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A Novel and Effective Strategy for the Construction of "Tube-Like" Double Resorcin[4]arenes

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Abstract

The synthesis of rigid tube-shape structures from resorcin[4]arene units combined in the "head-to-tail" manner is described. Tetrabromomethylenecalix-[4]resorcinarene with all OH-groups connected via methylene bridges was used as a starting material. Reaction with *p*-hydroxybenzaldehyde led to the tetraaldehyde derivative and the following condensation with resorcinol resulted in formation of a third aromatic rim. An electrochemical study comparing properties of both resorcin[4]arene and its tube-shaped analogs was performed.

Introduction

Tube and channel structures are known as advanced modules for rational design of molecular materials. Their shape allows the formation of supramolecular assemblies via peripheric functional groups as well as via interactions with the inner and outer surfaces of the cavity. Great attention is paid to the development of channel structures nowadays.

A variety of synthesis of carbon nanotubes popular in microelectronics was described in [1]. Asfari *et al.* [2] report two ways of nanotube modification by metalo-clusters – use them to fill the tube cavity and to cover the surface of nanotubes. The authors of [3] presented an approach to immobilization of receptor peptide molecules on the surface of carbon nanotubes. On the other hand, it is well known that the biological channels formed by amino-acid aromatic residuals provide the substrate advance to the active centers of cholinesterase, whereas Gramicidin A channels transport H^+, Na^+ and K^+ [4].

Development of synthetic transport systems (ionic carriers, ionic channels) allows better understanding of the role of channel proteins and forms basics for design of advanced drug delivery systems. Artificial channel structures compatible with the bilayer vesicles were discussed in [5]. It was demonstrated that derivatives of calix[4]resorcinarene bearing long hydrophobic tails are able to integrate into bilayer membranes forming ionic channels [6]. Na^+-selectivity of a long-chain phenoxyalkylresorcin[4]arenes in both bulk liquid membranes and planar lipid bilayer conditions has been established [7].

Here we present a synthesis of the tube-like structures with resorcin[4]arene units combined in the "head-to-tail" manner. Head-to-tail connected double calix[4]arenas were constructed from 4-tert-butylcalix[4]arene and 2 O-protected phenolic units attached via either links as describes in [8].

Experimental

II: A mixture of dry I (3 g, 2.52 mmol), anh. K_2CO_3 (10 g, 72.4 mmol) and *p*-hydroxy-benzaldehyde (1.25 g, 10.24 mmol) in 150 ml of dry CH_3CN was stirred and refluxing during 2 h and concentrated in vacuum. The residue was mixed with CH_2Cl_2 (150 ml) and 2N HCl (3 × 100 ml). The organic layer was separated, dried ($MgSO_4$), concentrated in vacuum and recrystallized (acetone) to afford 2.5 g (80%) of II, m.p. 360° (decay).

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.89 (s, 4H, CH=O), 7.8 (d, ^{3}J(H, H) = 8.7 Hz, 8H, CH (Ar_{orto})), 7.23 (s, 4H, CH (Ar)), 7.0 (d, ^{3}J(H, H) = 8.7 Hz, 8H, CH (Ar_{meta})), 5.75 (d, ^{2}J(H, H) = 7.23 Hz, 4H, O—CH_2—O), 5.0 (s, 8H, CH_2), 4.85 (t, ^{3}J(H, H) = 7.95 Hz, 4H, CH), 4.6 (d, ^{2}J(H, H) = 7.23 Hz, 4H, O—CH_2—O), 2.28 (q, ^{3}J(H, H) = 6.06 Hz, 8H, CH_2), 1.41–1.32 (m, 24H, CH_2), 0.93 (t, ^{3}J(H, H) = 7 Hz, 12H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): σ = 190.5, 163.4, 154.3, 138.2, 132.0, 130.3, 121.9, 121.5, 114.6, 100.0, 60.9, 36.9, 31.9, 30.0, 27.5, 22.6, 14.1; MS

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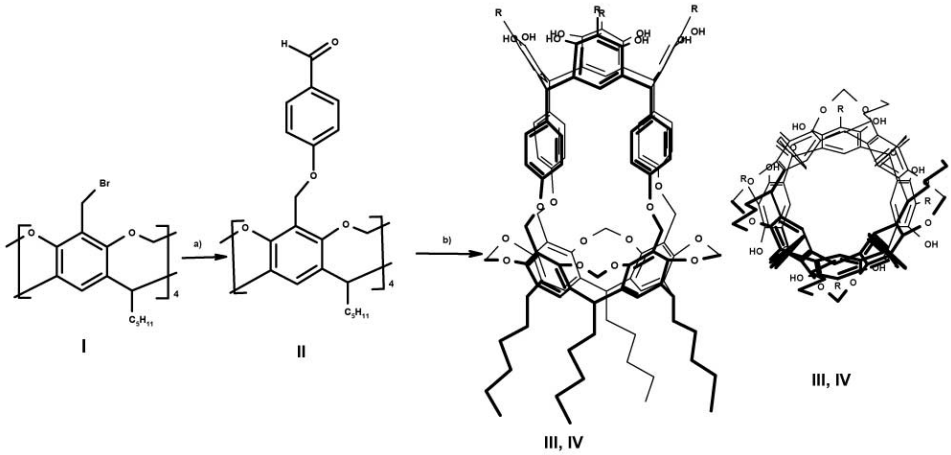


Scheme 1. Synthesis of tube-like resorcin[4]arenes: (a) 4 eq. HO—V_6H_4—COH, CH_3CN, K_2CO_3; (b) resorcinol (to obtain **III**, R=H) or methylresorcinol (to obtain **IV**, R=CH_3), 1,4-dioxan, HCl.

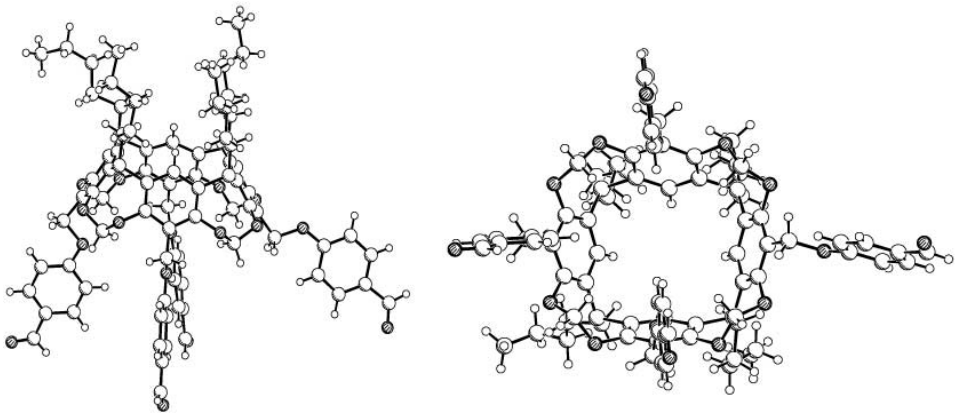
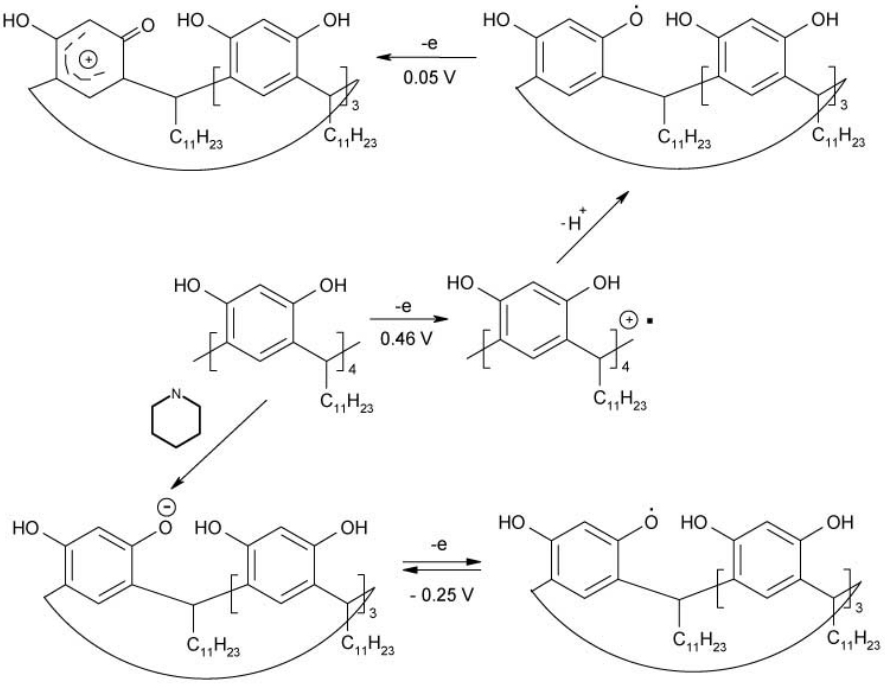


Figure 1. X-ray crystal structure of **II**.



Scheme 2. Resorcin[4]arene **V** oxidation in the presence and in the absence of piperidin.

m/z (%): 1375 (100) $[M + Na]^+$ [12]. Anal. calc. (%) for $C_{84}H_{88}O_{16}$: C 74.5, H 6.5; found: C 74.6, H 7.09.

III: A mixture of II (1.96 g, 1.45 mmol), resorcinol (0.64 g, 5.8 mmol), conc. HCl (0.36 g) and 1,4-dioxan (60 ml) was stirred at r.t. for 50 h, concentrated in vacuum. The residue was mixed with acetone (2 ml), the dense mass and than; light-red crystals were formed. Crystals were collected, washed with acetone (10 ml, −20 °C) and dried in vacuum. The yield of III was 0.87 g (35%), m.p. 360° (decay).

^{1}H NMR (300 MHz, [D_6] DMSO, TMS): δ = 8.62 (s, 8H, OH), 7.68 (s, 4H, CH (Ar)), 6.62 (d, ^{3}J(H, H) = 8.1 Hz, 8H, CH (Ar_{orto})), 6.45 (s, 4H, CH (Ar)), 6.32 (d, ^{3}J(H, H) = 8.1 Hz, 8H, CH (Ar_{meta})), 6.15 (s, 4H, CH (Ar)), 5.9 (d, ^{2}J(H, H) = 6.8 Hz, 4H, O—CH_2—O), 5.66 (s, 8H, CH2), 4.94 (s, 4H, CH), 4.69 (t, 3J(H, H) = 7.9 Hz, 4H, CH), 4.42 (d, 2J(H, H)=6.9 Hz, 4H, O—CH_2—O), 2.4 (m, 8H, CH_2), 1.4–1.2 (m, 24H, CH_2), 0.9 (t, ^{3}J(H,H) = 7 Hz, 12H, CH_3); ^{13}C NMR (75 MHz, [D_6], 25 °C, TMS): δ = 155.36, 153.32, 152.58, 137.82, 137.34, 136.12, 129.57, 123.68, 122.7, 121.36, 114.98, 110.55, 100.0, 60.89, 40.2, 36.79, 31.35, 30.57, 27.33, 22.21, 13.87; MS *m/z* (%): 1719 (100) $[M + Na]^+$. Anal. calc. (%) for $C_{108}H_{104}O_{20}$ (1720): C 75.34, H 6.04; found: C 74.9, H 6.0.

IV: A mixture of cavitand II (1.97 g, 1.45 mmol), 2-methylresorcinol (0.72 g, 5.8 mmol), conc. HCl (0.36 g) and 1,4-dioxan (100 ml) was stirred at r.t. for 48 h and then concentrated in vacuum. The residue was mixed with acetone (3 ml), as result the dense mass and then yellow crystals were formed. Crystals were collected by filtration, washed with acetone (15 ml, −20 °C) and dried in vacuum. The yield of IV was 1.08 g (42%), m.p. 360° (decay).

^{1}H NMR (300 MHz, [D_6] DMSO, TMS): δ = 7.85 (s, 8H, OH), 7.67 (s, 4H, CH (Ar)), 6.67 (d, ^{3}J(H, H) = 8.0 Hz, 8H, CH (Ar_{orto})), 6.6 (s, 4H, CH (Ar)), 6.33 (d, ^{3}J(H, H) = 8.0 Hz, 8H, CH (Ar_{meta})), 5.86 (d, ^{2}J(H, H) = 6.9 Hz, 4H, O—CH_2—O), 5.81 (s, 8H, CH_2), 4.74 (s, 4H, CH), 4.7 (t, ^{3}J(H, H) = 7.89 Hz, 4H, CH), 4.45 (d, ^{2}J(H,H) = 6.9 Hz, 4H, O—CH_2—O), 2.5 (m, 8H, CH_2), 1.94 (s, 12H, CH_3), 1.45–1.25 (m, 24H, CH_2), 0.87 (t, ^{3}J(H, H) = 6.97 Hz, 12H, CH_3); ^{13}C NMR (75 MHz, [D_6], 25 °C, TMS): δ = 155.48, 153.27, 150.37, 143.8, 137.32, 136.2, 130.49, 125.2, 123.62, 122.74, 115.17, 111.1, 61.0, 44.9, 36.9, 31.29, 30.56, 27.32, 22.17, 13.85, 10.07; MS *m/z* (%): 1775 (100) $[M]^+$. Anal. calc. (%) for $C_{112}H_{112}O_{20}$ (1775): C 75.67, H 6.3; found: C 75.3, H 6.35.

X-ray crystal structure analysis of **II**: formula $C_{84}H_{88}O_{16}{\cdot}C_3H_6O$, M = 1407.59, colorless crystal 0.50 × 0.40 × 0.15 mm, a = 15.001 (1), b = 19.678(1), c = 26.814 (1) Å, β = 92.73 (1)°, V = 7906.2 (7) Å^3, ρ_{calc} = 1.183 g cm^{-3}, μ = 0.81 cm^{-1}, empirical absorption correction ($0.960 \leq T \leq 0.988$), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 0.71073 Å, T = 198 K, ω and φ scans, 15493 reflections collected ($\pm h, \pm k, \pm l$), [$(\sin\theta/\lambda)$ = 0.50 Å^{-1}, 8431 independent (R_{int} = 0.050) and 5239 observed reflections [$I \geq 2\sigma(l)$], 870 refined parameters, R = 0.167, wR^2 = 0.383, max. residual

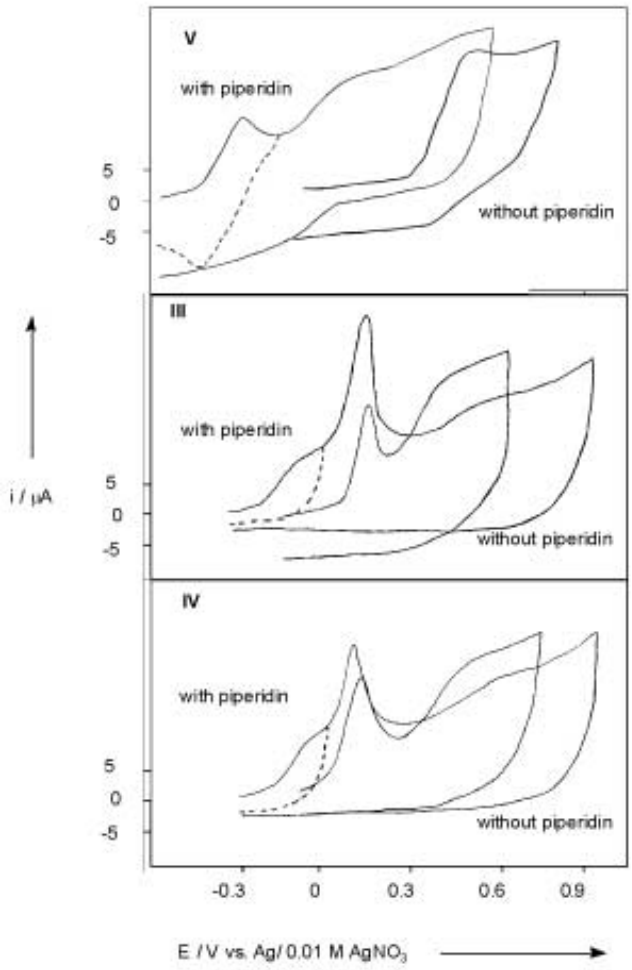


Figure 2. Cyclic voltammograms of **V**, **III** and **IV** in the presence and absence of piperidin.

electron density 1.14 (−0.47) e Å^{-3}, hydrogens calculated and refined as riding atoms.

Structure analysis was done as confirmation of the chemical composition. The result suffers from the weakly diffracting crystals.

The molecule is heavily disordered, one of the subunits (C41—O65) can only be refined with one relative ordered subunit (C11—O35) as a model (SAME command). CHO-groups at the phenyl substituents are refined with restraints (SADI command), in the worse subunit in addition some atoms have to been treated as isotropic (ISOR command). The phenyl groups were refined as rigid groups, the alkyl chains with geometrical restraints (SADI command). The solvent molecule is refined with isotropic thermal parameters and geometrical restrains (DFIX and FLAT commands). In addition the remaining electron density around 0.5, 0.5, 0.5 could not be assigned in a chemical meaningful way.

Data set was collected with a Nonius KappaCCD diffractometer, equipped with a rotating anode generator Nonius FR591. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN [13], absorption correction SORTAV [14], structure solution

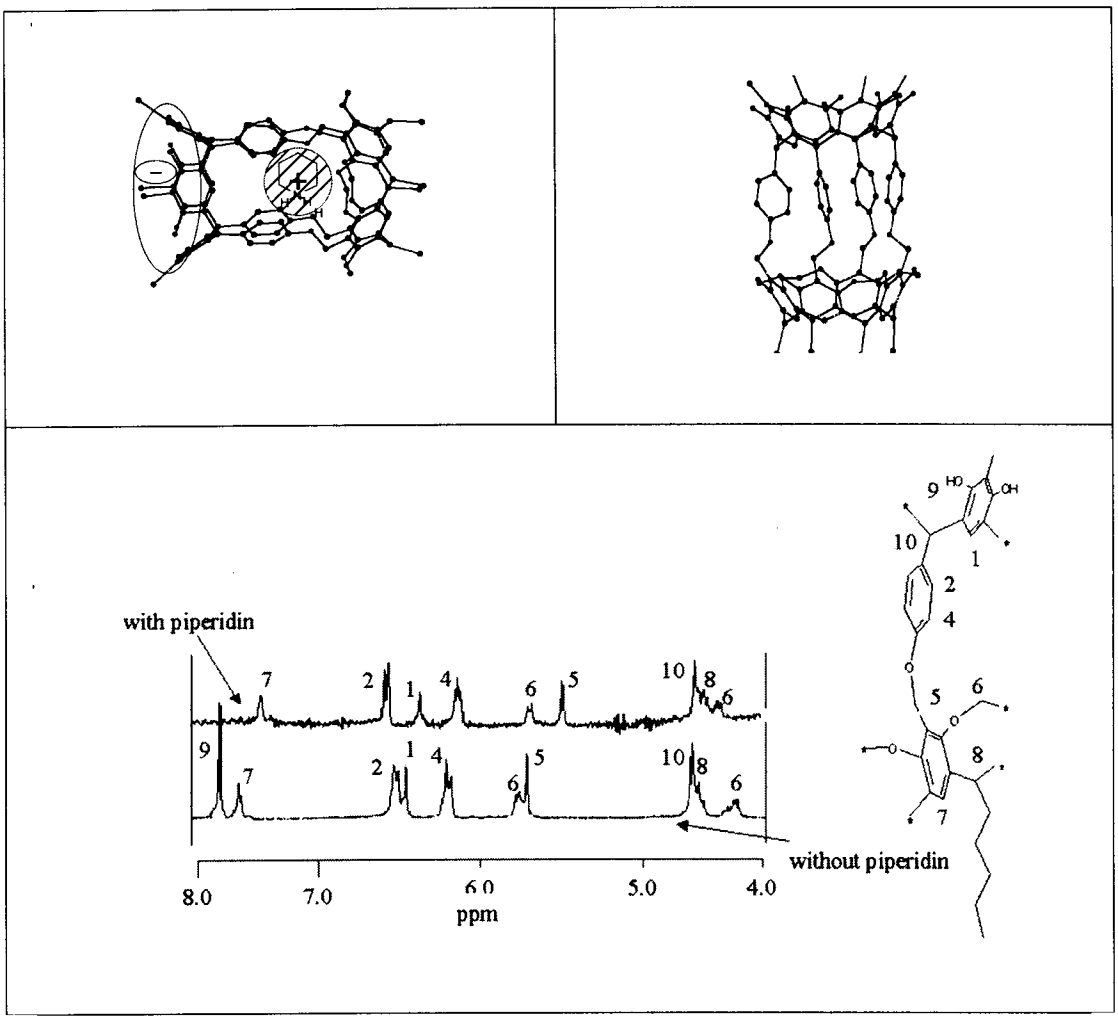


Figure 3. NMR ^{1}H of **IV** and aggregation of **IV** with piperidine.

SHELXS-97 [15], structure refinement SHELXL-97 [16], graphics SCHAKAL [17].

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication CCDC-183681. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223) 336-033, e-mail: deposit@ccdc.cam.ac.uk].

Results and discussion

The tetrakis(bromomethyl)calix[4]resorcinarene used as a starting material was synthesized as described in [9]. The rigid shape of its cavity was provided by methylene bridges between phenoxy-groups.

The tetraaldehyde **II** was prepared by reaction of **I** with *p*-hydroxybenzaldehyde (Scheme 1) and its structure was confirmed by X-ray analysis (Figure 1).

Further condensation of **II** with resorcinol or methylresorcinol resulted in the macrocycles **III** and **IV**, respectively. This approach does not have obvious limitations and can be applied for the synthesis of aromatic molecular tubes of desirable size.

^{1}H NMR-spectra characteristics of **III** and **IV** displayed formation of the second resorcin[4]arene ring. Signals of the methylene bridge of the new resorcin[4]arene macrocycle formed by condensation were observed at 4.94 ppm (**III**) and 4.74 ppm (**IV**) as well as the signals of new resorcinarene aromatic rings at 6.15 and 6.45 ppm (**III**) and at 6.6 ppm (**IV**).

For additional confirmation the formation of the second resorcin[4]arene cavity and the conservation of its electrochemical examination of compounds **III** and **IV** was performed [10]. As was shown earlier [11] the electron transfer process for calix[4]resorcinarene **V** is similar to that observed for bulky phenols – difficult reduction and easy oxidation (Scheme 2).

The latter is irreversible but becomes easier and reversible in the presence of base. Electrochemical oxidation of **III** and **IV** was observed as one irreversible peak at the same potential as for calix[4]resorcinarene **V** (E_o^{ox} = 0.46 V), Figure 2.

It was concluded that in all examined compounds resorcin[4]arene macrocycle is a redox center and it is not

influenced neither by methyl group in **IV** nor by the nature and space organization of the "tail".

In contrast to calix[4]resorcinarene **V**, on the voltammograms of **III** and **IV**, additionally to oxidation peak a low potential peak with $E^{ox}_{p,ads} = 0.20$ V and 0.13 V, respectively, was registered. The intensity of adsorption peak increases with the time of the electrode incubation in solution. Therefore, the adsorption of **III** and **IV** on the electrode surface was suggested, while for better soluble **V** it does not occur.

As expected, the addition of a base, piperidin, in solutions of **III–V** led to the easier oxidation of all compounds ($E^{ox}_p = 0.0$ V (**III**), 0.02 V (**IV**), −0.25 V (**V**)). However, addition of piperidin resulted in reversible oxidation only in the case of **V**, whereas for **III** and **IV** it was still irreversible. The intensity of oxidation peak increases with the increase of piperidin concentration. According to [11], oxidation was ascribed to the formation of the calix[4]resorcinarene radical, which was proved by EPR-spectroscopy. In comparison to **V** the observed decrease of the oxidation potential of **III** and **IV** is much smaller and no cavitand radical was proved by EPR. Therefore, it was suggested that life-time of radicals of **III** and **IV** is shorter than that in case of **V**. Also, no dependence of oxidation peak intensity on the piperidin concentration was observed. On the base of these results it was suggested that aggregation of **III** and **IV** with piperidine on the electrode surface takes place.

In order to confirm the aggregation of **IV** with piperidine, observed in the electrochemical study, ^{1}H NMR spectroscopy was used. The disappearance of the hydroxy-protons signal of **IV** (7.85 ppm) displayed their interaction with piperidin. On the other hand, the downfield shift of the bridged methylene protons (from 4.45 to 4.65 ppm) was accompanied by the change of their spin-spin constants and downfield shift of the aromatic protons signal of the middle bend (from 6.67 to 6.87 ppm) agree with inclusion of piperidin into the tube.

Acknowledgment

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