ORGANIC
LETTERS

2004
Vol. 6, No. 5
791−794

Selective Binding of Aromatic Amines by Self-Assembled Monolayers of a Calix[6]crown-4 Derivative

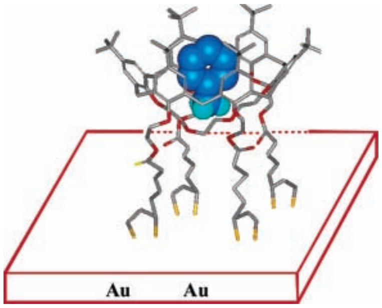
Sheng Zhang and Luis Echegoyen*

Department of Chemistry, Clemson University, Clemson, South Carolina 29634

luis@clemson.edu

Received January 7, 2004

ABSTRACT



A *p-tert*-butylcalix[6]crown-4 derivative immobilized on gold surfaces via self-assembly, endowed with a rigid cavity, can serve as a remarkably efficient sensor for aniline compared to alkylamines. The stability of the inclusion complex is attributed to the size fit and to the multipoint recognition motifs between the host monolayer and the guest aniline.

In biological and natural systems, amines are among the most important small molecules due to their widespread occurrence and physiological activity. Many studies have focused on the design and development of organic ammonium sensors.[1] Crown ethers were the first receptors used in this field, but more recently cryptands and cucurbituril have been employed.[2−4] The potential of calix[*n*]arenes as sensors for organic ammonium cations and other biologically important molecules such as amino acids and peptides has been given considerable attention.[5] Shinkai et al. reported that sulfonatocalix[n]arenes can bind one ($n = 4, 6$) or two anilinium ions ($n = 8$).[6] The same author suggested that calix[6]arene in its cone conformation could be a good host to include a quaternary ammonium cation.[7] Notable examples also include the selective recognition of isomeric butylammonium cations published by Pappalardo.[8−10] For specific guests such as alkylammonium cations, a drastic increase in selectivity was observed when calix[5]arene instead of its larger analogue, calix[6]arene, was used as receptor.[8] One of the principal determinants for controlling the formation of inclusion complexes is a good size correspondence between the guest and the host.

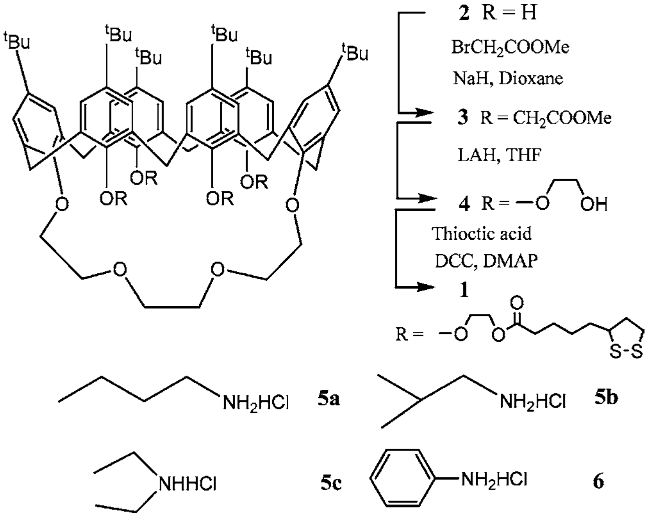
To explore the potential applications of calix[*n*]arenes as ammonium sensors, we decided to prepare suitable receptors based on calix[6]arene. A conformationally fixed calix[6]arene cavity is very difficult to obtain because of its flexibility. It is well-known that more rigid cavities can form more stable inclusion complexes. To prepare a more rigid

---

(1) Bühlmann, P.; Pretsch, E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1592.
(2) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529.
(3) Buschmann, H.-J.; Mutihac L.; Jansen, K. *J. Inclusion Phenom.* **2001**, *39*, 1.
(4) Meschke, C.; Buschmann, H.-J.; Schollmeyer, E. *Polymer* **1998**, *40*, 945.
(5) Abraham, W. *J. Inclusion Phenom.* **2002**, *43*, 159.
(6) Shinkai, S.; Araki, K.; Manabe, O. *J. Am. Chem. Soc.* **1988**, *110*, 7214.
(7) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933.
(8) Arnaud-Neu, F.; Fuangswasdi, S.; Notti, A.; Pappalardo, S.; Parisi, M. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 112.
(9) De Salvo, G.; Gattuso, G.; Notti, A.; Parisi, M. F.; Pappalardo, S. *J. Org. Chem.* **2002**, *67*, 684.
(10) Giannetto, M.; Mori, G.; Notti, A.; Pappalardo, S.; Parisi, M. F. *Anal. Chem.* **1998**, *70*, 4631.

10.1021/ol049957n CCC: $27.50 © 2004 American Chemical Society
Published on Web 02/05/2004

Scheme 1. Synthesis of the Calix[6]crown-4 Derivative **1**



calix[6]arene cavity, we synthesized the target compound **1**, making the calix[6]arene cavity in a frozen cone conformation by introducing a crown ether bridge at the lower rim of the calix[6]arene.[11] Then, the cavity was further immobilized by the formation of self-assembled monolayers on gold surfaces. Their recognition ability for ammonium cations was probed using CV and impedance spectroscopy. Most reports about the binding between calix[*n*]arenes and organic cations have been done in solution.[5−9,12,13] Reports about the incorporation of calix[*n*]arenes into SAMs to investigate their ammonium cation recognition properties are very rare.[14]

The synthetic procedure to prepare the target compound **1** is depicted in Scheme 1. Calix[6]crown-4 derivative **2** was obtained by reacting *p*-*tert*-butylcalix[6]arene with triethylene glycol ditosylate according to a published procedure.[11] Further treatment of **2** with methyl bromoacetate in dioxane[15] using NaH as a base produced **3** in a yield of 56%. Reduction of **3** with $LiAlH_4$ in dry THF gave compound **4** in 62% yield. Subsequent treatment of **4** with thioctic acid in the presence of DCC and DMAP afforded the target compound **1** (74%). The structure and conformation of **1** were confirmed by ^1H and ^{13}C NMR, MS, and elemental analysis.[16] The ^1H NMR spectrum shows two singlets in a ratio of 1:2 for the *tert*-butyl groups, the doublets for the methylene bridge protons and three single peaks for the protons on the benzene rings, indicating a 1,4-bridged cone calix[6]arene product.

Gold bead electrodes were made from gold wire as described earlier.[17−19] SAMs of **1** were prepared by dipping the gold beads into CH_2Cl_2 solutions of **1** for 48 h. After immersing the monolayer modified gold bead into CH_2Cl_2 for 10 min, they were rinsed with copious CH_2Cl_2 and dried under a stream of Ar. SAM modified gold beads were used as working electrodes to record cyclic voltammograms in an electrolyte consisting of 0.1 M NaCl and 1 mM $Ru(NH_3)_6$-Cl aqueous solution with a platinum mesh and Ag/AgCl as counter and reference electrode, respectively. Electrochemical impedance experiments were conducted in the same electrolyte at the formal redox potential of the $Ru(NH_3)_6^{3+/2+}$ probe, using a frequency range between 1K Hz and 0.1 Hz.

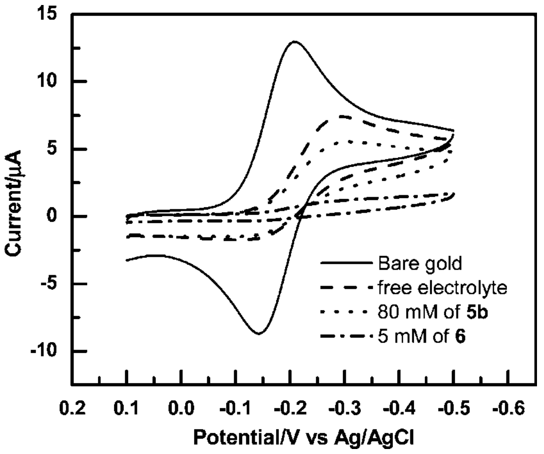


Figure 1. Cyclic voltammogram of $Ru(NH_3)_6^{3+/2+}$ in 0.1 M NaCl at bare gold (solid line) and SAM of **1** modified gold electrodes before (dashed line) and after addition of 80 mM **5b** (dotted line) or 5 mM **6** (dashed dotted line) at a scan rate of 0.1 v/s.

SAMs derived from **1** were characterized by observing their CV blocking effect on the $Ru(NH_3)_6^{3+/2+}$ redox couple as shown in Figure 1 (dashed line). Compared to the CV response of the redox couple at a bare gold electrode (solid line), a pronounced attenuation of the cathodic current and an almost complete disappearance of the corresponding anodic current reveal that SAMs on gold surfaces block the redox processes reasonably well. Figure 1 (dotted line) shows the CV response for the $Ru(NH_3)_6^{3+/2+}$ redox couple at a SAM modified electrode in the presence of 80 mM of isobutylammonium chloride, suggesting further inhibition of electron transfer at the interface. This observation demonstrates that the calix[6]crown-4 cavity can bind the positively charged ammonium cations, which electrochemically inhibits the approach of the positively charged redox probe. However, the binding forces between the calix[6]crown-4 derivative SAM and the alkylammonium cations are not very strong since the observed current reduction is not so pronounced. In sharp contrast, addition of anilinium chloride to the electrolyte results in a dramatic decrease of the faradaic current, as shown in Figure 1 (dashed dotted line). Both

---

(11) Li, J. S.; Chen, Y. Y.; Lu, X. R. *Tetrahedron* **1999**, *55*, 10365.

(12) Cho, Y. L.; Rudkevich, D. M.; Rebeck, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 9868.

(13) Bohmer. V.; Cort, A. D.; Mandolini, L. *J. Org. Chem.* **2001**, *66*, 1900.

(14) Nakano, K.; Tanaka, S.; Takagi, M.; Shinkai, S. *Bunseki Kagaku* **2002**, *51*, 409. Nakano, K.; Tanaka, S.; Takagi, M.; Shinkai, S. *Chem. Lett.* **2000**, 60.

(15) Chen, Y. Y.; Yang, F. F.; Gong, S. L. *Tetrahedron Lett.* **2000**, *41*, 4815.

(16) Characterization data of **1** are available from Supporting Information

(17) Zhang, S.; Echegoyen, L. *Tetrahedron Lett.* **2003**, *44*, 9079.

(18) Bandyopadhyay, K.; Liu, H.; Liu, S.-G.; Echegoyen, L. *Chem. Commun.* **2000**, 141.

(19) Liu, H.; Liu, S.-G.; Echegoyen, L. *Chem. Commun.* **1999**, 1493.

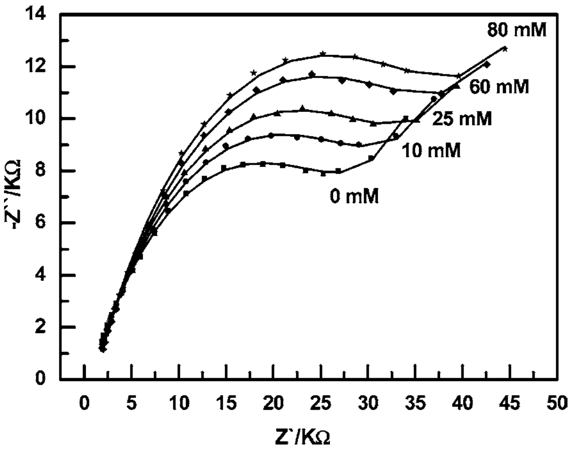


Figure 2. Impedance response of $Ru(NH_3)_6^{3+/2+}$ at the monolayer modified gold electrode in the absence and presence of increasing concentrations of **5b**. The solid lines represent the fits of the experimental points.

cathodic and anodic currents almost completely disappeared. Note that only 5 mM anilinium chloride was added to the electrolyte, compared to 80 mM in the case of isobutylammonium chloride. This means that the SAMs exhibited a remarkable recognition ability for anilinium chloride relative to alkylammonium cations. As a control, the CV response of the redox couple at a bare gold electrode in the presence of 30 mM of anilinium chloride is exactly the same as that in the absence of ammonium cations.

The SAMs of **1** were further investigated by electrochemical impedance spectroscopy. Figure 2 shows the complex impedance response of the redox couple at a monolayer modified gold electrode in the presence of increasing concentrations of isobutylammonium chloride. A simple Randles equivalent circuit[20] to describe the impedance consists of a charge-transfer resistance, R_{ct}, in series with a Warburg impedance and in parallel with a total interfacial capacitance. The R_{ct} value of the monolayer can be affected by changes in the surface charge and is thus capable of detecting the effect of the charged guest species when bound to the SAMs. Addition of isobutylammonium chloride to the electrolyte increases the R_{ct} value from 32.5 KΩ in the absence of ammonium cations to 50.5 KΩ in the presence of 80 mM of isobutylamine hydrochloride (shown in Figure 2). This indicates some interaction between the guest and the calix[6]crown-4 SAMs and the consequent repulsion of the positively charged redox probe, consistent with the CV blocking observations. Addition of diethylammonium and *n*-butylammonium chloride to the electrolyte gives rise to an increase of the R_{ct} value. The alkylammonium cations interact with the host monolayer in the following order: *n*-butylammonium > isobutylammonium > diethylammonium. This sequence follows the expected dependence based on steric factors.

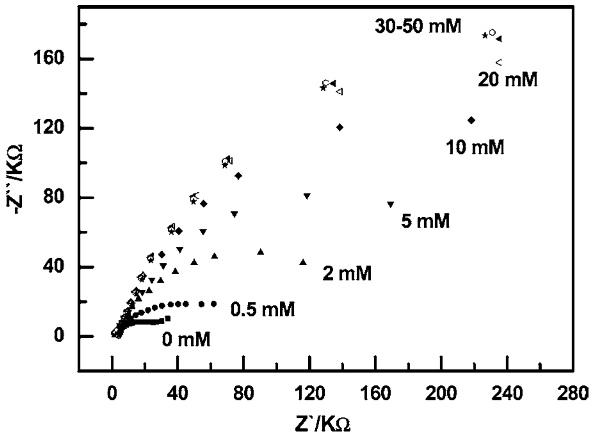


Figure 3. Impedance response of $Ru(NH_3)_6^{3+/2+}$ at the monolayer modified gold electrode in the absence and presence of increasing concentrations of **6**.

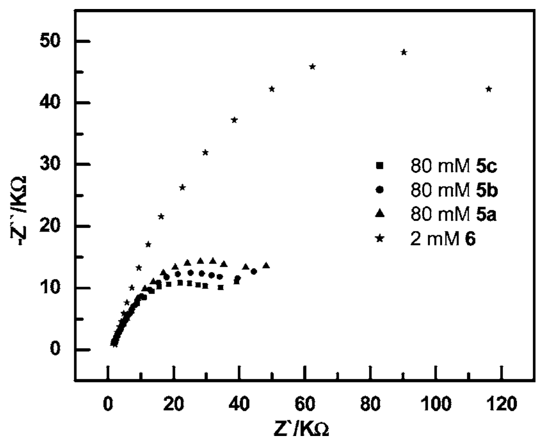


Figure 4. Impedance response of $Ru(NH_3)_6^{3+/2+}$ at the monolayer modified gold electrode in the presence of 80 mM of **5a**−**c** and 2 mM of **6**.

More interestingly, the binding affinity of the same monolayer toward anilinium chloride is much larger. As shown in Figure 3, addition of anilinium chloride to the electrolyte results in a dramatic increase in the value of R_{ct} from 32.5 KΩ in the absence of ammonium cations to a limiting value of 507.9 KΩ in the presence of aniline hydrochloride above 30 mM. Competition experiments were also conducted. In the presence of an 80 mM concentration of any of the alkylammonium chlorides, addition of 2 mM anilinium chloride to the electrolyte gave rise to a remarkable increase of the R_{ct} value, indicating that all ammonium salts are effectively displaced by anilinium chloride. Figure 4 shows a comparison of the response of **1** with alkylammonium and anilinium chloride. In the presence of an 80 mM concentration of any alkylammonium chloride, the largest R_{ct} value is 52.6 KΩ. However, addition of only 2 mM

---

(20) Finklea, H. O.; Snider, D. A.; Fedyk, J.; Sabatani, E.; Gafni, Y.; Rubinstein, I. *Langmuir* **1993**, *9*, 3660.

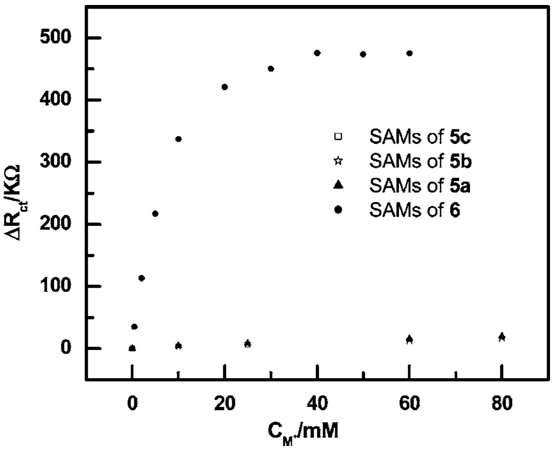


Figure 5. Comparative plot of the change of R_{ct} versus concentrations of **5a**−**c** and **6**.

anilinium chloride to the electrolyte gave a R_{ct} value of 145.6 KΩ, showing that anilinium chloride interacts with the monolayer much more strongly than the alkylammonium cations. The remarkably efficient recognition of anilinium chloride by SAMs of **1** is probably related to a good size correspondence between the calix[6]crown-4 cavity and the guest aniline. Several attraction forces such as the cation−π interaction, hydrophobic interaction, and CH_3−π and π−π stacking between anilinium and the host monolayer may contribute to the molecular recognition.[5,8,9,21]

Figure 5 shows a plot of ΔR_{ct} versus concentrations of different ammonium cations. The monolayers show an initially linear and steep increase in R_{ct} at low concentrations of anilinium chloride. Once the concentration of the guest reaches 30 mM, the R_{ct} approaches a limiting value. This observation reveals that the binding sites on the surface are saturated when the concentration of guest cations in the electrolyte is high enough. Furthermore, SAMs of **1** exhibit a linear increase in R_{ct} with increased concentrations of the three alklyammonium cations. However, the increase of R_{ct} is very slow compared to the significant increase of R_{ct} in the case of anilinium chloride.

We also studied the binding affinity of **1** toward other biogenic aromatic amines such as dopamine. Dopamine is of special importance because it belongs to a family of catecholamine neurotransmitters.[22] Both CV blocking experiments and impedance spectroscopy showed that SAMs of **1** exhibit much better recognition for dopamine than for the alkylammonium salts. They are thus a potential candidate for sensing dopamine and its analogues. Efforts to improve the selectivity of the sensor for dopamine are currently in progress.

In conclusion, SAMs of a calix[6]crown-4 derivative, **1**, were formed on gold surfaces and their ammonium cation recognition properties were investigated by cyclic voltammetry and impedance spectroscopy. A remarkably sensitive response for anilinium was observed and is attributed to a proper size fit and multipoint binding forces between the host and the guest. By suitable modification, the system could become a potential receptor for biologically important amines.

Acknowledgment. Financial support from the National Science Foundation (Grant No. CHE-0135786) is greatly appreciated.

Supporting Information Available: Characterization data for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049957N

---

(21) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/pi Intercation, Evidence, Nature and Consequences*; Wiley-VCH: New York, 1998.

(22) Inoue, M. B.; Velazquez, E. F.; Inoue, M.; Fernando, Q. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2113.