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Calix[6]arene mono-diazonium salt synthesis and covalent immobilization onto glassy carbon electrodes

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ABSTRACT

This paper describes the fast synthesis of a mono-aminated calix[6]arene. The immobilization of this macrocycle onto glassy carbon electrodes via diazonium salt chemistry and the electrochemical characterization of the grafted organic layer are also reported.

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Keywords: Calix[6]arene Diazonium salt Electrochemical grafting Covalent modification of carbon electrodes

1. Introduction

Functional electrodes are of great importance in several research areas, and especially for sensing purposes. The binding of complexing groups at the surface of the electrode allows the pre-concentration of the analyte, and thus ensures a better electrochemical response. In this context, the use of diazonium salts offers a very versatile method for the covalent grafting of several organic functions at the surface of conductive electrodes.^{1, 2} Our group recently reported the grafting of 4-carboxyphenyl diazonium salt for the detection of pollutants such as copper, lead or uranyl.³⁻⁵ In order to ensure a better selectivity of our sensors, we are now looking for molecules which are more selective towards a selected analyte. The complexing properties of macrocycles have been extensively studied, as the size of their cavity can be carefully choosen to host the desired analyte. Calixarenes are known as good chelatants for metallic ions, and especially calix[6]arene has a well-known affinity for the uranyl ion.^{6, 7,8} (Scheme 1) Calixarene-grafted electrodes would thus be of interest for the detection of uranyl in water.

Scheme 1: Structure of calix[6]arene

The calixarene can be either incorporated into the electrode material, or placed at the electrode surface by various methods. For example, calix[6]arene and an intermolecular complex between calix[6]arene and methyl viologen were incorporated to carbon paste modified electrodes, respectively for the detection of folic acid or the electroanalytical reduction of dioxygen.^{9,10} Calix[6]arene was incorporated as dopant in polypyrrole for uranyl complexation¹¹ or, together with TOPO ligand, was incorporated into a PVC membrane for the preparation of ion selective electrodes.¹² Langmuir-Blodgett films of calix[4]arene were developed for mercury detection.¹³ Becker et al. described the use of a negatively charged p-sulfonatocalix[6]arene interacting with a positively charged monolayer at the surface of an electrode, for uranyl detection.¹⁴ For analytical applications, the use of more robust bonds than simple electrostatic interactions are required. Gold electrodes can be easily modified by SAMs, and several examples of thiolated calixarene derivatives can be found in the literature: a thiolated calix[4]arene derivative was very recently assembled at an electrode surface for impedimetric biological assay¹⁵, or for the development of lead⁹ or uranyl¹⁶ sensors. However, for electroanalytical purposes, thiols present an inconvenient due to their possible oxidation. Calix[4]arenes bearing polypyrrole moieties were also polymerized at an electrode.^{17, 18} The phenolic moieties of the calixarene itself were also used for its electropolymerisation at an electrode surface.¹⁹ Cailler and Simonao also patented calix[4]arene derivative bearing pendant

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arms functionalized by diazonium salts for cesium complexation. $^{\rm 20}$

With uranyl complexation in mind, covalent grafting of the calix[6]arene via the lower rim^{21, 22} is impossible as it fully participates to the complexation of the metal ions. The upper ring must thus be functionalized, and the lower ring has to remain free. Lagrost et al. have recently reported the covalent grafting of a calix[4]arene, as a template for the nanostructuration of surfaces.²³ The grafting was realized via the formation of a tetradiazonium salt at the upper ring of the calixarene, and the subsequent electrografting on a glassy carbon surface. The number of anchoring points is not determined in that case, but is probably more than one per molecule. If one considers detection applications, the number of grafting points on the calix[6]arene should not be too elevated; in the case of calix[6]arene the complexation of ions is not due to the presence of pendant complexing arms, but to the size of the calixarene cavity itself. In order to allow the free conformational movements of the calix[6]arene, the anchoring of the macromolecule by only one point was preferred, in order to avoid any excess of rigidity in the film structure. We thus envisaged the synthesis of a calix[6]arene bearing only one diazonium group. The synthesis was envisaged as follow: first, the mono-nitration of the calix[6]arene, then the reduction of the nitro group and finally the formation of the diazonium salt in order to allow the electrografting of the macrocycle at the surface of a glassy carbon electrode. Our results are reported herein.

2. Discussion

2.1. Synthesis of the mono-amino calix[6]arene

We chose to use a protection-deprotection procedure: five of the six phenol groups of the calix[6]arene were protected by benzoyl groups. This reaction leads to penta-O-benzoylated calix[6]arene 2 in 55% yield.²⁴ In a second step, mono-nitration was then realized with 1.1 equivalent of nitric acid in an acetic acid/dichloromethane mixture to $3^{25, 26}$ As expected, mononitration occurred selectively on the para position of the more reactive free phenol group.²⁷ Compound 3 was the only compound obtained and the crude was used without further purification. Hydrolysis of the benzoyl groups was conducted in a mixture of sodium hydroxide and ethanol, under reflux. At first insoluble, the penta-protected calix[6]arene became soluble upon deprotection, leading to the fully deprotected derivative 4 in a 57% yield (two steps). Reduction of the nitro moiety of compound 4 was performed by zinc dust with hydrazinium monoformate as hydrogen donor in methanol, at 60°C²⁸ to give the mono-aminated calix[6]arene 5 in a 70% yield. (Scheme 2)



Scheme 2: Synthetic method. Reagents and conditions: (i) BzCl (5.1 equiv), pyridine, rt, overnight, 55%; (ii) nitric acid (1.1 equiv), dichloromethane/acetic acid: (3/1), 0 °C, 2 hours then rt, overnight; (iii) NaOH 15 wt%, EtOH, reflux, 7 hours, 57%; (iv) hydrazinium monoformate (7 mL), zinc dust (0.9 g), MeOH, 60°C, overnight. Bz = benzoyl.

2.2. Synthesis of the diazonium salt of calix[6]arene

Diazonium salts are relatively unstable and are mostly used as obtained in further reactions. Their formation are usually performed using diazotization agents in acidic water or acetonitrile.¹ In our case, both of the above conditions were tested on mono-amino calix[6]arene **5**, despite its low solubility in these solvents, even, in a case acetonitrile/sulfolane mixture (Table 1). There are indeed, to the best of our knowledge, very few studies reporting the synthesis of diazonium salts in other solvents. Thus, the formation of diazonium derivative **6** was performed using NaNO₂ in aqueous HBF₄ or NOBF₄ in acetonitrile as diazotization agents. As diazonium salt **6** may be unstable, the reactions were performed at low temperature and isolated with tetrafluoroborate as counterion.²⁹

Table 1. Synthesis of the diazonium salt^a



^aThe crude diazonium salt **6** was engaged as obtained in the grafting step

Upon addition of NOBF₄ in a suspension of calix-6-arene in an acetonitrile/sulfolane³⁰ 1/1 mixture, the reactants become soluble and the medium quickly turns to a reddish solution. The desired product **6** was then obtained by precipitation in diethyl ether (table 1, entry 1). The experiment was also conducted in a fluoroboric acid aqueous solution (table 1, entry 2). In this case the calix[6]arene stays insoluble even after the addition of sodium nitroxide, and we thus allowed the reaction to be performed in heterogeneous medium during 4 hours.

Both experiments lead to the formation of diazonium salt **6**. The infrared spectra (see **Supplementary Information**) showed in each case the expected characteristic $v_{N=N}$ band at 2222 cm⁻¹. It is interesting to note that the reaction could be performed in water despite the lack of solubility of the starting material and of the desired product.

2.3. Grafting of calix[6] arene on glassy carbon electrode

As it was mentioned before, the solubility of the diazonium salt of calix[6]arene is very low in acidic water. As a consequence, the electrografting experiments were performed in acetonitrile. The grafting step was performed by cyclic voltammetry (10 cycles), from the open circuit potential to - 0.9V, using a 1 mM solution of diazonium salt in a acetonitrile solution of tetrabutylammonium tetrafluoroborate (NBu₄BF₄, 0.1M) as a supporting electrolyte.

The cyclic voltammogram (Figure 1) shows a broad irreversible wave (around -0.4V) on the first scan that disappears after a few cyclic voltammetry scans. This behavior is characteristic of the grafting of diazonium salts: the disappearance of the wave corresponds to the formation of an organic layer on the surface that blocks the access of the diazonium cations to the electrode. Electrode rinsing under sonication in acetonitrile was performed in order to remove organic compounds adsorbed but not grafted on the surface.



Figure 1: Cyclic voltammograms (first cycles, 0.1 V.s^{-1} .) in ACN + 0.1 M NBu₄BF₄ at glassy carbon electrode with (black) or without (grey, dotted line) 1 mM Calix[6]arene diazonium salt.

In order to study the electrochemical behavior of the grafted electrode, cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) were performed with grafted electrodes into electrolyte solutions containing a redox probe, i.e. potassium ferricyanide.

As can be seen in Figure 2 and Figure 3, significant differences in the CV and EIS spectra were observed between calixarenegrafted electrodes and control experiments, whereby similar electrochemical procedure was performed but in a calixarene-free solution.

For the control non-grafted electrode, cyclic voltammetry in the presence of ferricyanide probe shows well-defined reduction and oxidation peaks, with a low peak-to peak potential separation (i.e. ΔE equals to 75 mV), suggesting a fast and reversible electron transfer process. In the case of the calixarene-grafted electrode, the increase in the electron transfer resistance can be detected by a significant drop in the anodic and cathodic peak currents, accompanied by an important shift in peak potentials. These observations are characteristic of a decrease in the electron transfer kinetics of the ferricyanide probe, due to the blocking effect of the grafted organic layer.



Figure 2: Cyclic Voltammograms obtained at glassy carbon electrode after cycling in a 0.1M acetonitrile solution of NBu_4BF_4 with (black) or without (grey) calix[6]arene in the presence of 1 mM K₃Fe(CN)₆ electrochemical probe + 0.1 M KCl aqueous solution. Scan rate is 200 mV.s⁻¹.

The EIS response is nearly a straight line for the control experiment (Rct equals to 1.1 k Ω), showing that the non-grafted surface of the electrode exhibits an expected fast electron transfer process with a diffusion limited step. The attachment of the calix-6-arene at the electrode surface leads to an increase in the electron transfer resistance (Rct), resulting in increases in the semicircular section of the Nyquist plot. As discussed for the CV experiment, this behavior evidences a blocking effect of the grafted organic layer on the electron transfer. However, the variations of Rct remain modest (Rct equals to 18.8 k Ω), indicating that the layer is probably not compact. This could be

due to the size of the macrocycle; steric hindrance may account for the quite low capacitance value and the possible observation of electrochemical processes at the grafted electrode. This was already observed by Sustrova et al. who showed by cyclic voltammetry and EIS that tetra-thiolated calix[4]arene form less compact monolayers at polycrystalline gold surface than linear undecanethiol.³¹



Figure 3: Nyquist plots of electrochemical impedance spectra obtained at glassy carbon electrode after cycling in a 0.1M acetonitrile solution of NBu₄BF₄ with (black) or without (grey) calix[6]arene in the presence of 1 mM K₃Fe(CN)₆ electrochemical probe + 0.1 M KCl aqueous solution. Fixed potential of 180 mV \pm 10 mV within the frequency range of 10²-10⁶ Hz, 5 points per decades of frequencies.

3. Conclusion

In summary, mono-aminated calix[6]arene was synthesized and its corresponding diazonium salt was successfully electrografted at the surface of glassy carbon electrodes. Characterization of the resulting electrodes shows an expected blocking effect of the grafted organic layer and the value of the observed charge transfer resistance suggest that it is probably of moderated compactness. The well-known affinity of calix[6]arene towards uranyl make these functional electrodes good candidates for its selective detection in water samples. Evaluation of the analytical performances of this electrode material is currently in progress.

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Supplementary Material

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Supplementary data associated with this article can be found in the online version.