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Synthesis and electrochemical study of nitrophenyl derivatives of β-cyclodextrin

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ABSTRACT: A series of nitrophenyl β-cyclodextrin derivatives: *mono*[6-deoxy-6-(4-nitrobenzamido)]-*per-O*-methyl-β-cyclodextrin (R_1—Ph—NO_2), *mono*[6-deoxy-6-(3-nitrobenzamido)]-*per-O*-methyl-β-cyclodextrin (R_2—Ph—NO_2) and *heptakis*[6-deoxy-6-(4-nitrobenzamido)-2,3-di-*O*-methyl]-β-cyclodextrin [R_3—(Ph—NO_2)$_7$] were synthesized. Purity and composition of the obtained substances were checked. Electroreduction of nitro groups of the new synthesized compounds was investigated on mercury electrode using cyclic voltammetry and chronocoulometry. The parameters of the reduction processes of —NO_2 groups of the investigated compounds were found not to be comparable to the reduction of nitrobenzene under the same experimental conditions. Moreover, the electroreduction of nitro groups in these nitrophenyl derivatives was dependent on pH, the type of the studied compound, and slightly on the solvent composition. All the reactants were strongly adsorbed on mercury electrode. In the case of R_3—(Ph—NO_2)$_7$, its seven nitro groups were reduced practically at the same potential, and no radical anion formation was observed. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: nitrophenyl-β-cyclodextrin; mercury electrode; cyclic voltammetry; inhibition of electrode reactions

INTRODUCTION

Nitroaromatic compounds infiltrate into biosphere from industry processes, drugs and pesticides. These substances can be introduced into living organisms as drugs or toxins. It is known that the biological, therapeutic and toxic properties of the nitro compounds can be connected with electrochemical characteristics of the nitro group reduction and the formation of a nitro radical anion which exhibits cytotoxicity towards cellular systems.[1,2]

Therefore, the electrochemical properties of nitroaromatic compounds were extensively studied and the data obtained are reviewed herein.[3–22] Electrochemical reduction of nitrobenzene ($PhNO_2$) on the mercury electrode in aqueous solutions in the absence of inhibitors involves a single four-electron irreversible process:

$$PhNO_2 + 4e^- + 4H^+ \rightarrow PhNHOH + H_2O \qquad (1)$$

The reduction wave of the $PhNO_2$/PhNHOH process was shifted to more negative potential upon increasing concentration of the reactant.[8] This observation was ascribed to the adsorption of nitrobenzene on the mercury electrode.[16]

In acidic media, the phenylhydroxylamine is further reduced to aniline according to the two-electron step mechanism. The general scheme for reduction of nitroaromatic compounds on the mercury electrode was published previously.[3,14,15] Later, the electroreduction mechanism of aromatic nitro compounds in aqueous solutions was also investigated in details.[19–27]

In alkaline solutions, in the presence of inhibitors[3,5,10,11,22] and in aprotic solvents,[3,28,29] the four-electron electrode process described by Eqn (1) splits into two steps. In the first step, the NO_2 group was reversibly reduced to radical anion according to the one-electron process. At more negative potential, the irreversible three-electron reduction of radical anion to phenylhydroxylamine was observed. The potential of the latter process was dependent on pH, solvent composition and inhibitor concentration. The radical anion was very stable in aprotic media but it was also detected in alkaline aqueous solutions during EPR measurements[10,30,31] and using electrochemical methods.[10,14]

In water–organic mixtures, nitrobenzene was reduced in two well-separated steps according to one- and three-electron reduction mechanism.[3,23,32,33] Such behaviour is caused by adsorption of the organic component of the mixture on a mercury electrode.

The electrochemical characteristics of 2-, 3- and 4-nitroanisoles in the water–ethanol and water–DMF

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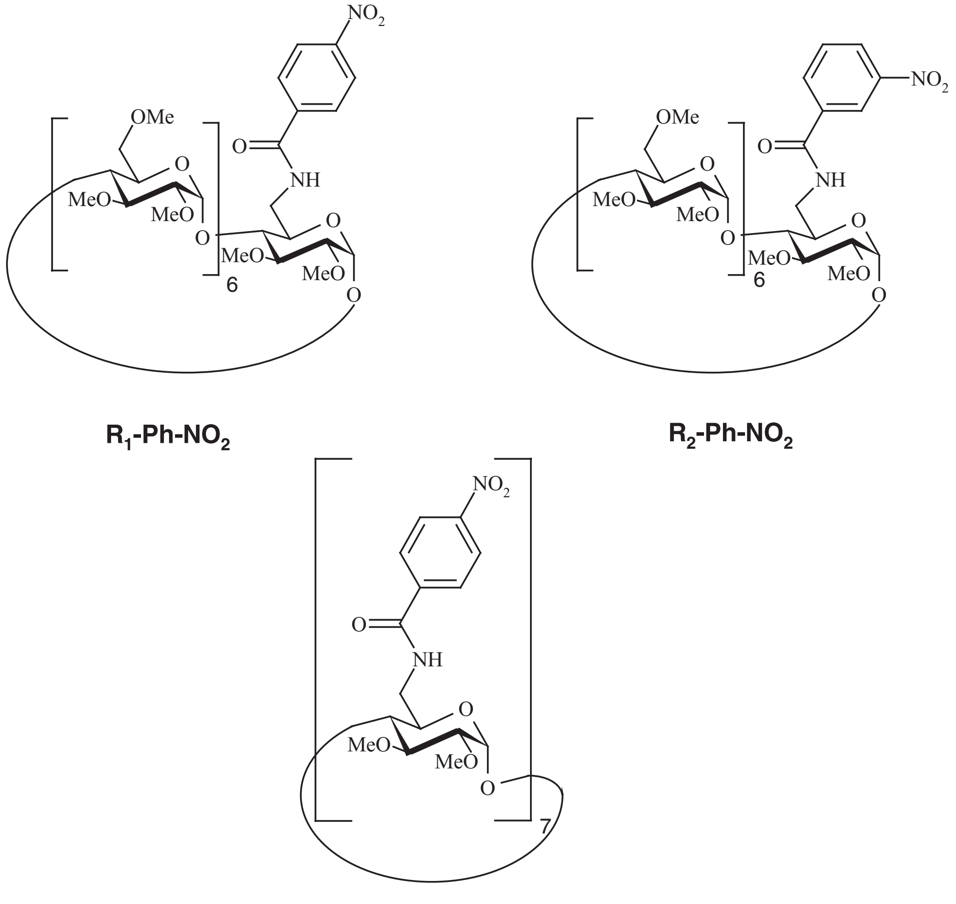
mixtures in the pH range of 2–12 was described previously.[34] In protic media, the 3-nitroanisole isomer exhibited an irreversible well-defined voltammetric peak over the entire pH range when investigated on the mercury electrode in a reaction involving four electrons to give the hydroxylamine derivative. However, in the case of 4-nitroanisole, the successive formation of nitro radical anion was observed at pH 10.5. In water–DMF solutions at $\text{pH} \geq 10.5$, the formation of radical anions was also observed for all the investigated nitroanisoles. The radical anions were more stable in DMF solution than in its mixtures with water.

During recent years, nitroimidazole derivatives have often been studied because of their therapeutic properties. The investigations have mainly been focused on the electroreduction of their nitro groups.[35–37] For the 4- nitroimidazole derivative in aqueous solution, only one voltammetric peak related to the four-electron electroreduction of its nitro groups, NO_2/NHOH, is observed in the pH range of 2–12.[36] The formation of radical anions was observed in mixed and nonaqueous media.

In the present work, we prepare and consider new nitrophenyl derivatives of β-cyclodextrin: *mono*[6-deoxy-6-(4-nitrobenzamido)]-*per-O*-methyl-β-cyclodextrin (R_1—Ph—NO_2), *mono*[6-deoxy-6-(3-nitrobenzamido)]-*per-O*-methyl-β-cyclodextrin (R_2—Ph—NO_2), and *heptakis*[6-deoxy-6-(4-nitrobenzamido)-2,3-di-*O*-methyl]-β-cyclodextrin [R_3—(Ph—NO_2)$_7$] (Fig. 1). The new compounds are electrochemically reduced on the mercury electrode in aqueous and water–MeCN (acetonitrile) solutions at different pHs. It follows from the works of Coleman[38] that in water–organic solvent mixtures the solubility of cyclodextrins increases. Water–acetonitrile mixtures were chosen because there are a lot of electrochemical studies carried out in such mixtures. The possible adsorption on mercury electrode has also been studied.

The purpose of our studies has been to establish the effects of large, non-electroactive moieties in molecules containing nitro groups on their electrochemical properties. It follows from our studies that, for such compounds, there are important differences in their electrochemical behaviour in comparison to nitrobenzene. We have also found that the formation of radical anion in case of our compounds is hindered in alkaline solutions and water–organic mixtures as well.



R_1-Ph-NO_2

R_2-Ph-NO_2

R_3-(Ph-NO_2)$_7$

Figure 1. Structural formulas of *mono*[6-deoxy-6-(4-nitrobenzamido)]-*per-O*-methyl-β-cyclodextrin (R_1–Ph–NO_2), *mono*[6-deoxy-6-(3-nitrobenzamido)]-*per-O*-methyl-β-cyclodextrin (R_2–Ph–NO_2) and *heptakis*[6-deoxy-6-(4-nitrobenzamido)-2,3-di-*O*-methyl]-β-cyclodextrin [R_3–(Ph–NO_2)$_7$]

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RESULTS AND DISCUSSION

Influence of the solution pH on reduction of NO_2 group in nitrophenyl derivatives of β-cyclodextrin: R_1—Ph—NO_2, R_2—Ph—NO_2 and R_3—(Ph—NO_2)7 on mercury electrode

The cyclic voltammetric curves were recorded over the potential range from 0.1 to -1.8 V in the Britton–Robinson buffered solutions at pHs 7 and 11 with 0.5 M $NaClO_4$ as a background electrolyte and 10^{-4} M or 5×10^{-5} M as a reactant concentration. In neutral solutions containing R_1—Ph—NO_2 or R_2—Ph—NO_2, in the first polarization cycle two cathodic peaks were observed, one at the potential of about -0.64 V, and the other at about -1.4 V. Selected CV curves are presented in Figs. 2 and 3. Electrochemical behaviour of the reactants with one NO_2 group is similar to that of nitrobenzene under similar conditions.[3]

The cathodic peak (I) observed for R_1—Ph—NO_2 and R_2—Ph—NO_2 corresponds to the four-electron irreversible reduction of the NO_2 group to hydroxylamine derivative, comparable to the reaction (1).

The shape of the first cathodic peaks (I) and non-linear dependence of I_{pc}(I) on $v^{1/2}$ for all the investigated compounds suggested that the reactants were adsorbed on the mercury electrode.

The cathodic peak (III) appearing at the potential of about -1.4 V is probably connected with the adsorption – desorption process of the reactants because at the same potential the adsorption – desorption peaks of the permethylated cyclodextrins were observed on the double layer capacitance curves.[39] Its desorption may accelerate the electroreduction of nitroderivatives from the bulk. This electroreduction was inhibited by the adsorbed reactant.

The anodic peak observed at the potential close to zero in the reverse scan is related to the oxidation of R—Ph—NHOH to R—Ph—NO obtained in the process (1) in the cathodic step as in the case of nitrobenzene. In the second and subsequent cycles, a new cathodic peak (II) appearing at the potential close to zero was observed. The cathodic and anodic peaks (II) are connected with the following reaction:

$$\mathrm{R-Ph-NHOH \leftrightarrow R-Ph-NO + 2H^+ + 2e^-} \quad (2)$$

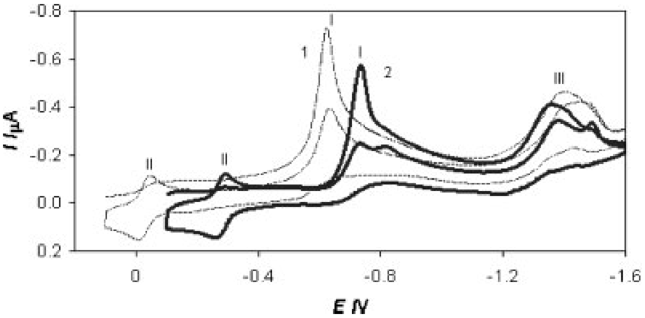

Figure 2. Cyclic voltammograms (two first runs) of R_1–Ph–NO_2 in aqueous solution with pH 7 (curve 1) and pH 11 (curve 2). The solution contained 0.5 M $NaClO_4$, Britton–Robinson buffer and 10^{-4} M reactant. Scan rate 0.1 $V \cdot s^{-1}$

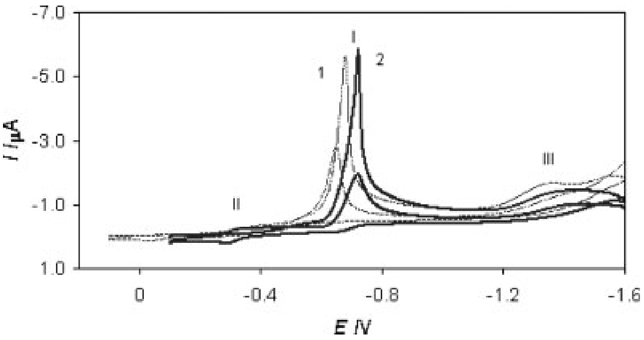

Figure 3. Cyclic voltammograms (two first runs) of R_3–(Ph–NO_2)$_7$ in the solution with pH 7 (curve 1) and pH 11 (curve 2). The solution contained 0.5 M $NaClO_4$, Britton–Robinson buffer, 10^{-4} M reactant and 30 vol. % MeCN. Scan rate 0.1 $V \cdot s^{-1}$

The evaluated cathodic peak potentials E_{pc}(I) for the electroreduction of R—Ph—NO_2 to R—Ph—NHOH in solutions at pHs 7 and 11 are presented in Figs. 4 and 5. The formal potentials (E_f) of the system R—Ph—NHOH/R—Ph—NO were calculated from the following relation (E_{pc}(II) + E_{pa}(II))/2 using the cathodic (E_{pc}(II)) and anodic (E_{pa}(II)) peak potentials obtained from CV curves. The obtained data show that, in alkaline solution, the E_f of R—Ph—NHOH/R—Ph—NO system was equal to -0.316 ± 0.016 V, and it was only slightly dependent

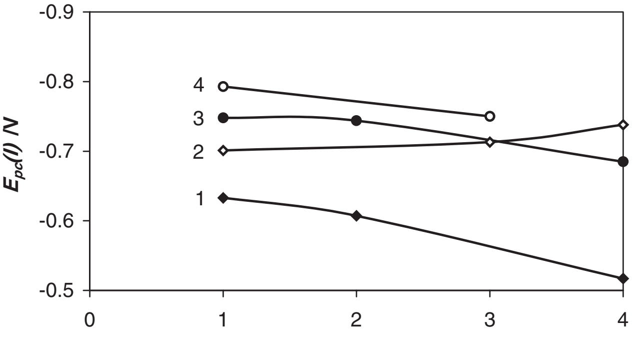

Figure 4. The dependence of E_{pc}(I) for electroreduction of NO_2 group to corresponding hydroxylamine derivatives for: 1 – R_1–Ph–NO_2, 2 – R_2–Ph–NO_2, 3 – R_3–(Ph–NO_2)$_7$ and 4 – Ph–NO_2 obtained in aqueous solutions (lines 1 and 3) and in 30 vol. % MeCN–water mixtures (lines 2 and 4), in solutions with pH 7 (lines 1 and 2) and with pH 11 (lines 3 and 4). The solutions contained also 0.5 M $NaClO_4$, Britton–Robinson buffer, 10^{-4} M reactants 1, 2 and 4 and 5×10^{-5} M R_3–(Ph–NO_2)$_7$. Scan rate 0.2 $V \cdot s^{-1}$

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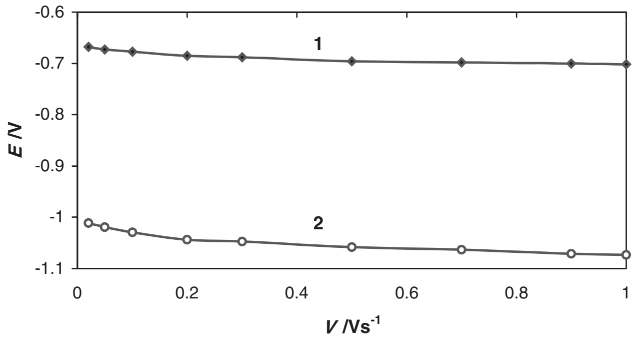

Figure 5. The dependence of E_{pc}(I) of Ph–NO$_2$ (nitrobenzene) electroreduction to PhNHOH on scan rate in aqueous solution (curve 1) and in 30 vol. % MeCN–water mixture for PhNO$_2^{\bullet-}$/PhNHOH process (curve 2). The solutions contained 0.5 M NaClO$_4$, Britton–Robinson buffer with pH 11 and 10^{-4} M nitrobenzene

on the type of reactant and the solution composition. The formal potentials of the reactants were about 0.230–0.270 less negative in alkaline solutions than in neutral solutions in agreement with theory (0.059 V per one pH unit $\times 4 = 0.236$ V) of reversible processes.

Studies at pH 7

In neutral solutions, for the reactant with seven NO$_2$ groups in the molecule, the shape of cyclic voltammogram was very similar to that observed for the reactants with only one NO$_2$ group. Also one cathodic peak in the potential range of -0.64 to -0.72 V was observed (Fig. 3, curve 1). However, this peak was more than 10 times higher than that observed for the reactants such as R$_1$—Ph—NO$_2$ and R$_2$—Ph—NO$_2$, and the reduction charge of the R$_3$—(Ph—NO$_2$)$_7$ species was about seven times higher than that observed for the R$_1$—Ph—NO$_2$ and R$_2$—Ph—NO$_2$ electroreduction processes (calculated for equal concentrations of all the reactants). Thus we can assume that the peak corresponds to electroreduction of all the nitro groups of R$_3$—(Ph—NO$_2$)$_7$ according to the equation:

$$R_3-(Ph-NO_2)_7+7\cdot 4H^+ +7\cdot 4e^- \rightarrow R_3-(Ph-NHOH)_7+7H_2O \qquad (3)$$

For the R$_3$—(Ph—NHOH)$_7$/R$_3$—(Ph—NO)$_7$ system, only one cathodic peak and one anodic peak were observed at potentials similar to those characteristic of the R$_1$—Ph—NO$_2$ and R$_2$—Ph—NO$_2$ reactants. The currents of those peaks were strongly dependent on the electrode polarization range of potentials. When the electrode was polarized to the potential more negative than -1.4 V, the current peaks (II) became then lower because the reactant was desorbed from the mercury electrode surface.

Studies at pH 11

At pH 11, the electrochemical behaviour of the investigated compounds was different (Figs. 2 and 3, curves 2 and Fig. 6). All the peaks were observed at more negative potentials, as it was expected. In the second and subsequent cycles, the cathodic peak (I) of the R$_1$—Ph—NO$_2$ electroreduction was split into two steps. Also a new anodic peak was observed at potentials about 60 mV less negative than E_{pc}(I). For R$_2$—Ph—NO$_2$, the separation of the peak (I) into two steps was observed already in the first cathodic run. Therefore, the four-

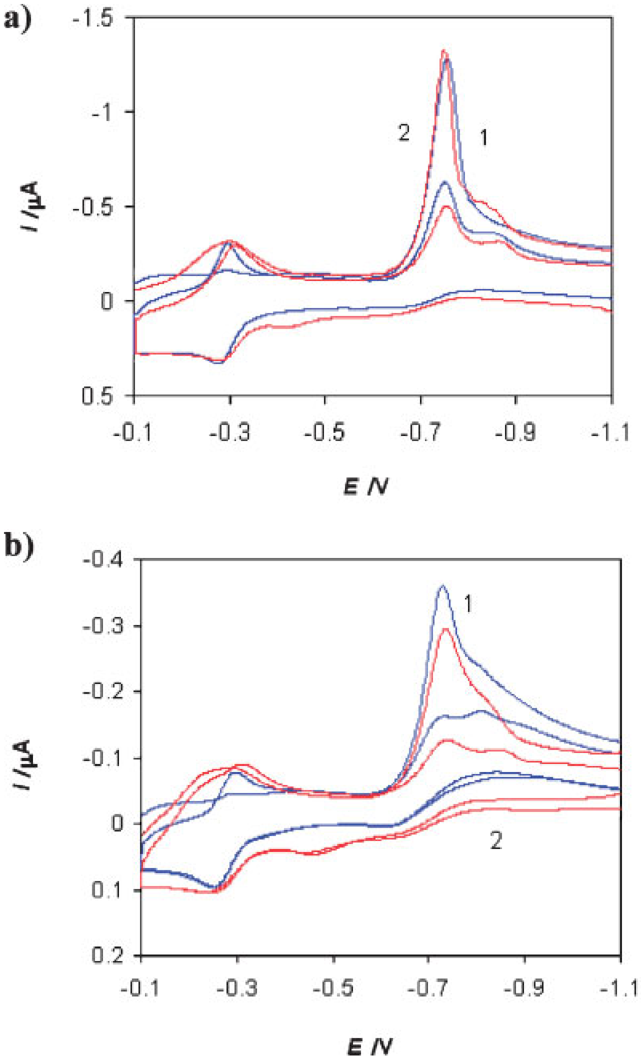

Figure 6. Cyclic voltammograms (first two runs) of R$_1$–Ph–NO$_2$ (curve 1) and R$_2$–Ph–NO$_2$ (curve 2) for different scan rates: (a) 0.3 and (b) 0.05 V$\cdot$s^{-1}, in aqueous solutions with pH 11. In the solution was 0.5 M NaClO$_4$, Britton–Robinson buffer and 10^{-4} M reactant

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electron process occurs in two steps: the first being a one-electron process with the reversible formation of the radical anion:

$$\mathrm{R - Ph - NO_2 + e^- \leftrightarrow R - Ph - NO_2^{\bullet -}} \tag{4}$$

and the second one, at more negative potential, corresponding to a three-electron irreversible process:

$$\begin{aligned} &\mathrm{R - Ph - NO_2^{\bullet -} + 3e^- + 3H_2O} \\ &\quad \mathrm{\rightarrow R - Ph - NHOH + 4OH^-} \end{aligned} \tag{5}$$

The separation of the cathodic peak (I) depended on the rates of the adsorption equilibration of R_1—Ph—NO_2 and R_2—Ph—NO_2 as well as on electronic and steric effects in the benzene ring (*meta* and *para* isomers of disubstituted benzene).[34] For R_2—Ph—NO_2 the beginning of separation of the peak (I) into two steps was already observed in the first cathodic run at scan rates $v \geq 0.1\ \mathrm{V \cdot s^{-1}}$ (Fig. 6a) and the separation of the peak (I) was observed for both reactants for lower scan rates (Fig. 6b).

However, in the case of R_3—(Ph—NO_2)$_7$ no separation of the four-electron wave was observed in the carried out experiments.

Investigation of adsorption of R_1—Ph—NO_2, R_2—Ph—NO_2 and R_3—(Ph—NO_2)$_7$ on mercury electrode

In order to determine the surface concentration of modified cyclodextrins adsorbed on the mercury electrode, single-step chronocoulometric experiments were carried out using the static mercury drop electrode. Initial and final potentials at -0.40 and -1.1 V, respectively, were selected.

The amount of the adsorbed compounds was determined from the plots of Q^t *versus* $t_p^{1/2}$. All these plots were linear, and at $t_p = 0$, they intersected the Q axis at positive (absolute) values. At the constant initial potential, using different pulse times and changing the time of equilibration at the initial potential from 2 to 10 s, the obtained $Q_{\mathrm{Ads}} + \Delta Q_{\mathrm{dl}}$ values were similar within the experimental error and equal to about $0.1\ \mu\mathrm{C \cdot cm^{-2}}$. The change of double layer charge (in comparison to Q_{Ads}) can be neglected because the modified cyclodextrins: *per*(2,3-di-*O*-methyl)-β-cyclodextrin (DM-β-CD) and *per*(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CD) were strongly adsorbed on the mercury electrode in the potential range from –0.4 to –1.2 V, where the differential capacity was low and changed only slightly.[39] Therefore, we could assume that the obtained data were approximately equal to Q_{Ads}.

The surface concentration, Γ, was calculated from the obtained charges, $Q_{\mathrm{Ads}} = nF\Gamma$, the electron numbers n used in those calculations were taken from reactions (1) and (3).

The results of Q_{Ads} and Γ (for all the investigated compounds obtained from such analyses) are given in Table 1. The obtained data suggest that during the preequilibrium times used (2–10 s), the adsorption equilibrium was established. It follows from the obtained data that the investigated compounds are strongly adsorbed on the mercury electrode from neutral and alkaline solutions. The Q_{Ads} of R_1—Ph—NO_2 is lower in the presence of MeCN, due to competitive adsorption of MeCN and R_1—Ph—NO_2 molecules on the electrode surface.

The surface concentration of R_3—(Ph—NO_2)$_7$ was practically independent of its concentration from 4×10^{-5} M, exhibiting at higher concentrations plateau of the adsorption isotherm. Thus we could assume that at a concentration exceeding 4×10^{-5} M the mercury electrode was fully covered by the molecules of R_3—(Ph—NO_2)$_7$. This conclusion is also supported by the literature, suggesting that the modified cyclodextrins totally covered the mercury electrode when their concentration in the investigated solutions was even as low as 10^{-4} M.[39] In view of the above result, we were able to calculate from the measured maximal charges Γ_m

Table 1. The charges and surface concentrations of R_1–Ph–NO_2, R_2–Ph–NO_2 and R_3–(Ph–NHOH)$_7$ compounds adsorbed on the mercury electrode from the aqueous solutions containing 10^{-4} M reactants, 0.5 M $NaClO_4$ and Britton–Robinson buffer with pH 7 or 11

	pH 7		pH 11	
Reactant	Q_{ads} [μC/cm^2]	Γ [mol/cm^2]	Q_{ads} [μC/cm^2]	Γ [mol/cm^2]
R_1–Ph–NO_2	22.6	5.8×10^{-11}	23.6	6.1×10^{-11}
	13.4[a]	3.5×10^{-11}[a]	18.4[a]	4.8×10^{-11}[a]
R_2–Ph–NO_2	18.1	4.6×10^{-11}	20.4	5.2×10^{-11}
R_3–(Ph–NO_2)$_7$[a]	—	—	134.9	5.0×10^{-11}
R_3–(Ph–NO_2)$_7$[a,b]	130.3	4.8×10^{-11}	128.4	4.7×10^{-11}
R_3–(Ph–NO_2)$_7$[a,c]	—	—	123.9	4.6×10^{-11}

Initial potential $E_i = -0.40$ V.
[a] Data obtained for 30 vol. % of MeCN.
[b] Data obtained for 5×10^{-5} M R_3–(Ph–NO_2)$_7$.
[c] Data obtained for 2×10^{-5} M R_3–(Ph–NO_2)$_7$.

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Table 2. Values of surface area of the mercury electrode occupied by one molecule of reactant (P) obtained from aqueous solutions containing 10^{-4} M reactants, 0.5 M $NaClO_4$ and Britton–Robinson buffer with pH 7 or 11

	pH 7	pH 11
Reactant	P (nm^2)	P (nm^2)
R_1–Ph–NO_2	2.86	2.72
R_2–Ph–NO_2	3.61	3.19
R_3–$(Ph–NO_2)_7$[a]	—	3.32
R_3–$(Ph–NO_2)_7$[a,b]	2.89	3.53

[a] Data obtained for 30 vol. % of MeCN.

[b] Data obtained for 5×10^{-5} M R_3–$(Ph–NO_2)_7$.

(maximal surface concentration) the surface occupied by one molecule of reactant P. The calculated data are presented in Table 2.

It was observed that the seven energetically equivalent nitro groups of R_3—$(Ph—NO_2)_7$ react at the same potential in one well-defined sharp peak. The shape of the cathodic voltammetric peak, and also the charges found for the adsorbed reactant show that the reaction occurs from the adsorbed state. The orientation of the reactant on the electrode surface is, to some extent, a matter of speculation. Literature data show that the values of the surface occupied by one molecule of β-cyclodextrin perpendicularly orientated to the electrode surface was 2.59 nm^2.[40] Considering the size of the adsorbed molecules and their number per square centimetre, it may be concluded that the studied molecules are also orientated perpendicularly. For a practically totally covered electrode there are two possibilities of such orientations of cyclodextrin molecules: either (i) with the hydrophobic groups on the electrode surface and the NO_2 group in the solution or (ii) with the NO_2 group on the electrode surface. The case (i) was found earlier by Galus *et al.*[40] for the adsorption of native β-cyclodextrin on the mercury electrode. The case (ii) was proposed by Coleman *et al.*[41] for the adsorption for amphiphilic cyclodextrins adsorbed on modified gold electrodes.

We suppose that the nitro groups of the investigated reactants were orientated towards the electrode surface. Since in the first case the electron transfer should occur on a rather long distance, what seems to be less probable.

The influence of inhibitors on the reduction of NO_2 group of nitrophenyl derivatives on mercury electrode

In order to explain in more detail the mechanism of the electroreduction of new nitro compounds, we have also investigated both Ph—NO_2 (nitrobenzene) and the R_1—Ph—NO_2 reactant in water–MeCN solutions. The obtained data are shown in Figs. 7 and 8.

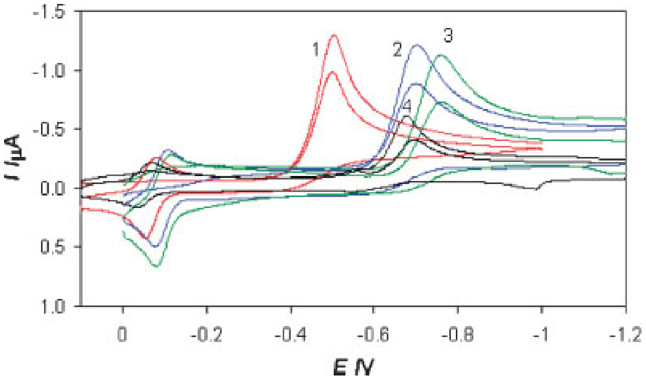

Figure 7. Cyclic voltammograms (first two runs) of Ph–NO_2 (nitrobenzene) in aqueous solution at pH 7 (curve 1) and in 30 vol. % MeCN–water mixture (curve 2); CV for Ph–NO_2 in presence of 10^{-4} M *per*(2,3,6-tri-*O*-methyl)-β-cyclodextrin in 30 vol. % MeCN–water mixture (curve 3) and CV for R_1–Ph–NO_2 in 30 vol. % MeCN–water mixture (curve 4). The solutions composition: 0.5 M $NaClO_4$, Britton–Robinson buffer and 10^{-4} M reactant. Scan rate 0.1 V · s^{-1}

We can see that, in neutral solutions containing MeCN, the cathodic peak of the electroreduction of $PhNO_2$ to PhNHOH is shifted to a more negative potential by about 0.20 V (Fig. 7, curves 1 and 2), whereas in the case of R_1—Ph—NO_2 the peak potential is changed only by about 0.05 V under the same conditions (Fig. 2, curve 1 and Fig. 7, curve 4). The data show that the electroreduction of nitrobenzene is inhibited by MeCN adsorbed molecules, that are capable to cover practically totally the mercury electrode surface.[42] A similar effect was observed earlier in several water–organic mixtures.[3] The inhibiting effect of MeCN is lower in the case of the R_1—Ph—NO_2/R_1—Ph—NHOH process due to desorption of MeCN by adsorbed molecules of R_1—Ph—NO_2.

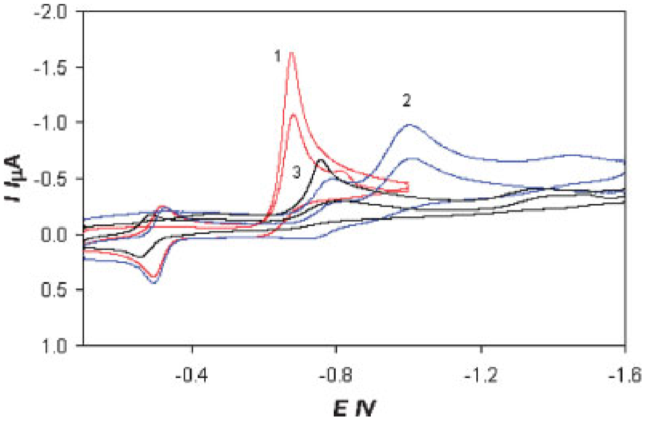

Figure 8. Cyclic voltammograms (first two runs) Ph–NO_2 (nitrobenzene) at pH 11 in aqueous solution (curve 1), and in 30 vol. % MeCN–water mixture (curve 2); CV for R_1–Ph–NO_2 in 30 vol. % MeCN–water mixture (curve 3). The solutions composition: 0.5 M $NaClO_4$, Britton–Robinson buffer and 10^{-4} M reactant. Scan rate 0.1 V · s^{-1}

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We have also added the modified cyclodextrin [*per*(2,3,6-tri-*O*-methyl)-β-cyclodextrin] to the solution of nitrobenzene in 30 vol.% MeCN–water mixture, and it has been found that under these experimental conditions, the cathodic electroreduction of $PhNO_2$ to PhNHOH is strongly inhibited because the cathodic peak of this process has been observed at a more negative potential (Fig. 7, curve 3) compared to that in the absence of permethylated cyclodextrin.

The influence of MeCN on the $PhNO_2$ electroreduction was spectacular at pH 11. In the presence of MeCN, the four-electron Ph—NO_2/Ph—NHOH process was split into two steps described by Eqns (4) and (5), and the potentials of both peaks were more negative than those observed in the Ph—NO_2 electroreduction in aqueous solutions. The inhibiting effect of the adsorbed MeCN molecules on the R_1—Ph—NO_2 electroreduction on the mercury electrode was not so evident. In this case, only one four-electron wave corresponding to the electroreduction of R_1—Ph—NO_2 to R_1—Ph—NHOH was observed in the presence of MeCN (Fig. 8, curve 3, $E_{pc}(\mathrm{I}) = -0.760\,\mathrm{V}$), and the potential of this cathodic peak was only more negative by 0.026 V than that observed for the same system in aqueous solutions (Fig. 2, curve 2, $E_{pc}(\mathrm{I}) = -0.734\,\mathrm{V}$). The evaluated cathodic peak potentials $E_{pc}(\mathrm{I})$ of electroreduction of R—Ph—NO_2 to R—Ph—NHOH in two solutions of different pH are presented in Fig. 4.

The potential values obtained in the solution with 30 vol. % MeCN were corrected for liquid junction potential. The corrected values of $E_{\mathrm{pc}}(\mathrm{I})$ and formal potentials were by 0.023 V more negative than the experimental values.[43]

From the obtained data, we can see that in aqueous solutions at pH 7, and at scan rates higher than $0.1\,\mathrm{V \cdot s^{-1}}$, the peak potentials of the non-inhibited electroreduction of R—NO_2 to R—NHOH change in the range: Ph—NO_2 > R_2—Ph—NO_2 > R_1—Ph—NO_2 (Fig. 4, curve 1). Inhibition of this process can be caused by a strong adsorption of the β-cyclodextrin moiety of the investigated nitrophenyl derivatives.

In the water–MeCN solution the R—NO_2 electroreduction is more strongly inhibited by the presence of the organic solvent than in aqueous solution (Fig. 4, curve 2), and the peak potentials of the studied systems change in the opposite direction: R_1—Ph—NO_2 > R_3—(Ph—NO_2)$_7$ > Ph—NO_2. This is due to the competitive adsorption of MeCN and the reactants.

In alkaline solutions (pH = 11), the adsorbed MeCN molecules inhibited and split the four-electron process into the 1e-reversible $PhNO_2/PhNO_2^{\bullet -}$ and the three electron-irreversible $PhNO_2^{\bullet -}$/PhNHOH process, and shifted its potential to more negative values. The formal potential of the $PhNO_2/PhNO_2^{\bullet -}$ system was equal to $-0.698 \pm 0.003\,\mathrm{V}$, and the peak potential of the $PhNO_2^{\bullet -}$/PhNHOH process was about 0.30 V more negative and depended on the scan rate (Fig. 5, curve 2).

It follows from the obtained data that in aqueous solutions at pH 11 the peak potentials of the R—NO_2 electroreduction changed in the order: Ph—NO_2 > R_2—Ph—NO_2 ≈ R_1—Ph—NO_2 (Fig. 4, curve 3). In the presence of MeCN, the electroreduction of R_1—Ph—NO_2 was more strongly inhibited than that of R_3—(Ph—NO_2)$_7$ (Fig. 4, curve 4).

The R—Ph—NHOH/R—Ph—NO process described by Equation (2) was practically reversible, since the difference of $\Delta E = E_{pa}(\mathrm{II}) - E_{pc}(\mathrm{II})$ was $28 \pm 3\,\mathrm{mV}$ at scan rates 0.1 to $1\,\mathrm{V \cdot s^{-1}}$. Only for reactant R_1—Ph—NO_2, ΔE was about 50 mV in the solution at pH 7.

For R_3—(Ph—NO_2)$_7$ we have also observed only one cathodic and one anodic peak (II); probably the seven —NHOH groups produced by electroreduction of NO_2 groups reacted at the same potential according to the reaction:

$$\begin{aligned} &R_3 - (\mathrm{Ph} - \mathrm{NHOH})_7 \\ &\quad \leftrightarrow R_3 - (\mathrm{Ph} - \mathrm{NO})_7 + 7 \cdot 2\mathrm{H}^+ + 7 \cdot 2\mathrm{e}^- \end{aligned} \tag{6}$$

The pH influence on the R—Ph—NHOH/R—Ph—NO process is strong, and its formal potential is about 0.25 V more negative in solution at pH 11 than at pH 7 in agreement with the theory (0.059 V × 4 = 0.236 V). This process is only slightly influenced by the reactant structure and takes place in the potential range in which the reactants are not adsorbed on the mercury electrode.

The peak (I) currents for the electroreduction of R_1—Ph—NO_2 and R_2—Ph—NO_2 on the mercury electrode were lower than that observed for nitrobenzene electroreduction. This may be caused by lower diffusion coefficients for such large reactants and also by inhibiting the influence of these reactants adsorbed on the mercury electrode.

CONCLUSIONS

We have found that nitrophenyl derivatives of β-cyclodextrin are strongly adsorbed on the mercury electrode. The adsorption becomes lower in the presence of MeCN and depends to some extent on the composition of the solutions used here. The parameters of the electrochemical behaviour of the reactants depend on: (i) their molecular structure, (ii) pH of the investigated solutions and (iii) the presence of MeCN.

Because of the presence of the β-cyclodextrin residue in the molecules having NO_2 groups attached to the reactants, R_1—Ph—NO_2, R_2—Ph—NO_2 and R_3—(Ph—NO_2)$_7$, are reduced on the mercury electrode at more negative potentials than nitrobenzene. The β-cyclodextrin residue in the reactant molecules hinders the formation of the ion radicals and diminishes the inhibiting influence of the adsorbed MeCN molecules on the mercury electrode. We have found that the seven NO_2 groups of

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the R_3—$(Ph—NO_2)_7$ molecule are reduced virtually at the same potential, and the NO_2 groups of the reactant were perpendicularly orientated to the electrode surface. Under the present experimental conditions, we have not observed the formation of the radical anion of the R_3—$(Ph—NO_2)_7$ compound. This phenomenon can be explained in terms of electronic interactions between the seven NO_2 groups in the molecule. Possible fast electron transfers between anion radicals in the molecule decrease the stability of the radical and can facilitate the electroreduction process leading to the formation of the hydroxylamine derivative in one step.

EXPERIMENTAL

Electroreduction and adsorption of reactants were investigated using cyclic voltammetry (CV) and chronocoulometry. The measurements were carried out using a CH Instruments (Cordova, TN), model 660 electrochemical analyser connected to a computer. Cyclic voltammetric curves were analysed using the Nicholson equation for quasi-reversible processes, while for irreversible processes the equation, which describes the peak current potential was used.[44]

Single-step chronocoulometric experiments[44] were used to determine the surface concentration of adsorbed reactants. The chronocoulometric Q–t curves were recorded for initial potentials ranging from −0.30 to −0.50 V and for pulse times changing from 0.01 to 0.1 s The time of equilibration (before the pulse application) was changed from 1 to 10 s. The Q–t curves were described using equation:

$$Q = \frac{2n\mathrm{FAD}_{\mathrm{ox}}^{1/2} c_{\mathrm{ox}}^{0} t_{\mathrm{p}}^{1/2}}{\pi^{1/2}} + Q_{\mathrm{dl}} + Q_{\mathrm{Ads}} \qquad (7)$$

D_{ox} and c_{ox}^{0} describe diffusion coefficients and concentrations of reactants, respectively. Whereas, Q_{dl} and Q_{Ads} stand for the charge of the double layer and the charge of adsorbed reactant, respectively.

Electrochemical studies were carried out in a three-electrode cell with a water jacket at 25 ± 0.1 °C. Static mercury drop electrode (SDME) was used as a working electrode, while the platinum foil ($2\,\mathrm{cm}^2$) served as a counter electrode. All the potentials were measured against a calomel electrode (SSCE) with saturated sodium chloride. In all the studied solutions, 0.5 M $NaClO_4$ was used as a supporting electrolyte, and all the measurements were carried out in the presence of a Britton–Robinson buffer. The reactant concentration was equal to 10^{-4} or 5×10^{-5} M (in the case of R_3—$(Ph—NO_2)_7$). Because of low solubility of *heptakis*[6-deoxy-6-(4-nitrobenzamido)-2,3-di-*O*-methyl]-*β*-cyclodextrin in aqueous solutions, the experiments were carried out in 30 vol. % mixture of MeCN and water.

Doubly distilled and deionised water (Mili-Q, Millipore, Austria) and acetonitrile (MeCN) (from Merck) were used for preparation of the solutions. The compounds were synthesized using the following procedures.

Mono[6-deoxy-6-(4-nitrobenzamido)]-per-O-methyl-*β*-cyclodextrin (R_1—Ph—NO_2)

Mono(6-amino-6-deoxy)-*per*-*O*-methyl-*β*-cyclodextrin[45] (1.10 g, 0.78 mmol) was dissolved in a solution of DMF (2 mL) and MeCN (12 mL). Then, 4-nitrobenzoic acid (0.26 g, 1.6 mmol) and DCC (dicyclohexylcarbodiimide, 0.42 g, 2.0 mmol) were added. The reaction mixture was stirred overnight and evaporated to dryness under reduced pressure. Solid residue was purified by chromatography on silica gel using a mixture of acetone/hexane 3:1 (v/v) and 1:1 (v/v). 0.19 g of pure product R_1—Ph—NO_2 was obtained as white bubbles, yield 15.5%, $[\alpha]_{\mathrm{D}}^{20} + 127.4^{\circ}$ (*c* 1, $CHCl_3$); R_F 0.57 (acetone–hexane 1:1); ESIMS: *m/z* 1628.7 [R_1—Ph—$NO_2 + HN_3Na$], calcd 1628.7.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.19–3.21 (m, 7H, 7H-2); 3.37–3.41 (m, 7H, 7H-4); 3.49–3.69 (m, 67H, 7H-3, 20OMe); 3.79–3.95 (m, 21H, 7H-5, 7H-6a, 7H-6b); 5.00–5.19 (m, 7H, 7H-1); 7.72 (t, 1H, $J_{\text{H-N,H-6a}} = 5.5$ Hz, $J_{\text{H-N,H-6b}} = 5.5$ Hz, H-N); 7.56 (d, 2H, $J_{\text{H-2Ph,H-3Ph}} = 8.0$ Hz, $J_{\text{H-5Ph,H-6Ph}} = 8.0$ Hz, H-2Ph, H-6Ph); 8.29 (d, 2H, H-3Ph, H-5Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 49.32 (C-6—NH); 58.39-59.21 (OMe); 60.87–61.56 (C-6); 71.07–71.39 (C-5); 81.10–82.18 (C-2,3,4); 99.26–99.54 (C-1); 123.65; 128.14; 143.91; 147.84 (Ar); 170.32 (C=O).

Mono[6-deoxy-6-(3-nitrobenzamido)]-per-*O*-methyl-β-cyclodextrin (R_2—Ph—NO_2)

Hydrochloride of *mono*(6-amino-6-deoxy)-*per*-*O*-methyl-*β*-cyclodextrin[45] (0.23 g, 0.16 mmol) was dissolved in pyridine (6 mL), then 3-nitrobenzoyl chloride (0.12 g, 0.65 mmol) was added. The reaction mixture was stirred overnight and then it was evaporated to viscous oil under reduced pressure. The solution of the obtained oil in methylene chloride was washed with HCl(aq), water, $KHCO_3$(aq), then with water again and, finally, it was dried under anhydrous magnesium sulphate and evaporated to bubbles under reduced pressure. The crude product was purified by chromatography on silica gel using a mixture of acetone/hexane 1:1 (v/v) and 2:1 (v/v). 0.09 g of pure product R_2—Ph—NO_2 was obtained as white bubbles, yield 36%, $[\alpha]_{\mathrm{D}}^{20} + 139.1^{\circ}$ (*c* 1, $CHCl_3$); R_F 0.40 (acetone–hexane 1:1); ESIMS: *m/z* 1585.7 [R_2—Ph—NO_2 + Na] and 804.7 [R_2—Ph—NO_2 + 2Na], calcd 1585.7 and 804.7, respectively.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.19–3.21 (m, 7H, 7H-2); 3.35–3.41 (m, 7H, 7H-4); 3.50–3.67

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(m, 67H, 7H-3, 20OMe); 3.80–3.95 (m, 21H, 7H-5, 7H-6a, 7H-6b); 5.04–5.24 (m, 7H, $J_{\text{H-1,H-2}} = 3.5$ Hz, 7H-1); 7.71 (t, 1H, $J_{\text{H-N,H-6a}} = 5.5$ Hz, $J_{\text{H-N,H-6b}} = 5.5$ Hz, H-N); 7.65 (t, 1H, $J_{\text{4Ph,5Ph}} = 8.0$ Hz, $J_{\text{5Ph,6Ph}} = 7.5$ Hz, H-5Ph); 8.18 (d, 1H, $J_{\text{2Ph,6Ph}} = 1.0$ Hz, H-6Ph); 8.37 (d, 1H, $J_{\text{2Ph,4Ph}} = 1.0$ Hz, H-4Ph); 8.68 (d, 1H, H-2Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 40.91 (C-6—NH); 58.28–59.34 (OMe); 61.19–61.64 (C-6); 70.90–71.45 (C-5); 79.85–82.46 (C-2,3,4); 98.71–100.13 (C-1); 122.22; 125.95; 129.69; 133.20; 136.29; 148.25 (Ar); 165.21 (C=O).

Heptakis[6-deoxy-6-(4-nitrobenzamido)-2,3-di-O-methyl]-β-cyclodextrin (R_3—(Ph—NO_2)$_7$)

Heptakis(6-amino-6-deoxy-2,3-di-*O*-methyl)-β-cyclodextrin[46] (1.13 g, 0.85 mmol) was dissolved in mixture of DMF and MeCN [1:6 (v/v), 63 mL]. Then, 4-nitrobenzoic acid (1.83 g, 11 mmol) and DCC (3.0 g, 14.6 mmol) were added. The reaction mixture was stirred for 24 h at room temperature and then evaporated to dryness under reduced pressure. The crude product was purified by chromatography on silica gel using a mixture of acetone and hexane 3:1 (v/v) as an eluent. After two subsequent crystallizations from ethanol product R_3—(Ph—NO_2)$_7$ was obtained in the form of white crystals (0.37 g, 18.5% yield). Mp 182–184 °C; $[\alpha]_D^{20} + 44.2^o$ (*c* 1, $CHCl_3$); R_F 0.43 (2:1 acetone–hexane); ESIMS: *m/z* 2390.8 [R_3—(Ph—NO_2)$_7$ + Na], calcd 2390.8.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.26 (dd, 7H, $J_{\text{H-1,H-2}} = 3.5$ Hz, $J_{\text{H-2, H-3}} = 9.0$ Hz, 7H-2); 3.39 (t, 7H, $J_{\text{H-4, H-5}} = 8.5$ Hz, $J_{\text{H-3,H-4}} = 8.5$ Hz, 7H-4); 3.54 (s, 21H, 7O-Me); 3.58 (t, 7H, 7H-3); 3.63 (s, 21H, 7O-Me); 3.74–3.86 (m, 7H, 7H-5); 4.03–4.09 (m, 14H, 7H-6a, 7H-6b); 5.12 (d, 7H, 7H-1); 7.73 (t, 7H, $J_{\text{H-N,H-6a}} = 5.5$ Hz, $J_{\text{H-N,H-6b}} = 5.5$ Hz, 7H-N); 7.78 (d, 14H, $J_{\text{H-2Ph,H-3Ph}} = 8.5$ Hz, $J_{\text{H-5Ph,H-6Ph}} = 9.5$ Hz, 7H-2Ph, 7H-6Ph); 8.00 (d, 14H, 7H-3Ph, 7H-5Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 40.70 (C-6); 58.81; 61.11 (OMe); 70.64 (C-5); 81.08; 81.60; 82.88 (C-2,3,4); 99.63 (C-1); 123.48; 128.36; 139.61; 149.37 (Ar); 166.55 (C=O).

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