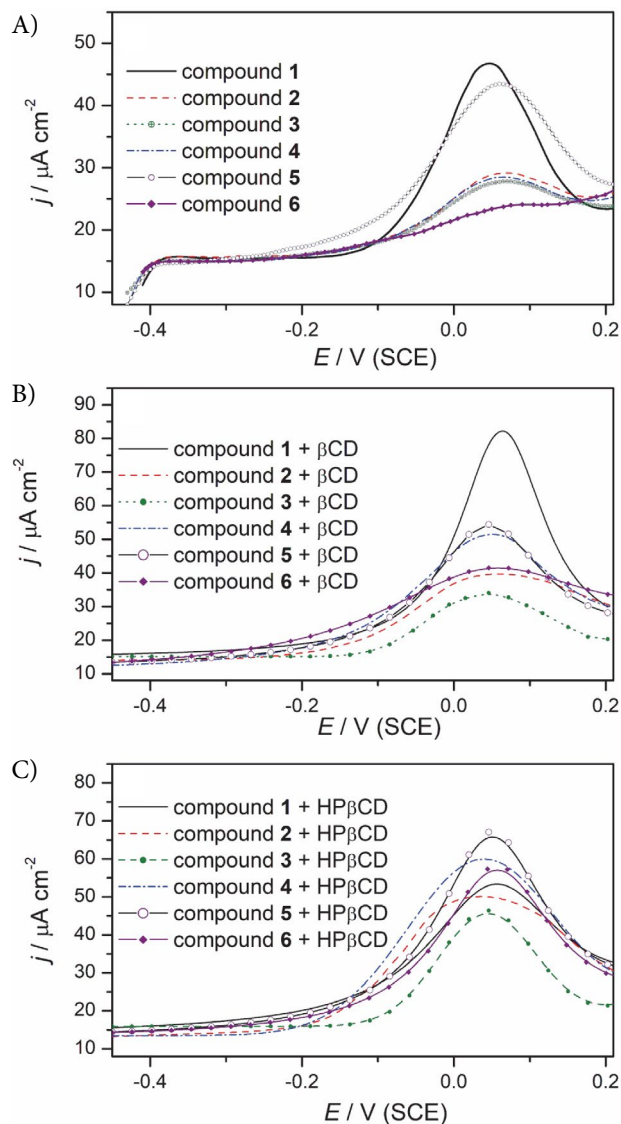
Figure 5. SWVs of investigated compounds (A); of the inclusion complexes of the investigated compounds with βCD (1:1) (B) and of the inclusion complexes of the investigated compounds with HPβCD (1:1) (C), obtained on Au electrode using 0.05 M NaHCO₃. Accumulation time: 0.2 s at E = − 0.45 V; step size 5 mV, pulse size 75 mV, frequency 10 Hz, scan rate 50 mV s⁻¹.

Figure 6. Bar plots of the peak current densities obtained by the oxidation of the free succinimides and their inclusion complexes with βCD (A) and HPβCD (B) derived from Fig. 5 and their difference (network grid bar).

β-cyclodextrin and (2-hydroxypropyl)-β-cyclodextrin are prepared and examined in this work by SWV.

Figure 5A shows the SWVs of the selected succinimides recorded at the Au electrode in 0.05 M NaHCO₃. Their 1:1 inclusion complexes with β-cyclodextrin are presented in Fig. 5B and their 1:1 inclusion complexes with (2-hydroxypropyl)-β-cyclodextrin are presented in Fig. 5C.

The SWV measurements reveal well defined peak at potential E_p = ~ 60 mV (Fig. 5) and the higher currents at E_p for both inclusion complex of the succinimides (Fig. 5B and 5C) comparing to succinimides presented in Fig. 5A. It indicates that the complexation of succinimides improves their electrooxidation ability.
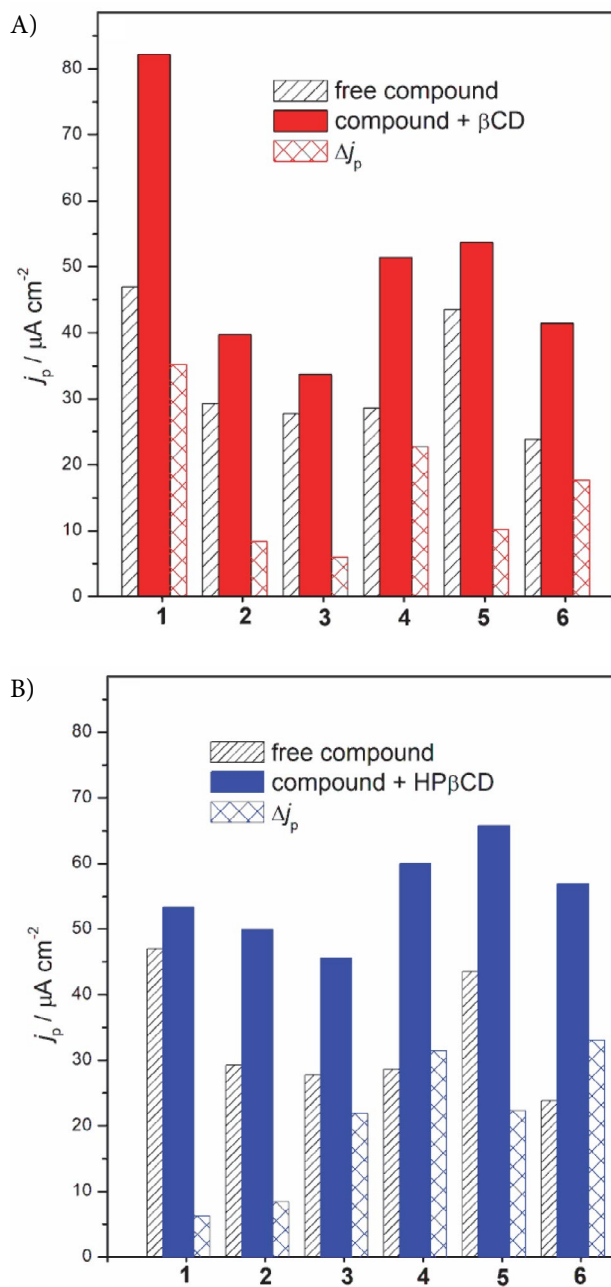
According to Fig. 5A higher currents of the SWV signal for the compounds **1** and **5** in the region of Ep are observed. The highest peak current is observed for compound **1** complexated with ßCD as is presented in Fig. 5B. Concerning the inclusion complexes with HPßCD, the highest peak current is observed for compound **5** according to Fig. 5C.

The difference between the peak current of free compound and inclusion complex (Dj_p), presented in Fig. 6 is a characteristic of improved electrooxidation ability. Re-

garding the inclusion complexes of succinimides with βCD, the highest Dj_p is noticed for compound **1**, while for the inclusion complexes of succinimides with HPβCD the highest Dj_p is observed for compound **6**. According to the computational analysis for the free compounds reported earlier,[21] the obtained improved electrooxidation ability of the investigated succinimides was ascribed to the influence of the structural parameters. Namely, the monophenyl succinimide derivatives (**1**, **3**, **5**) were characterized by the formation of radical and anion at position C3, while 3,3-diphenyl succinimide derivatives (**2**, **4**, **6**) can form only one species of radical and anion as consequences of deprotonation at position C4.[21]

The complexing pattern likely involves hydrophobic *N*-phenyl ring bound in the hydrophobic cavity by van der Waals interactions. The structure is additionally stabilized through the formation of hydrogen bonds between carbonyl groups of succinimide and hydroxyl groups outside the cavity (Fig. 7). Thusly, the part of the molecule responsible for electrochemical activity is preserved and available for oxidation process in the complex. The stabilization of the formed anion/radical through the hydrogen bonds and non specific interactions in CD:succinimide complex may be the reason for improved electrochemical activity with regard to corresponding succinimide. Proposed complexing mode is in accordance with complex formed between cyclodextrin and maleimides reported earlier.[32]
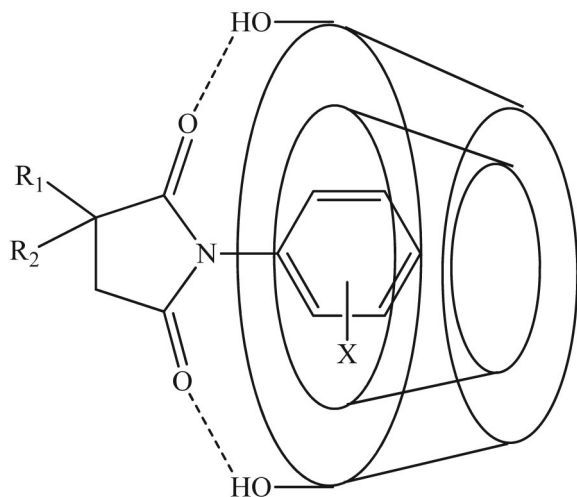

Figure 7. Schematic illustration of the succinimide:cyclodextrin complex.

For consideration of complex activity, three structural factors should be taken into account: structure of the employed CD, electronic nature of substituent at *N*-phenyl ring and the presence/absence of phenyl group at the position 3 of succinimide ring.

As can be seen from the data given in Fig. 6, except for compound **1**, where inclusion complex with βCD

showed higher electrochemical activity, inclusion complexes with HPβCD were more electrochemically active. The presence of hydroxypropyl groups additionally stabilize complex since this cyclodextrin provides more hydrophobic microenvironment convenient for *N*-phenyl ring and thus interactions in greater extent than in the case of βCD. The prominent activity of **1** with βCD is observed, while with HPβCD the highest activity is observed for **5**.

From Fig. 6, it can be observed that introduction of phenyl ring in the position 3 of the succinimide ring has a different impact on the electrochemical activity depending on the nature of the substitutent in *N*-phenyl ring. Namely, unsubstituted (**1**) and *meta*-Cl substituted (**5**) diphenyl-succinimide: CD complexes show higher activity than corresponding threephenylsuccinimides:CD complexes (**2** and **6**, respectively), while for **3** and **4**, the opposite trend is observed. For both CD, the lowest electrochemical activity is observed for compound **3** which could be attributed to the weak mesomeric effect of chlorine atom affecting accumulation of electron density and hindering the formation of radicals and anions during the electrooxidation of molecule. On the basis of the obtained electrochemical activity, it can be concluded that introduction of phenyl ring in **3**, noticeable increases the current of complexes of **4** indicating that phenyl group contributes in stabilization of this particular anion/radical forms. For other compounds (**1** and **5**), by insertion of phenyl ring (**2** and **6**) the lower electrochemical activity is observed due to destabilization of complex caused both by conformational changes of the molecule and weakening of the interactions between host and guest molecules. Different behavior of different positioned chlorine atoms is related to diverse electronic effect in *meta*- and *para*- positions. As mentioned before, chlorine in *para*- position (**3**, **4**) exerts weak mesomeric positive effect, while *meta*-chlorine (**5**, **6**) exhibit strong negative inductive effect causing withdrawal of electron density and stabilization of the obtained anion/radical.

The overall conclusion is that the effects of different groups and different cyclodextrins on the electrochemical activity of the complexes is complicated and involves synergetic interplay of each effect both through the electronic nature of the substituents and the strength of the interactions between guest and host molecules.

4. Conclusions

The complex formation between selected succinimides and β-cyclodextrin and (2-hydroxypropyl)-β-cyclodextrin was confirmed with ATR spectral analysis. The stability constants for compound **1** were determined by cyclic voltammetry and calculated as $K_{βCD} = 350.87$ M^{-1} and $K_{HPβCD} = 250.67$ M^{-1}. The SWV measurements reveal well defined peak at potential $E_p = \sim 60$ mV and the higher currents at E_p for both inclusion complex of the succinimides comparing to the free compounds. It indicates that the

complexation of succinimides improves their electrooxidation ability. The highest peak current in this study is observed for compound **1** complexated with ßCD. Inclusion complexes with HPβCD of succinimide derivatives (**2**, **3**, **4**, **5**, **6**) were more electrochemically active in regard to the inclusion complexes with βCD since the presence of hydroxypropyl groups additionally stabilize complex through interaction with the succinimide molecule. The complexing mode is suggested and involves entering of hydrophobic *N*-phenyl ring into the hydrophobic cavity of cyclodextrins which is additionally strengthened by hydrogen bonds between carbonyl groups of succinimide and hydroxyl groups outside the cavity. Different electrochemical activity of the complexes is caused by synergetic interplay of the substituent effects at *N*-phenyl ring, absence/presence of the phenyl group at the position 3 of succinimide ring and the structure of the employed CD on the stability of the formed radical/anion and its interactions with corresponding CD.

Acknowledgment

5. References

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Povzetek

Z ATR spektralno analizo smo potrdili tvorbo kompleksa med izbranimi sukcinimidi in β-ciklodekstrinom ter (2-hidroksipropil)-β-ciklodekstrinom. S cirkulično voltametrijo smo določili stabilnostne konstante za spojino **1** in izračunali vrednosti konstant $K_{βCD}$ in $K_{HPβCD}$ kot $K_{βCD}$ = 350.87 M^{-1} in $K_{HPβCD}$ = 250.67 M^{-1}. SWV meritve so pokazale dva dobro definirana vrhova pri potencialu E_p = ~ 60 mV in, v primerjavi s prostimi spojinami, višje tokove pri E_p za oba vključitvena kompleksa s sukcinimidom. To kaže, da vključevanje sukcinimidov v ciklodekstrine izboljša njihovo elektrooksidativno sposobnost. Najvišji tok pri vrhu smo v tej študiji opazili za spojino **1** kompleksirano z ßCD. Vključitveni kompleks derivatov (**2**, **3**, **4**, **5**, **6**) sukcinimida z HPβCD so bili bolj elektrokemijsko aktivni v primerjavi z vključitvenim kompleksom z βCD, ker prisotnost hidroksipropilnih skupin dodatno stabilizira kompleks preko interakcij z molekulo sukcinimida. Predlagali smo način tvorbe kompleksa, ki vključuje vstop hidrofobnih *N*-fenilnih obroče v hidrofobno votlino ciklodekstrina, kar je dodatno okrepljeno še z vodikovimi vezmi med karbonilnimi skupinami sukcinimida in hidroksilnimi skupinami izven votline. Različno elektrokemijsko aktivnost kompleksov povzroči sinergistična interakcija med substituenti na *N*-fenilnem obroču, odsotnost/prisotnost fenilnih skupin na položaju 3 v sukcinimidnem obroču in struktura uporabljenega CD s svojim vplivom na stabilnost nastalega radikala/aniona ter njegove interakcije z ustreznim CD.