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Electrochemical Detection of Host–Guest Interactions of Dicarboximide Pesticides with Cyclodextrins

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Abstract

Electrochemical methods sensitively detect the formation of host–guest complexes of cyclodextrins and three redox-active pesticides: vinclozoline (3-(3,5-dichlorophenyl)-5-methyl-5-vinyl-1,3-oxazolidine-2,4-dione), iprodione (3-(3,5-dichlorophenyl)-*N*-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide), and procymidone (3-(3,5-dichloro-phenyl)-1,5-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione). The protecting environment of the CD cavity allows a four-electron heterogeneous reaction leading to a preferential cleavage of the C–Cl bonds and conservation of the heterocycle structure for a further second electron transfer step. This interpretation is supported by numerical simulation of the voltammetric curves and by quantum-chemical calculations of the LUMO changes of vinclozoline. Electrochemical detection of these host–guest interactions is far superior to the spectral methods.

Introduction

The formation of host–guest complexes of cyclodextrins (CDs) with many types of organic, inorganic and organometallic compounds is detected mainly by various spectroscopic methods based on changes of spectra upon complexation [1]. Application of electrochemical techniques to detection of the inclusion complexes is much less common. The electrochemical measurements can prove the formation of CD complexes either from a decrease of the diffusion-limited currents resulting from a change of the diffusion coefficient or as a rather subtle shift of the redox potential [2–4]. The latter effect is a safe criterion for the reversible redox systems [5], whereas the irreversible electron transfer reactions may bring complications due to the coupling of electron transfer kinetics to the subsequent chemical steps or due to the influence of the adsorptive inhibition of CDs accumulated at the electrode surface [6, 7]. In recent years the possible alternation of the mechanism of electrode processes due to the protection of some electroactive groups by the cavity of CD has been reported. Among these reports is the stabilization of electrogenerated *p*-nitrophenolate anion [8], 10-methylphenothiazine [9], the influence of CD on the dimerization of methylalkylviologen radicals [10, 11] and the influence of CD on the redox process of quinoid compounds [12]. Several electroanalytical methods and sensors based on the selectivity differences of CDs were developed [13–16]. Our previous studies of pesticides and their incorporation into the molecular cavities were oriented towards the effects of CDs on the mechanism of electron transfer-initiated chemical decomposition of redox intermediates. We applied the electrochemical methods for elucidation of the host–guest complexation of CDs with difenzoquat (1,2-dimethyl-3,5-diphenyl-pyrazolium cation) [17], atrazine (2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine) [18] and vinclozoline [19]. The reduction product of difenzoquat due to the cleavage of a substituent is a neutral compound and forms much stronger complex with CD than the original reactant. Reduction of uncomplexed atrazine proceeds only in the protonized form (e.g. at low pH), whereas the hydrogen bonding in its inclusion complex renders the electron transfer possible even in neutral solutions. Vinclozoline inside the CD cavity experiences the protection of its oxazolidine-dione moiety and preferentially cleaves the C–Cl bonds on the benzene ring.

In this communication, we will show that not only the β-CD, but all three CDs influence to a different degree the redox mechanism of all three dicarboximide-type pesticides: vinclozoline, procymidone and iprodione (Scheme 1). This electrochemical effect is observed in spite of the fact that the spectroscopic and preparative methods do not confirm the formation of host–guest complexes with all three cyclodextrins. Interactions of pesticides with CDs yield very pronounced signals on the electrochemical current-potential curves despite of the absence of any detectable spectroscopic changes. The potentiality of cyclic voltammetry and similar electrochemical methods for elucidation of the host–guest interactions of intermediates and final products is explored in this paper.

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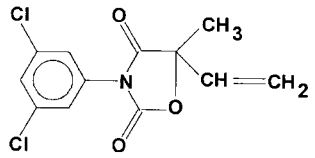
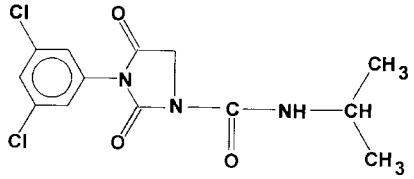
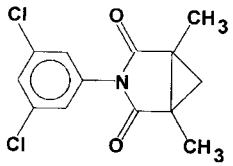
vinclozoline **1**



iprodione **2**



procymidone **3**



Scheme 1.

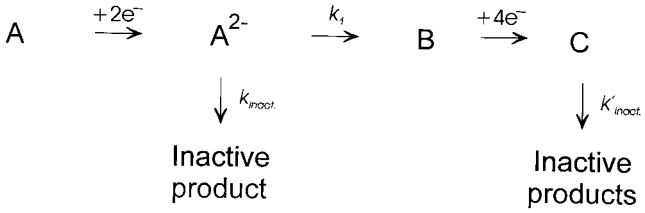
Experimental

The electrochemical measurements were made using a laboratory-built electrochemical system consisting of a fast rise-time potentiostat interfaced to a personal computer via the IEEE-interface card, PcLab model 748 (AdvanTech Co., USA). The voltage source was a 12-bit D/A card, PcLab model 818. A three-electrode electrochemical cell was used. Ag | AgCl | 1 M LiCl reference electrode was separated from the test solution by a salt bridge. The redox potential of ferrocene in DMSO against this reference electrode was 0.505 V. Two types of working electrode were used: a valve-operated static mercury electrode SMDE2 (Laboratorní Přístroje, Prague) and a dropping mercury electrode (DME) with a mechanical drop-time regulator. Platinum net was used as the auxiliary electrode. Oxygen was removed from the solution by a stream of argon. A protecting argon layer blanketed the solution surface during the entire experiment. Vinclozoline, iprodione and procymidone with a purity certificate of pesticide standards were purchased in a crystalline form from Ehrenstorfer, Augsburg (Germany) and were used for electrochemical measurements. Dimethylsulfoxide (DMSO) and tetrabutylammonium hexafluorophosphate of "Analysis Grade" were obtained from Fluka. Supporting electrolyte was dried before use.

Results and discussion

Electrochemistry of uncomplexed vinclozoline, iprodione and procymidone in DMSO

More or less similar electrochemical features characterize three pesticides investigated in this study. All compounds in a free uncomplexed form are reduced at negative potentials in two redox steps. This common behavior is given by the presence of identical redox active groups in their structures. Compounds **1–3** can accept electrons leading to a subsequent cleavage of C–N bonds and elimination of the heterocycle or to the C–Cl bond cleavage linked to the reduction of C=O groups. Further redox steps, at still negative potentials, involve the reduction of fragments resulting from a primary redox process. The first reduction of all three



Scheme 2.

pesticides is observed at the polarographic half-wave potential around –2.0 V, which corresponds to the voltammetric peak potential between –2.1 and –2.3 V. The free forms are reduced by two electrons in the first step. Product identification and the complex redox mechanism was described by us recently [20] and here we refrain from details. Figure 1 shows a representative example of the reduction of these compounds, here demonstrated on a cyclic voltammogram of iprodione. One can conclude that in DMSO the reduction potentials, number of redox steps, the ratio of reduction current peaks and the oxidation peaks of products are the same as in another non-aqueous solvent used in our previous study. The main reduction products in the first redox step are dichloro- and chloro-anilines [20]. The second reduction is more complicated and is specific to each of the compounds **1–3**. Voltammetric curves shown in Figure 1 were recorded with different potentials of the sweep reversal and demonstrate, which of the two reduction waves yields the products responsible for anodic peaks at more positive potentials.

Two-step reduction, coupled with chemical reactions following the first and the second electron transfer, can be described by several mechanisms. We treated the problem of a most likely reaction sequence by means of the numerical simulations of cyclic voltammograms [21] of vinclozoline for scan rates from 0.5 to 100 V s^{-1}. On the basis of known final products, identified in our recent communication [20], the following reaction scheme was chosen:

It represents the best fit between the experiment and simulation over the range of scan rates studied. Symbols A, A^{2-}, B and C in Scheme 2 denote the parent pesticide, an unstable intermediate, the heterocycle fragment and its intermediate, respectively. Inactive products are chloro- and dichloro-anilines in the first step and the reduced heterocyclic derivatives in the second step [20]. This mechanism

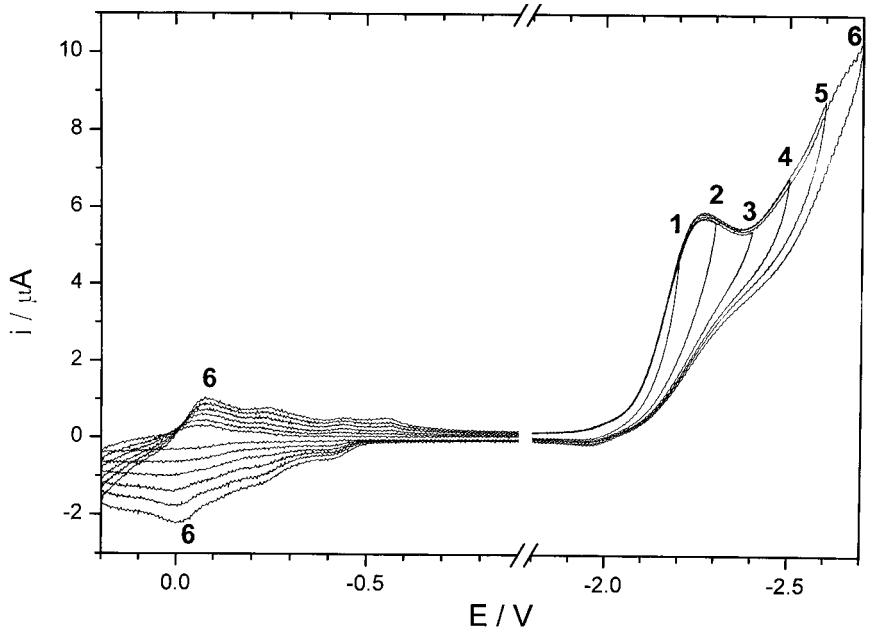


Figure 1. Cyclic voltammetry of 1×10^{-3} M iprodione in 0.1 M $TBAPF_6$ in DMSO at scan rate 0.5 V s^{-1}. Scan reversal potentials were –2.2 V (curve 1), –2.3 V (curve 2), –2.4 V (curve 3), –2.5 V (curve 4), –2.6 V (curve 5) and –2.7 V (curve 6).

is also consistent with impedance studies of the reduction kinetics of vinclozoline that yield the ratio of the first two kinetic steps [22]. The most probable values of the rate parameters were found as follows: $k_1 = 660\ s^{-1}$, $k_{inact.} = 1100\ s^{-1}$ and $k'_{inact.} = 1000\ s^{-1}$ with standard heterogeneous rate constant of the first step $k_{e1} = 2.1 \times 10^{-4}$ cm s^{-1}. These values will be used also in more complicated reaction schemes below.

Effect of CDs on reduction mechanism of vinclozoline, iprodione and procymidone

Figure 2 shows a similar experiment as in Figure 1 performed at various switching potentials in the presence of β-CD. The result is striking: both reduction peaks at –2.28 and –2.56 V increase in height in comparison with the peak height of free compounds (see Figure 1). Furthermore, the anodic peaks near –0.05 V are more developed and a new very sharp peak gradually intensifies near –0.5 V. It has adsorption character and its asymmetric shape points to an irreversible reduction of the reaction intermediate. Since the peak is observed only in the presence of both non-electroactive cyclodextrin and electroactive pesticide, it is most likely due to the reduction of a redox intermediate-CD complex. An unexpected feature of the voltammetric experiment is the fact that a sharp and intensive peak is observed also in the presence of two other cyclodextrins, see Figures 3–5, even though α-CD and γ-CD did not yield any indication of the host–guest complexation by another techniques. This supports a hypothesis that final reduction products may interact more strongly with CDs than the parent molecule in its oxidized state. An alternative hypothesis is that the primary electron transfer is strongly modified by CDs in the sense that more then two electrons may be involved in the first reduction step.

Effect of CDs on the two-step reduction

The stepwise addition of cyclodextrins increases the first voltammetric peak to a limiting value before or at equimolar concentrations of CD and pesticide, depending on the type of cyclodextrin, see Figures 3–5. The second, more negative reduction peak is increased to still higher values with further addition of CD, until it reaches the limiting current at approximately ten-fold excess of CD over the pesticide [19]. The effect of CD on the reduction mechanism of the pesticides is clearly demonstrated experimentally beyond any doubt. However, the interpretation of higher reduction currents in terms of the complex formation is not straightforward. Again the numerical simulation of the voltammograms was applied for elucidation of the most probable reaction sequence, though the large number of reactions and parameters associated with the most probable mechanism makes this task difficult. First, we considered an increase of the rates of subsequent chemical reactions as being responsible for the higher currents observed experimentally. However, such effect should change also the potential of current maximum, which was not observed. Another explanation could be based on the complexation equilibrium. It is well known that the formation of the complex of an electroactive compound renders its reduction thermodynamically more difficult. Therefore, the reduction potential (represented here as a peak potential) should shift towards the values that are more negative. Such a reaction scheme seems inapplicable in this case, because the experimental peak potentials are invariant to CD additions, unless both A and A^{2-} species form the complexes with similar values of the formation constants. Then the potential shifts could be mutually compensated. Recalling from our previous work that free forms yield chloroanilines (denoted as "inactive product"), while the cyclodextrin-complexed forms undergo dechlorin-

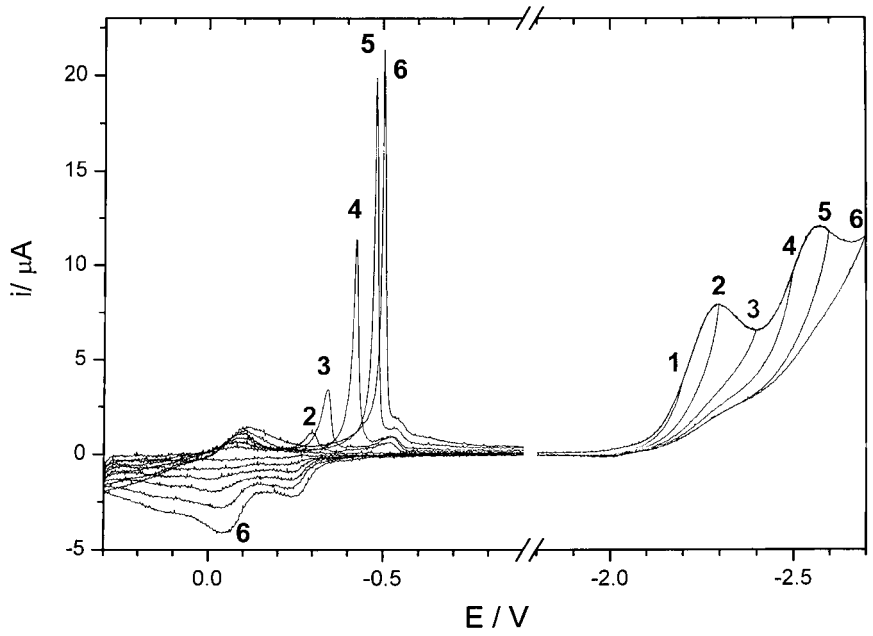


Figure 2. Cyclic voltammetry of 1×10^{-3} M iprodione and 11×10^{-3} M β-cyclodextrin in 0.1 M $TBAPF_6$ in DMSO at scan rate 0.5 V s^{-1}. Scan reversal potentials were –2.2 V (curve 1), –2.3 V (curve 2), –2.4 V (curve 3), –2.5 V (curve 4), –2.6 V (curve 5) and –2.7 V (curve 6).

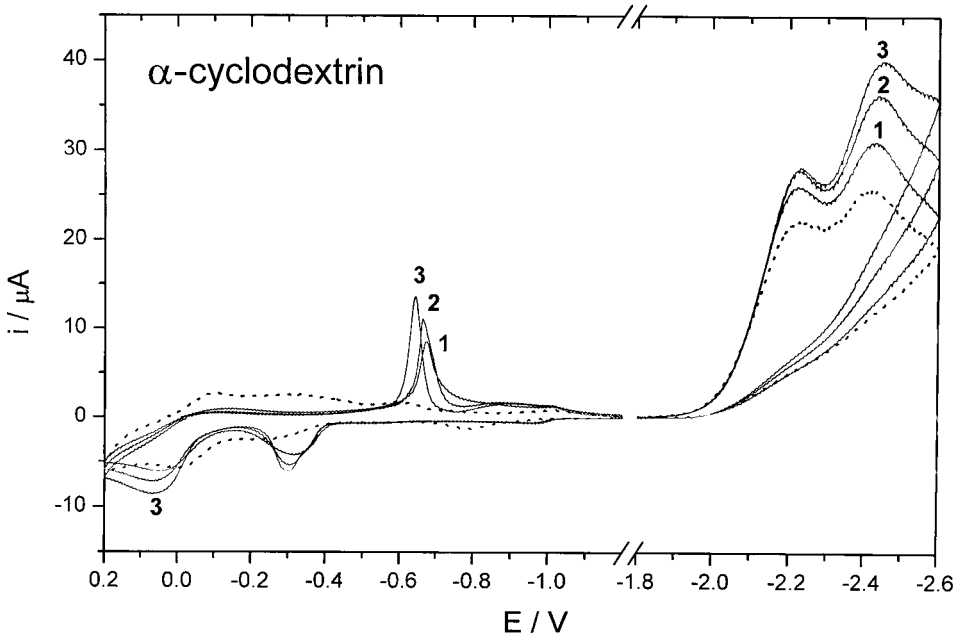
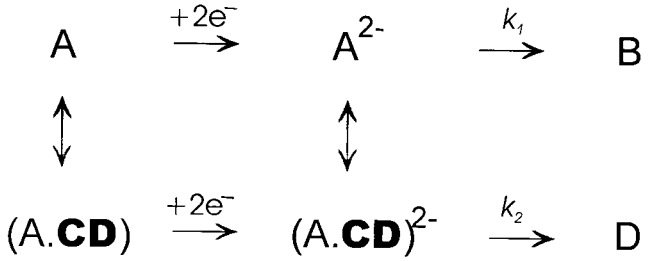
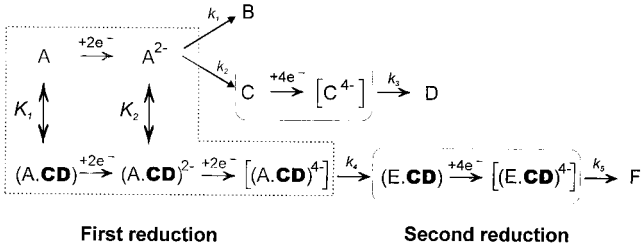


Figure 3. Cyclic voltammetry of 3×10^{-3} M vinclozoline in the absence (···) and presence (—) of 1×10^{-3} M (curve 1), 2×10^{-3} M (curve 2) and 3×10^{-3} M (curve 3) α-cyclodextrin in 0.1 M $TBAPF_6$ in DMSO at scan rate 0.5 V s^{-1}.

ation (yielding C), we started the digital simulation of the voltammetric curves using the following reaction scheme:



Scheme 3.



Scheme 4.

where k_1 and k_2 are the rate constants of the coupled chemical reactions. Incorporation of two chemical reactions

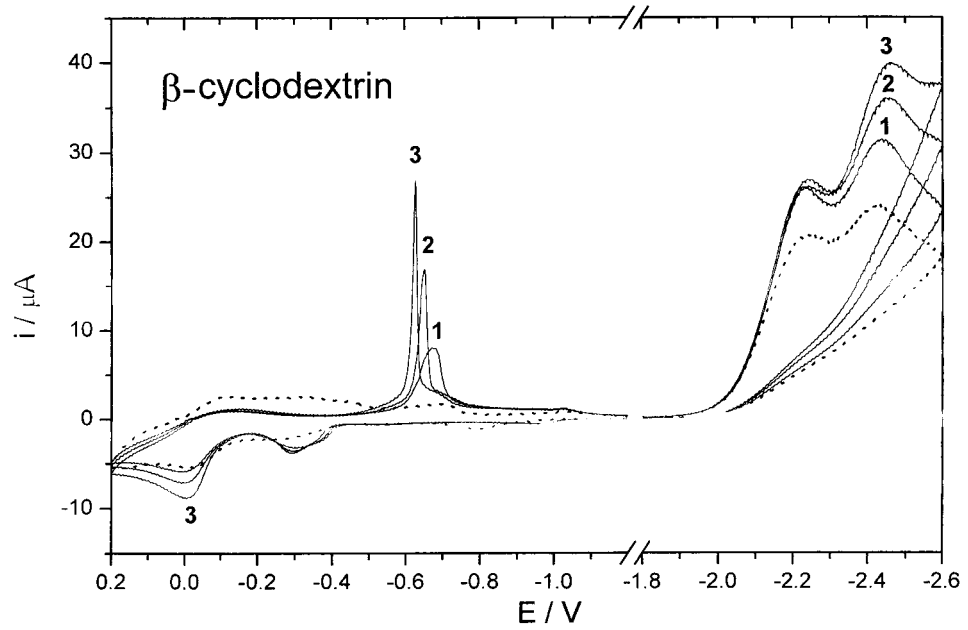


Figure 4. Cyclic voltammetry of 3×10^{-3} M vinclozoline in the absence (···) and presence (—) of 1×10^{-3} M (curve 1), 2×10^{-3} M (curve 2) and 3×10^{-3} M (curve 3) β-cyclodextrin in 0.1 M $TBAPF_6$ in DMSO at scan rate 0.5 V s^{-1}.

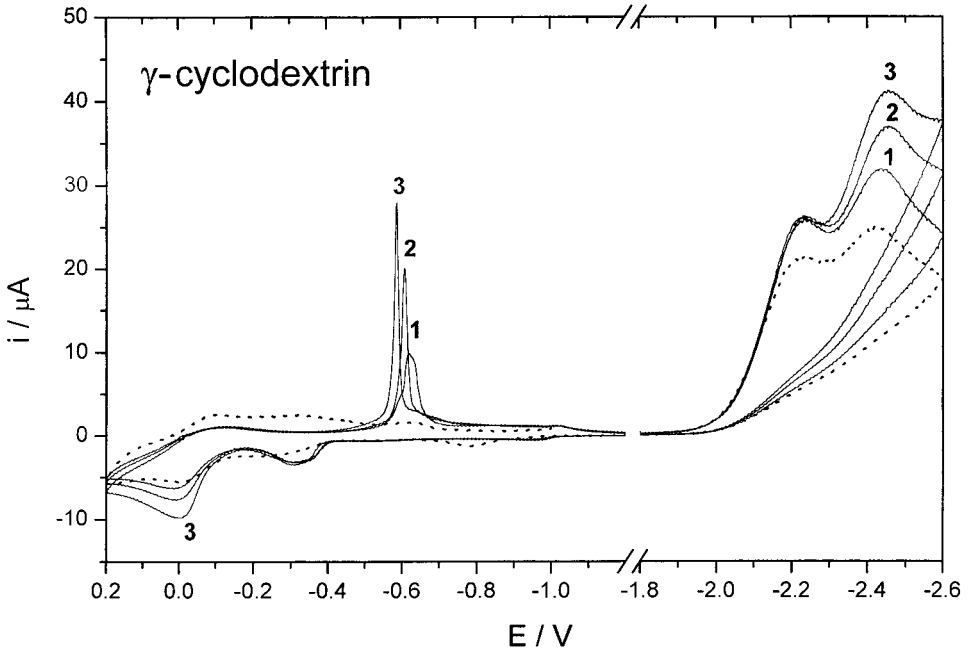


Figure 5. Cyclic voltammetry of 3×10^{-3} M vinclozoline in the absence (···) and presence (—) of 1×10^{-3} M (curve 1), 2×10^{-3} M (curve 2) and 3×10^{-3} M (curve 3) γ-cyclodextrin in 0.1 M $TBAPF_6$ in DMSO at scan rate 0.5 V s^{-1}.

$A^{2-} \rightarrow$ B and $(A.CD)^{2-} \rightarrow$ C is based on experimental findings. Cyclic voltammetry yields chemically irreversible peaks even at the highest scan rates available and therefore the primary redox product is unstable. Simulations according to Scheme 3 have to take into account that in the presence of CDs the preparative electrolysis yields [B] $\ll$ [C], which implies either that $k_1 \ll k_2$ or that the shift of complexation equilibrium is strongly in favor of (A.CD) and $(A.CD)^{2-}$. Both electron transfer reactions in Scheme 3 are slow heterogeneous processes, which follows from the observed irreversibility even at high rates of the voltage scan. Simulations performed with a wide range of parameters never gave a satisfactory fit of Scheme 3 with the experimental voltammograms. Major problem was the circumstance that a follow-up chemical reaction, like the $(A.CD)^{2-} \rightarrow$ C process can in some cases increase the first peak current, but at the same time shifts the peak potential to less negative values. This property follows from the theory [23]. It was seen in case of the cobaltocenium reduction, where the reduction product forms the complex with β-CD [24], but not in the present case. For these reasons we consider the Scheme 3 inapplicable.

An alternative interpretation of the increase of voltammetric peaks with CD concentration is based on the mech-

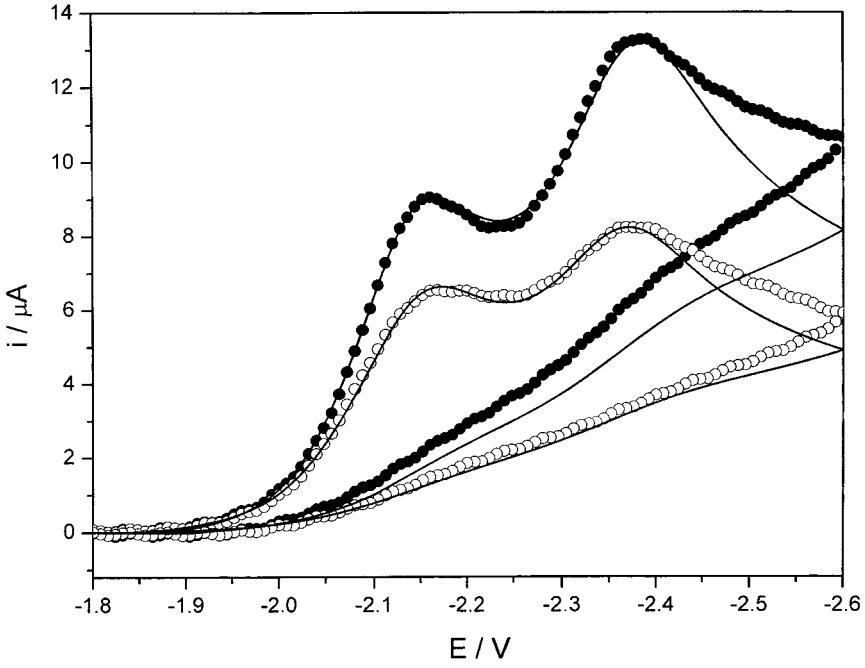


Figure 6. Cyclic voltammogram of 1×10^{-3} M vinclozoline in 0.1 M $TBAPF_6$ in DMSO at scan rate 0.5 V s^{-1} in the absence (○) and presence (●) of 1×10^{-3} M β-cyclodextrin. Solid lines represent the best fit of the experimental data using the redox mechanism of Scheme 4. The values of fitting parameters are summarized in the text.

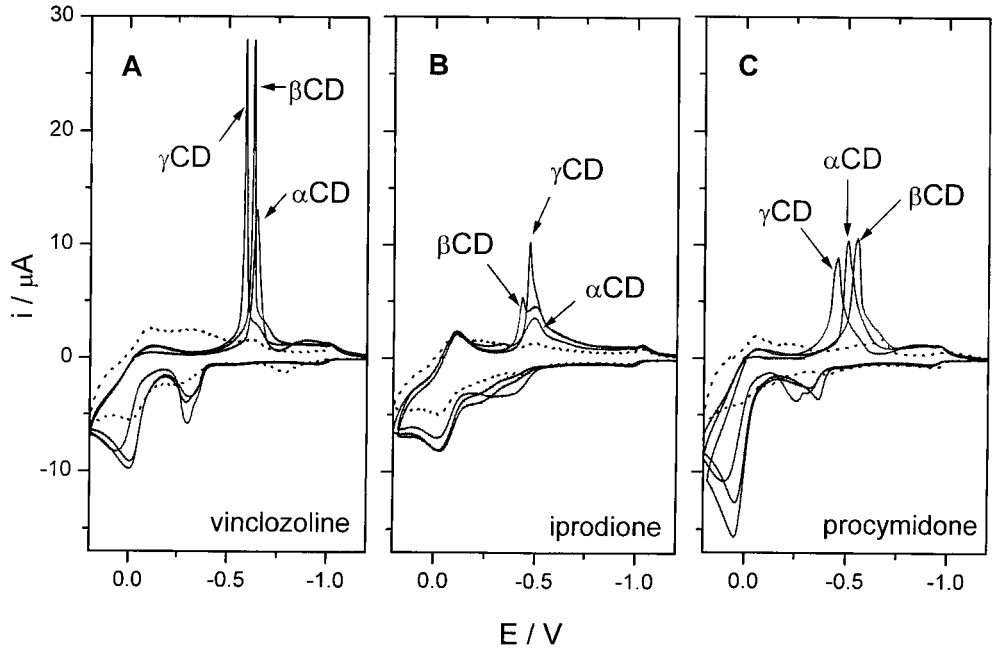


Figure 7. Anodic part of the cyclic voltammogram of 3×10^{-3} M vinclozoline (A), iprodione (B), and procymidone (C) in 0.1 M $TBAPF_6$ in DMSO at scan rate 0.5 V s^{-1} in the absence (···) and presence (—) of 3×10^{-3} M α-, β- and γ-cyclodextrin. Potential scan started at –1.8 V, continued in negative direction until it was switched back at –2.6 V. The sweep direction was switched again at +0.2 V.

anism, in which the protecting influence of CDs changes the total number of electrons transferred in the first reduction step. Since the pesticide-CD complex has a considerably lower diffusion coefficient, somewhat larger current of the first voltammetric peak could correspond to the transfer of four electrons, instead of two. Multi-electron transfers under the protecting environment of biological systems are frequent and represent an essential mechanism in achieving reactions requiring a high degree of activation. Enzyme nitrogenase, reducing di-nitrogen, may serve as an example. Hence, we developed a mechanism, in which the four-electron reduction takes place in the first reduction wave, prior to the first follow-up decomposition.

Products D and F in Scheme 4 are those yielding the anodic peaks in Figures 1 and 2, whereas B represents the redox inactive di- and mono-chloroanilines. This reaction scheme was designed for the best fit of the two reduction peaks with consideration of the number of final products

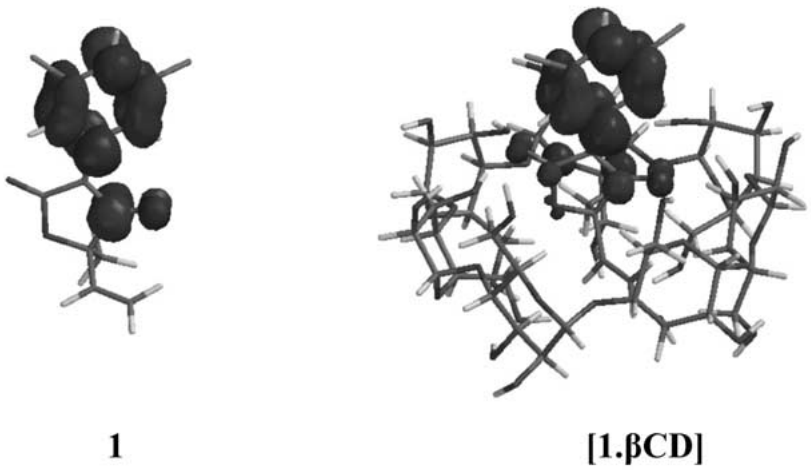


Figure 8. Molecular model of vinclozoline inclusion into the cavity of β-cyclodextrin. LUMO of free vinclozoline (left) and vinclozoline in the β-CD cavity (right) obtained by an AM1 semi-empirical quantum chemical method.

actually found. Due to a large number of reactions and their parameters, it is technically impossible to include also the simulation of the anodic processes of the final products. The comparison of representative experimental and simulated voltammograms is given in Figure 6. Parameters yielding such a fit were subject to requirements that they must provide sufficiently good fit also for higher scan rates and other ratios of pesticide and CD.

We can conclude that the enhancement of the first and the second reduction currents, observed in the presence of CDs, can be accounted for by a change of the ECE mechanism.[1] The protecting influence of CD cavity changes the number of transferred electrons in the first E-step from two to four. This is reflected in a preferential dechlorination process: the cleavage of two C–Cl bonds on the aromatic moiety of studied pesticides. The interpretation in terms of the Scheme 4 is supported by our previous report of the product distribution in the presence of β-CD.

Effect of CDs on voltammetry of products

The influence of CDs on the reduction currents is very similar for all three pesticides. The quantitative differences between α-, β-, and γ-CD on the redox degradation of dicarboximide pesticides are more pronounced on the redox processes of their reduction intermediates/products. Especially the height of a sharp peak appearing between –0.5 and –0.7 V depends on the type of CD added. Figures 3–5 show the evolution of the height and the peak position for the case of vinclozoline in the presence of all three CDs. Similar comparison for all three pesticides at a constant concentration of CDs is shown in Figure 7. In all cases one can see a pair of anodic/cathodic voltammetric peaks, over which the sharp and intensive peak is superimposed. Regardless of the different structures of heterorings the redox pattern of resulting products is the same and hence the same electroactive groups have to be involved in the anodic/cathodic processes seen at –0.5 V. We mentioned earlier that two Cl atoms on the aromatic rings are preferentially cleaved in the presence of CDs. This suggests that two C=O groups on the heterocycles, the only probable redox active sites common to all three pesticides after the C–Cl bond cleavage, are involved in the electron exchange at –0.5 V. Fragments bearing these C=O functions are different for each of the three pesticides and hence the adsorption and inclusion properties giving rise to the sharp peak mentioned earlier are characteristic for each compound. An increased release of Cl^- anions in the presence of CDs (compared to free pesticides) can be deduced from a higher anodic wave near 0 V. This is in agreement with the entire suggested reaction scheme.

Molecular models of included pesticides

Preliminary calculations concerning the possible mode of pesticide inclusion into the CD cavity were obtained using a density-functional theory (DFT) method [25]. The conformation, where the molecule of pesticide approaches the β-CD cavity with its dichlorophenyl end is clearly less stable than the one depicted in Figure 8. Electronic structure calculations for vinclozoline and its inclusion complex with β-CD were done by a semi-empirical Austin model (AM1) [26] method within the Titan (Spartan) program package [27]. Substantial change of LUMO (e^- accepting orbital) upon the inclusion of pesticide into the CD cavity is consistent with our interpretation of the change of reduction mechanism in the first reduction step yielding different subsequent decomposition reactions.

Conclusions

Presented work deals with rather week complexes of dicarboximide pesticides with CDs. Any attempt to determine their stability constants in DMSO by spectroscopic methods like ^{1}H-NMR and UV-Vis more or less failed. The complex formation was confirmed by UV-VIS method only in case of the vinclozoline-βCD complex. This paper demonstrates the power of electrochemical methods, which reveal the complex formation on the basis of kinetic effects. All three pesticides yield two reduction waves. First irreversible

two-electron process changes upon addition of CD to a four-electron reduction. A striking feature of the first reduction process is also the fact that the peak potentials do not change with increasing concentration of the host compounds. This indicates that the stability constants of the reactant and the reduction product in the complex with CD have very similar values.

Acknowledgements

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