J|A|C|S
ARTICLES
Published on Web 12/01/2004

Assembly of a Supramolecular Capsule on a Molecular Printboard

Francesca Corbellini,[†] Alart Mulder,[†] Andrea Sartori,[†,‡] Manon J. W. Ludden,[†] Alessandro Casnati,[‡] Rocco Ungaro,[‡] Jurriaan Huskens,*[,†] Mercedes Crego-Calama,*[,†] and David N. Reinhoudt*[,†]

Contribution from the Laboratory of Supramolecular Chemistry and Technology, MESA+ Institute for Nanotechnology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands, and Dipartimento di Chimica Organica e Industriale, Universitá degli Studi di Parma, Parco Area delle Scienze 17/A, 43100 Parma, and Consorzio INSTM Via Varchi 59, Firenze, Italy

Received June 1, 2004; E-mail: j.huskens@utwente.nl; m.cregocalama@utwente.nl; d.n.reinhoudt@utwente.nl

Abstract: A molecular capsule based on ionic interactions between two oppositely charged calix[4]arenes, **1** and **2**, was assembled both in solution and on a surface. In solution, the formation of the equimolar assembly **1·2** was studied by ^{1}H NMR, ESI-MS, and isothermal titration calorimetry, giving an association constant (K_a) of 7.5×10^5 M^{-1}. A β-cyclodextrin self-assembled monolayer (β-CD SAM) on gold was used as a molecular printboard to anchor the tetraguanidinium calix[4]arene (**2**). The binding of tetrasulfonate calix[4]arene **1** was monitored by surface plasmon resonance spectroscopy. Rinsing of the surface with a high ionic strength aqueous solution allows the removal of the tetrasulfonate calix[4]arene (**1**), while by rinsing with 2-propanol it is possible to achieve the complete desorption of the tetraguanidinium calix[4]-arene (**2**) from the β-CD SAM. The K_a for the capsule formation on a surface is 3.5×10^6 M^{-1}, thus comparing well with the K_a determined in solution.

Introduction

Noncovalent interactions have been exploited in solution chemistry to direct the assembly of molecules into nanometer-sized supramolecular structures.[1] Considerable efforts have been devoted to the synthesis of molecular containers[2] possessing a confined space for the stabilization of reactive intermediates[3] and for catalysis.[4] In view of applications such as encapsulation of drugs and their active transport or delivery, the design of water-compatible, dynamic noncovalent containers is actively investigated. Various methodologies have been used to obtain molecular containers via noncovalent synthesis, mostly based on hydrogen bonding[5] or metal−ligand interactions.[6] Only recently, ionic interactions have been used to arrange components into reversible and well-defined molecular architectures.[7]

Currently there is considerable interest in nanoscience and nanotechnology focused on the development of functional

[†] University of Twente.
[‡] Universitá degli Studi di Parma.

(1) (a) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229−2260. (b) Greig, L. M.; Philp, D. *Chem. Soc. Rev.* **2001**, *30*, 287−302. (c) Higler, I.; Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **1998**, 2689−2702. (d) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382−2426. (e) Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem Rev.* **2000**, *100*, 853−908. (f) Stang, P. J.; Olenyuk, B. *Acc. Chem. Res.* **1997**, *30*, 502−518. (g) Olenyuk, B.; Fechtenkötter, A.; Stang, P. J. *J. Chem. Soc., Dalton Trans.* **1998**, 1707−1728.

(2) For reviews on molecular containers, see: (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (b) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018−1033. (c) Rudkevich, D. M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 393−413. (d) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488−1508. (e) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931−967. (f) Russel-Seidel, S.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972−983.

(3) (a) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024−1027. (b) Körner, S. K.; Tucci, F. C.; Rudkevich, D. M.; Heinz, T. *Chem.−Eur. J.* **2000**, *6*, 187−195. (c) Chen, J.; Körner, S.; Craig, S. L.; Rudkevich, D. M.; Rebek, J., Jr. *Nature* **2002**, *415*, 385−386. (d) Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **1999**, *121*, 1397−1398. (e) Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122*, 6311−6312. (f) Warmuth, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1347−1350. (g) Warmuth, R. *Chem. Commun.* **1998**, 59−60.

(4) (a) Warmuth, R. *J. Inclusion Phenom. Macrocyclic Chem.* **2000**, *37*, 1−37. (b) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50−52. (c) Kang, J.; Santamaria, J.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 7389−7390. (d) Kang, J.; Hilmersson, G.; Santamaria, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3650−3656. (e) Yoshizawa, M.; Takeyama, Y.; Kusukawa, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1347−1349. (f) Yoshizawa, M.; Takeyama, Y.; Okano, T.; Fujita, M. *J. Am. Chem. Soc.* **2003**, *125*, 3243−3247. (g) Makeiff, D. A.; Vishnumurthy, K.; Sherman, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 9558−9559. (h) Kusukawa, T.; Yoshizawa, M.; Fujita, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1879−1884.

(5) (a) Yamanaka, M.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 2939−2943. (b) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286. (c) Rebek, J., Jr. *Chem. Soc. Rev.* **1996**, *25*, 255−264. (d) Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643. (e) Rebek, J., Jr. *Acc. Chem. Res.*, **1999**, *32*, 278−286. (f) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469−472. (g) Kerchoffs, J. M. C. A.; van Leeuven, F. W. R.; Spek A. L.; Kooijman, H.; Crego-Calama, M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5717−5722. (h) Sansone, F.; Baldini, L.; Casnati, A.; Chierici, E.; Faimani, G.; Ugozzoli, F.; Ungaro, R. *J. Am. Chem. Soc.* **2004**, *126*, 6205−6206. (i) Rincón, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **2001**, *123*, 3493−3498. (j) Kobayashi, K.; Ishii, I.; Sakamoto, S.; Shirasake, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 10615−10624.

(6) (a) Kryschenko, Y. K.; Seidel, S. R.; Muddiman, D. C.; Nepomuceno, A. I.; Stang, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9647−9652. (b) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, 509−518. (c) Takeda, N.; Umemoto, K.; Yamaguchi, K.; Fujita, M. *Nature* **1999**, *398*, 794−796. (d) Jacopozzi, P.; Dalcanale, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 613−615. (e) Radhakrishnan, U.; Schweiger, M.; Stang, P. J. *Org. Lett.* **2001**, *3*, 3141−3143. (f) Leung, D. H.; Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 963−966. (g) Fox, O. D.; Leung, J. F. Y.; Hunter, J. M.; Dalley, N. K.; Harrison, R. G. *Inorg. Chem.* **2000**, *39*, 783−790.

 10.1021/ja046780j CCC: $27.50

materials for applications as (bio)sensors or electronical or optical devices.[8] The principles, such as chemical information and programmability, that govern supramolecular organization of molecules in solution have been transferred to surfaces to provide new materials that exhibit features such as dynamics and reversibility.[9] Self-assembled monolayers (SAMs) on gold[10] have been used to organize monomolecular films of supramolecular systems[11] and to study the binding interactions at the monolayer/solution interface.[12] Moreover, the understanding of the rules that govern the noncovalent association of molecules into more complex structures has allowed the construction of highly structured multilayer architectures on gold surfaces.[13]

The self-assembly of supramolecular containers on surfaces is thus far restricted to very few cases. The confinement of a resorcin[4]arene-based carceplex in a SAM on gold has been reported by our group.[14] Furthermore, the formation of a molecular cage based on metal−ligand coordination has been achieved at a surface, with one of the components directly anchored to a gold surface.[15]

We have recently reported that molecular capsules based on ionic interactions between two oppositely charged components can be formed.[7e−16] Here, we describe a strategy for the self-assembly of molecular containers based on ionic interactions at the surface, which involves the use of a molecular printboard[17] as a template to control the orientation and positioning of the molecules. We have defined a molecular printboard as a self-assembled monolayer on a surface that has recognition sites to which molecules can be anchored through specific interactions.

Our molecular printboard is a highly ordered β-cyclodextrin self-assembled monolayer (β-CD SAM) on gold. To build the supramolecular capsule on the surface, we used the noncovalent attachment of one component of the molecular capsule on the β-CD SAM followed by the self-assembly of the second component at the interface. We will demonstrate that the orthogonal noncovalent interactions involved in the anchoring and assembly of the molecular capsule allow the stepwise association and dissociation of the two components from the surface. The effectiveness of the formation of the molecular capsule on the solid support and in solution has been compared.

Results and Discussion

The molecular capsule **1·2** is the result of the self-assembly between the oppositely charged building blocks, that is, tetrasulfonate calix[4]arene **1** and the tetraguanidinium calix[4]arene **2** (Figure 1). Compound **2** was functionalized at the lower rim with four adamantyl units able to form stable inclusion complexes with native β-CD in solution and with surface-confined β-CD cavities (vide infra). The long poly(ethylene glycol) chains space the charged guanidinium groups of **2** from the β-CD cavities and allow the multivalent interaction with the molecular printboard.

Tetrasulfonate calixarene **1** was synthesized according to a literature procedure,[18] while compound **2** was prepared as outlined in Scheme 1. 1-Adamantyl tetraethylene glycol tosylate **3** was reacted with 5,11,17,23-tetra-*p*-*tert*-butyl-25,26,27,28-tetrahydroxy-calix[4]arene at 80 °C in dry DMF using NaH as a base to give the tetra(adamantyl-tetraethylene glycol)-functionalized calix[4]arene **4**. Substitution of the *tert*-butyl for nitro groups via an ipso-nitration reaction using glacial acetic acid and nitric acid gave tetranitro-calix[4]arene **5**. Low temperature and dry conditions are prerequisites for this reaction in order to prevent elimination of the adamantyl groups under the strongly acidic conditions used. Reduction of the nitro groups using hydrazine monohydrate and Pd/C in absolute ethanol gave the

(7) (a) Zadmard, R.; Schrader, T.; Grawe, T.; Kraft, A. *Org. Lett.* **2002**, *4*, 1687−1690. (b) Zadmard, R.; Junkers, M.; Schrader, T.; Grawe, T.; Kraft, A. *J. Org. Chem.* **2003**, *68*, 6511−6521. (c) Fiammengo, R.; Timmerman, P.; de Jong, F.; Reinhoudt, D. N. *Chem. Commun.* **2000**, 2313−2314. (d) Grawe, T.; Schrader, T.; Gurrath, M.; Kraft, A.; Osterod, F. *Org. Lett.* **2000**, *2*, 29−32. (e) Corbellini, F.; Fiammengo, R.; Timmerman, P.; Crego-Calama, M.; Versluis, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 6569−6575.

(8) (a) Swalen, J. D.; Allara, D. L.; Andrade, J. D.; Chandross, E. A.; Garoff, S.; Israelachvili, J.; MacCarthy, T. J.; Murray, R.; Pease, R. F.; Rabolt, J. F.; Wynn, K. J.; Yu, H. *Langmuir* **1987**, *3*, 932−950. (b) Mrksich, M.; Whitesides, G. M. *Trends Biotechnol.* **1995**, *13*, 228−235. (c) Shipway, A. N.; Katz, E.; Willner, I. *Chem. Phys. Chem.* **2000**, *1*, 18−52. (d) Willner, I.; Katz, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 1180−1218. (e) Leech, D. *Chem. Soc. Rev.* **1994**, *23*, 205−213. (f) Granick, S.; Kumar, S. K.; Amis, E. J.; Antonietti, M.; Balazs, A. C.; Chakraborty, A. K.; Grest, G. S.; Hawker, C.; Janmey, P.; Kramer, E. J.; Nuzzo, R.; Russell, T. P.; Safinya, C. R. *J. Polym. Sci., Part B: Polym. Phys.* **2003**, *41*, 2755−2793. (g) Matsui, H.; Porrata, P.; Douberly, G. E., Jr. *Nano Lett.* **2001**, *1*, 461−464. (h) Ball, P. *Nature* **2000**, *406*, 118−120. (i) Chen, J.; Reed, M. A.; Rawlett, A. M.; Tour, J. M. *Science* **1999**, *286*, 1550−1552. (j) Gittins, D. I.; Bethell, D.; Schiffrin, D. J.; Nichols, R. J. *Nature* **2000**, *408*, 67−69. (k) Fendler, J. H. *Chem. Mater.* **2001**, *13*, 3196−3210.

(9) (a) Lehn, J.-M. *Science* **1996**, *35*, 538−540. (b) Garcia-Lopez, J. J.; Zapotoczny, S.; Timmerman, P.; van Veggel, F. C. J. M.; Vancso, G. J.; Crego-Calama, M.; Reinhoudt, D. N. *Chem. Commun.* **2003**, 352−353. (c) Friggeri, A.; van Manen, H.-J.; Auletta, T.; Li, X.-M.; Zapotoczny, H.; Schönherr, H.; Vancso, G. J.; Huskens, J.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2001**, *123*, 6388−6395.

(10) (a) Ulman, A. *Chem. Rev.* **1996**, *96*, 1533−1554. (b) Ulman, A. *Acc. Chem. Res.* **2001**, *34*, 855−863. (c) Ulman, A. *An Introduction to Ultrathin Organic Films*; Academic Press: Boston, 1991. (d) Ulman, A. *Thin Films*; Academic Press: Boston, 1999; Vol. 23. (e) Gupta, P.; Loos, K.; Korniakov, A.; Spagnoli, C.; Cowman, M.; Ulman, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 520−523.

(11) (a) Dubois, L. H.; Nuzzo, R. G. *Annu. Rev. Phys. Chem.* **1992**, *43*, 437−463. (b) Rojas, M. T.; Königer, R.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1995**, *117*, 336−343. (c) Thoden van Velzen, E. U.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 3597−3598. (d) Huisman, B.-H.; Thoden van Velzen, E. U.; van Veggel, F. C. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Tetrahedron Lett.* **1995**, *18*, 3273−3276. (e) Nelles, G.; Weisser, M.; Back, R.; Wohlfart, P.; Wenz, P.; Wenz, G.; Mittler-Neher, S. *J. Am. Chem. Soc.* **1996**, *118*, 5039−5046. (f) Zhang, S.; Echegoyen, L. *Org. Lett.* **2004**, *6*, 791−794. (g) Nissink, J. W. M.; Wink, T.; van der Mass, J. H. *J. Mol. Struct.* **1999**, *479*, 65−73. (h) Yang, X.; McBranch, D.; Swanson, B.; Li, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 538−540.

(12) (a) Maeda, Y.; Fukuda, T.; Yamamoto, H.; Kitano, H. *Langmuir* **1997**, *13*, 4187−4189. (b) Arias, F.; Godinez, L. A.; Wilson, S. R.; Kaifer, A. E.; Echegoyen, L. *J. Am. Chem. Soc.* **1996**, *118*, 6086−6087. (c) Sigal, G. B.; Bamdad, C.; Barberis, A.; Strominger, J.; Whitesides, G. M. *Anal. Chem.* **1996**, *68*, 490−497. (d) Brown, S. A.; Easton, C. J.; Kelly, J. B. *J. Inclusion Phenom. Macrocyclic Chem.* **2003**, *46*, 167−173. (e) Banerjee, I. A.; Yu, L.; Matsui, H. J. *J. Am. Chem. Soc.* **2003**, *125*, 9542−9543. (f) Fragoso, A.; Caballero, J.; Almirall, E.; Villalonga, R.; Cao, R. *Langmuir* **2002**, *18*, 5051−5054. (g) Beulen, M. W. J.; Bügler, J.; De Jong, M. R.; Lammerink, B.; Huskens, J.; Schönherr, H.; Vancso, G. J.; Boukamp, B. A.; Wieder, H.; Offenhäuser, A.; Knoll, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Chem.−Eur. J.* **2000**, *6*, 1176−1183.

(13) (a) Hatzor, A.; Moav, T.; Cohen, H.; Matlis, S.; Libman, J.; Vaskevich, A.; Shanzer, A.; Rubinstein, I. *J. Am. Chem. Soc.* **1998**, *120*, 13469−13477. (b) Moav, T.; Hatzor, A.; Cohen, H.; Libman, J.; Rubinstein, I.; Shanzer, A. *Chem.−Eur. J.* **1998**, *4*, 502−507. (c) Hatzor, A.; Moav, T.; Yochelis, S.; Vaskevich, A.; Shanzer, A.; Rubinstein, I. *Langmuir* **2000**, *16*, 4420−4423. (d) Godínez, L. A.; Lin, J.; Muñoz, M.; Coleman, A. W.; Rubin, S.; Parikh, A.; Zawodzinski, T. A., Jr.; Loveday, D.; Ferraris, J. P.; Kaifer, A. E. *Langmuir* **1998**, *14*, 137−144.

(14) (a) Huisman, B. H.; Rudkevich, D. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1996**, *118*, 3523−3524. (b) Huisman, B. H.; Rudkevich, D. M.; Farrán, A.; Verboom, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **2000**, 269−274.

(15) (a) Levi, S.; Guatteri, P.; van Veggel, F. C. J. M.; Vancso, G. J.; Dalcanale, E.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 1892−1896. (b) Menozzi, E.; Pinalli, R.; Speets, E.; Ravoo B.-J.; Dalcanale, E.; Reinhoudt, D. N. *Chem.−Eur. J.* **2004**, *10*, 2199−2206.

(16) Corbellini, F.; Di Costanzo, L.; Crego-Calama, M.; Geremia, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2003**, *125*, 9946−9947.

(17) (a) Huskens, J.; Deij, M. A.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4467−4471. (b) Auletta, T.; Dordi, B.; Mulder, A.; Sartori, A.; Onclin, S.; Bruinink, C. M.; Péter, M.; Nijhuis, C. A.; Beijleveld, H.; Schönherr, H.; Vancso, G. J.; Casnati, A.; Ungaro, R.; Ravoo, B. J.; Huskens, J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 369−373.

(18) Fiammengo, R.; Timmerman, P.; Huskens, J.; Versluis, K.; Heck, A. J. R.; Reinhoudt, D. N. *Tetrahedron* **2002**, *58*, 757−764.

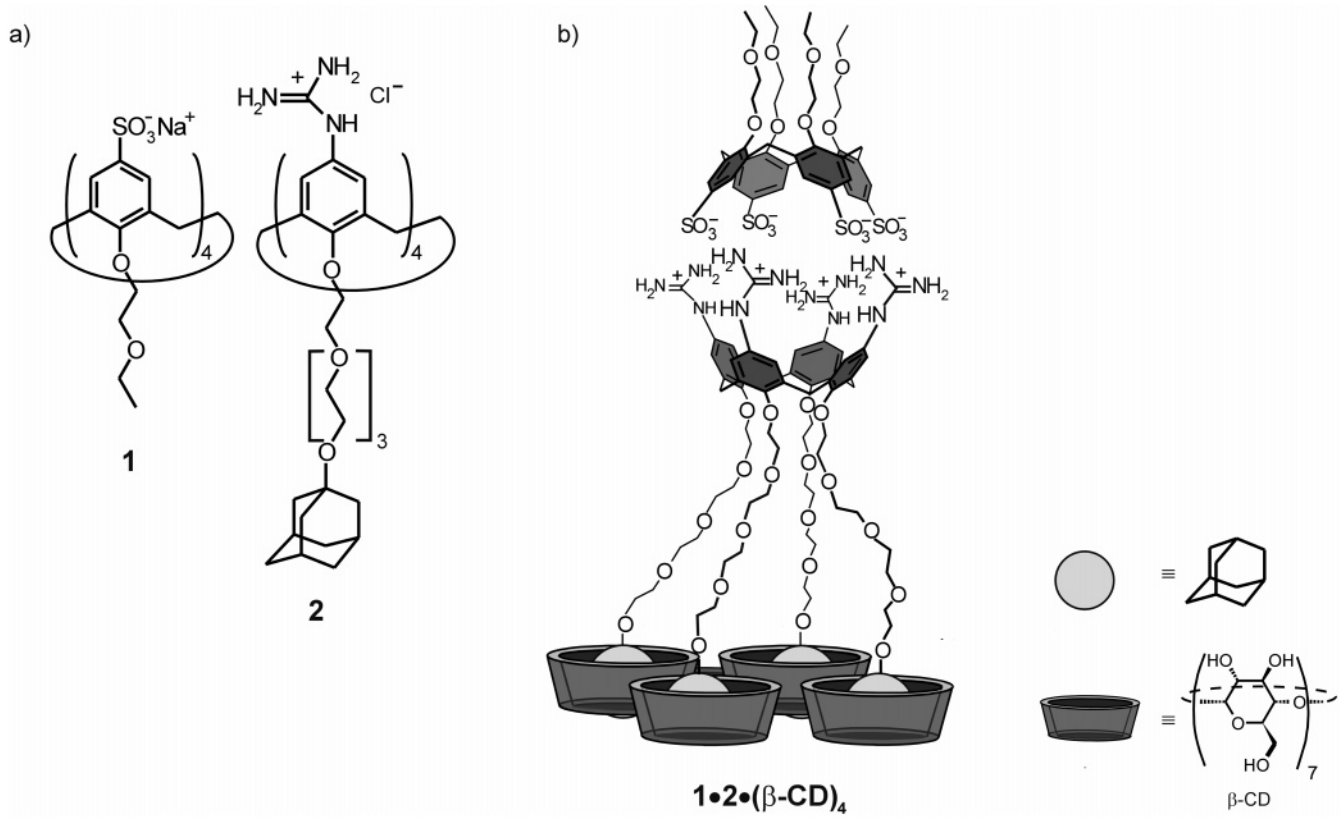


Figure 1. (a) Molecular building blocks of the capsule **1·2**. (b) Schematic representation of the molecular capsule **1·2·**(β-CD)$_4$ in solution. (β-CD = β-cyclodextrin).

tetraamine calix[4]arene **6** in nearly quantitative yield. Introduction of the BOC-protected guanidinium groups using bis-BOC-thiourea was performed under the conditions reported by Qian's group[19] and led to the formation of **7**. Specific removal of the BOC groups was achieved using 2 N HCl in dioxane, giving the desired product **2** as the tetrachloride salt.

Tetrasulfonate calix[4]arene **1** is soluble in water as a result of the charged groups and of the ethylene glycol chains inserted at the upper and lower rims of the calix[4]arene scaffold, respectively. Compound **2** also possesses four charges and long ethylene glycol chains that ensure water solubility. Nevertheless, precipitation was observed upon mixing the two components in water. This is a consequence of the neutralization of the charges upon capsule formation and of the presence of the four adamantyl groups which further limit the water solubility of the assembly. Upon addition of β-CD, which forms an inclusion complex with the adamantyl units of **2**, thus increasing the solubility of the **1·2** assembly in water by the formation of **1·2·**(β-CD)$_4$, a clear aqueous solution was obtained (Figure 1).

The formation of the molecular capsule **1·2** in 1×10^{-2} M β-CD in D_2O was studied by ^{1}H NMR. The ^{1}H NMR spectrum of an equimolar solution of **1** and **2** showed up- and downfield shifts for the resonances of the two components, indicating that a well-defined assembly was formed. Formation of undefined aggregates was ruled out as no broadening of the NMR signals was observed (Figure 2).

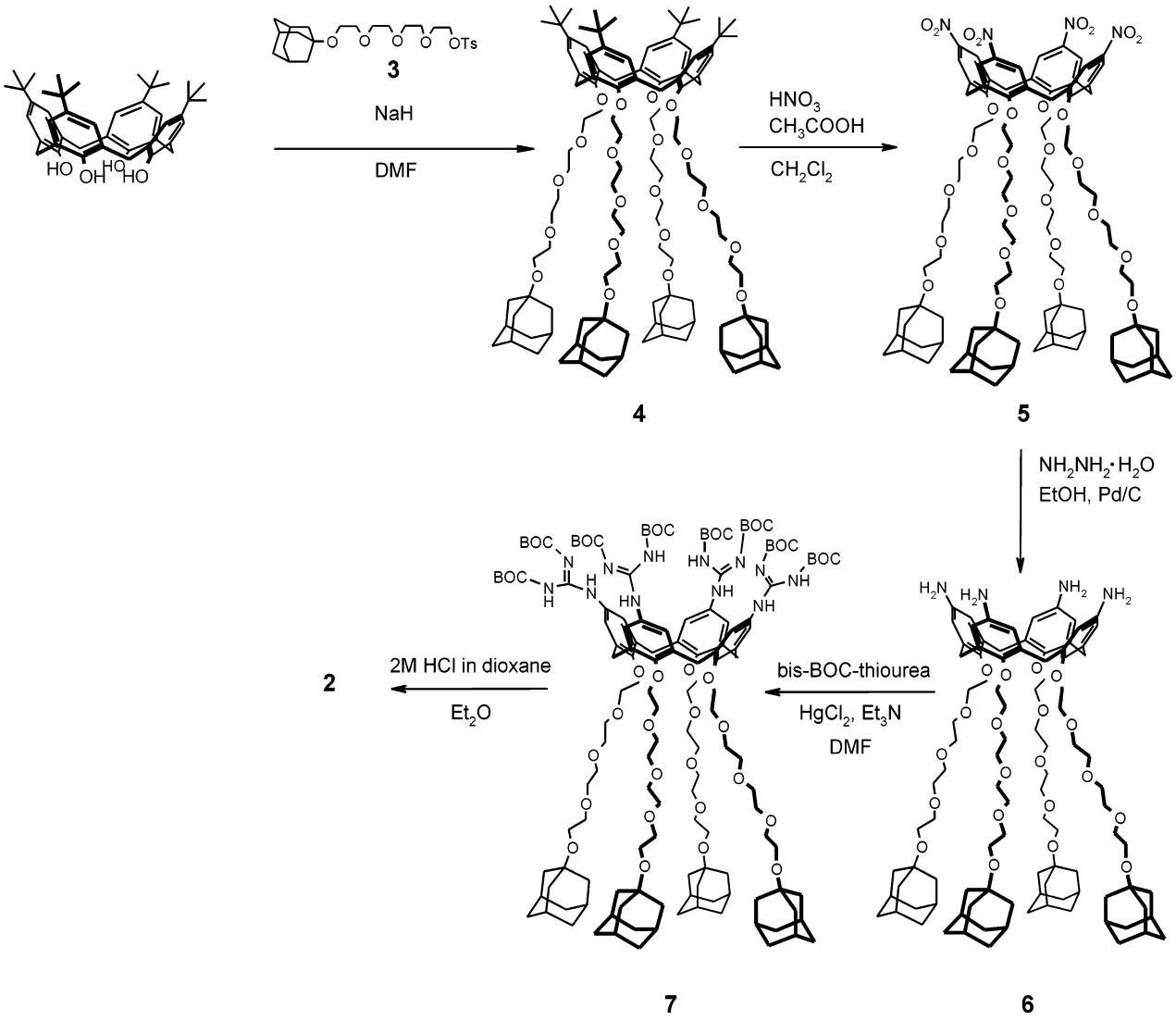
Upfield shifts were observed for the signals of the aromatic protons ($\Delta\delta$ = 0.01 ppm) and of the methylene bridge hydrogens ($\Delta\delta$ = 0.04 ppm and $\Delta\delta$ = 0.05 ppm) of the tetraguanidinium calix[4]arene **2**, while downfield shifts were observed for the resonances of the aromatic protons of **1** ($\Delta\delta$ = 0.06 ppm) and of the protons of the methylene bridge hydrogens ($\Delta\delta$ = 0.08 ppm and $\Delta\delta$ = 0.07 ppm). Small changes were also detectable for the signals of the ethylene glycol chains of **1** and **2** ($\Delta\delta_{max}$ = 0.05 ppm).

The strength of the capsule formation was studied by isothermal titration calorimetry (ITC) in H_2O containing β-CD (1×10^{-2} M). The presence of β-CD in both cell and buret avoids monitoring heat effects due to the β-CD−adamantyl interactions. The resulting enthalphogram (Figure 3) is indicative of the formation of a 1:1 assembly as suggested by the presence of an inflection point at a molar ratio of 1. The positive values for both $\Delta H°$ (2.5 kcal mol^{-1}) and $T\Delta S°$ (10.5 kcal mol^{-1}) account for an endothermic, entropy-driven process. As found for analogous systems,[7] the formation of molecular capsules based on ionic interactions is driven by the desolvation of the charged groups upon complex formation. Highly ordered solvent molecules are released into the bulk solvent, thus resulting in a gain in entropy that is reflected in the positive value for $T\Delta S°$. The unfavorable value for $\Delta H°$ suggests that the enthalpy needed to desolvate the charged groups overrides the enthalpy gained by self-assembly process. The data obtained from the titration were successfully fitted to a 1:1 binding model, giving an association constant K_a of $(7.5 \pm 1.2) \times 10^5$ M^{-1}.

Electrospray ionization (ESI) mass spectrometry provided further proof for the formation of the assembly **1·2**. The spectrum of an equimolar solution of **1** and **2** in MeOH shows the triply charged peak at m/z 998.6 corresponding to the [(**1·2**) + 3Na]$^{3+}$ species, together with a less intense peak at m/z 1486.5 attributable to the complex [(**1·2**) + 2Na]$^{2+}$.

(19) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677−7680.

Scheme 1. Synthetic Route to the Tetraguanidinium Calix[4]arene **2**



The strategy used to build the molecular capsule **1**·**2** at the surface involves the noncovalent positioning of **2** onto a β-CD SAM chemisorbed on a gold surface, followed by the self-assembly of the oppositely charged calix[4]arene **1** as schematically depicted in Figure 4. Previously, we have shown that adamantyl derivatives form strong inclusion complexes with the hydrophobic cavity of the β-CD both in solution and at the β-CD SAM.[20] In addition, larger organic structures functionalized with adamantyl (Ad) units have been ordered on a β-CD SAM through multiple (Ad)$-\beta$-CD interactions.[17]

Analogously, tetraguanidinium calix[4]arene **2** was fixed onto the β-CD SAM through the pendant adamantyl groups, while the cationic moieties of **2** are pointing upward, thus exposing the four positive charges to the outer face of the surface for the self-assembly of the negatively charged component (**1**) of the capsule (Figure 4).[17b] The stable binding of **2** onto the surface, ensured by the multivalent Ad$-\beta$-CD interactions, enables us to study the reversible formation of the molecular capsule **1**·**2**. In addition, this approach avoids synthetic modifications that the covalent attachment to bare gold would require.

To prove that the formation of four Ad$-\beta$-CD interactions ensures a stable binding of the tetraguanidinium calix[4]arene onto the molecular printboard, the adsorption process of **2** onto a β-CD SAM was investigated by surface plasmon resonance (SPR).[21] Figure 5 depicts the SPR sensogram obtained for the adsorption and attempted desorption of **2** in 4 mM β-CD solution, at β-CD SAM. The β-CD in solution was used to compete with the β-CD cavities of the SAM for the complexation of the adamantyl moieties and to ensure a controlled adsorption of **2** at the surface in order to obtain a densely packed layer.[22] After the adsorption of **2**, the system was equilibrated for 5$-$10 min and subsequently rinsed with an 8 mM β-CD solution. The initial adsorption rate for the adsorption of **2** was fast, as indicated by the rapid increase of the SPR signal upon addition of **2**. The absolute signal increase for this part (approximately 0.2°) is comparable to the signal increase for a bis(adamantyl)-calix[4]arene,[22] which may indicate a comparable surface coverage. Afterward, the SPR angle increased

(20) De Jong, M. R.; Huskens, J.; Reinhoudt, D. N. *Chem.*$-$*Eur. J.* **2001**, *7*, 4164$-$4170.

(21) Scuck, P. *Annu. Rev. Biophys. Biomol. Struct.* **1997**, *26*, 541$-$566.
(22) Mulder, A.; Auletta, T.; Sartori, A.; Casnati, A.; Ungaro, R.; Huskens, J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2004**, *126*, 6627$-$6636.
(23) Huskens, J.; Mulder, A.; Auletta, T.; Nijhuis, C. A.; Ludden, M. J. W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2004**, *126*, 6784$-$6797.

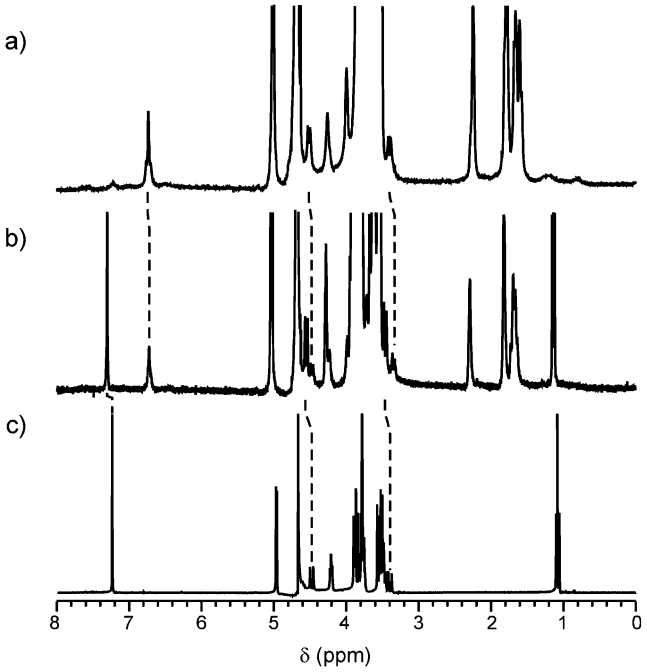


Figure 2. ^{1}H NMR spectra (1×10^{-2} M β-CD in D_2O, 298 K) of (a) **2**, (b) **1·2**, and (c) **1**.

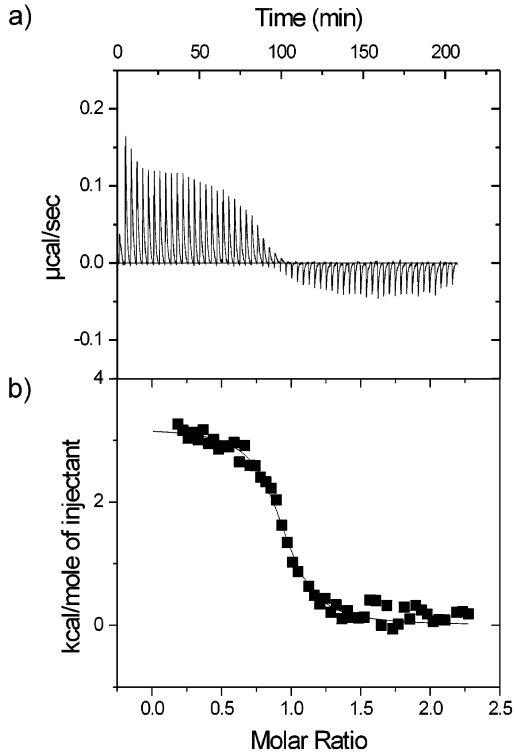


Figure 3. Calorimetric titration of **2** (5×10^{-5} M) with **1** (5×10^{-4} M) in H_2O containing β-CD (1×10^{2} M) and KCl (1×10^{-2} M) at 298 K. (a) Data of heat evolution with injection of **1**. (b) Resulting binding curve (markers) and best fit (line) to a 1:1 model.

slowly in time, probably as a result of reorganization of the monolayer and the adsorbed layer or as a consequence of nonspecific physisorption. Rinsing of the layer with an 8 mM β-CD solution did not lead to any decrease in the SPR signal. This indicates that **2** forms an extremely stable complex with the β-CD SAM as it cannot be removed from the surface even upon rinsing with a concentrated β-CD solution. The stable binding of **2** onto the molecular printboard is attributed to the formation of four Ad$-\beta$-CD interactions. We have recently demonstrated that strong, but reversible, assemblies on surfaces are achieved when two or three Ad$-\beta$-CD interactions are formed.[17a,23,24] Moreover, the adsorption of a tetraguanidinium bis(adamantyl)-calix[4]arene (analogous to compound **2**) onto a β-CD SAM has been investigated.[17b,22] These studies showed that a divalent Ad$-\beta$-CD binding ensures a strong ($K \approx 10^{10}$ M^{-1}), but reversible, attachment of the calix[4]arene derivatives to the surface. In both cases, the reversibility was observed only at high competitive β-CD concentrations in solution. The irreversibility observed here, even at high concentrations of competitive β-CD in solution, for the binding of **2** indicates that more than three Ad$-\beta$-CD interactions are involved. Furthermore, it is indicated by a recently developed model[23] and by experimental data on ferrocene-functionalized dendrimers[24] that guest molecules will bind with the maximum number of interactions that is sterically allowed. Therefore, these results are in line with what could be expected for a tetravalent complex between **2** and β-CD SAMs,[25] and it demonstrates that **2** could be used as a suitable platform to study the **1·2** capsule formation at the surface.

Formation of the molecular capsule **1·2** at the surface was studied by titration of **1** to a β-CD SAM saturated with **2** using a KCl (1×10^{-2} M) solution as background electrolyte, similar to the studies performed in solution by microcalorimetry and ^{1}H NMR spectroscopy. Figure 6 depicts the SPR sensograms obtained for additions of increasing amounts of **1** to a β-CD SAM saturated with **2** (solid line) and a bare β-CD SAM (dotted line). The latter is used as a reference layer.

Addition of **1** to the β-CD SAM saturated with **2** gives strong SPR responses, indicating the binding of **1** at the monolayer. In sharp contrast, the reference β-CD layer (without **2**) does not show any response at all upon addition of **1**. Rinsing of the cells with a 1×10^{-2} M KCl solution only led to a minor decrease in SPR signal (results not shown). Complete restoration of the SPR signals was instead obtained by rinsing the cells with a 1 M KCl solution. These results are indicative of a specific interaction between **1** and **2**. The limiting absolute signal increase observed for **1** (0.18°; see Figure 6, bottom) is comparable to the signal increase of **2** (see above). Together with the similar molecular weights of **1** and **2**, this indicates a comparable surface coverage and supports the assumption of the formation of a 1:1 complex. The incomplete restoration of SPR signals using a 1×10^{-2} M KCl solution implies slow dissociation rates at this background electrolyte concentration. Fitting of the titration curves using a Langmuir isotherm gave a complexation constant of $(3.5 \pm 1.6) \times 10^6$ M^{-1}. This association constant is in agreement with the association constant determined in solution by ITC, confirming the formation of a 1:1 complex at the surface, and thus the capsule formation. The somewhat larger value observed at the surface may indicate some form of positive cooperativity from neighboring molecules **2**, which are always in excess, in binding **1** from solution, which leads to stronger electrostatic interactions.[26]

The strategy adopted allows the disassembly of the components of the molecular capsule in two different steps. As shown,

(24) Nijhuis, C. A.; Huskens, J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2004**, *126*, 12266−12267.
(25) Estimation of the binding constant using the model presented in ref 21 yields an association constant in the order of 10^{15} M^{-1}.

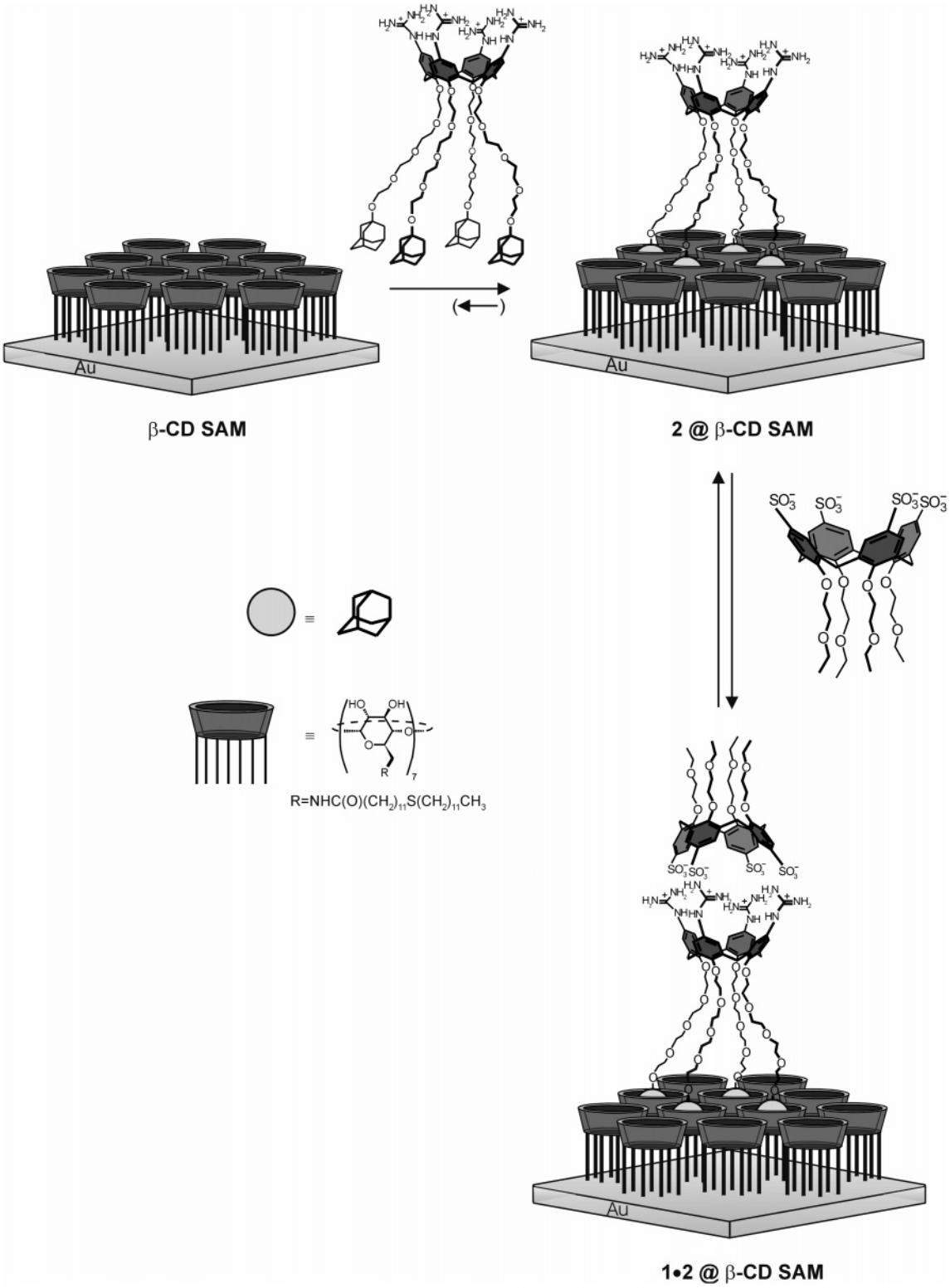


Figure 4. Schematic representation of the adsorption of **2** onto a β-CD SAM through hydrophobic interactions of the adamantyl units with the surface-confined β-CD cavities and of the subsequent self-assembly of the molecular capsule **1**·**2** at a surface through ionic interactions.

the disassembly of half of the capsule is accomplished upon rinsing with a concentrated salt solution (1 M KCl) that weakens the guanidinium−sulfonate interactions. The reversible nature of the Ad−β-CD hydrophobic interactions provides the possibility to disassemble the adamantyl derivative from the β-CD SAM.

An SPR experiment was carried out to study the stepwise self-assembly and disassembly of the molecular capsule at the surface (Figure 7). Analogous to what is reported in Figure 5, the addition of **2** to a bare β-CD SAM caused an increase of

(26) Binding of one molecule of **1** to two of **2** at the surface, however, is ruled out since then an 8+/4− ion pair is expected to form, which should lead to a K of approximately 10^{12} M^{-1} (see, e.g., Schneider, H.-J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; Wiley: Chichester, U.K., 2000), which is clearly too high to explain our results.

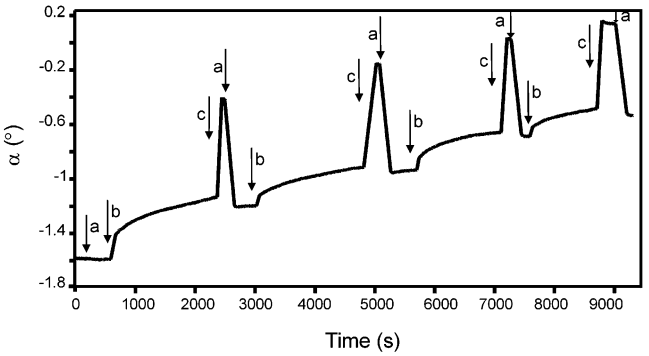


Figure 5. SPR sensogram for the adsorption of **2** followed by attempted desorption onto a β-CD SAM on a gold substrate. (a) 4 mM β-CD. (b) 0.1 mM **2** in 4 mM β-CD. (c) 8 mM β-CD. All solutions are in H_2O.

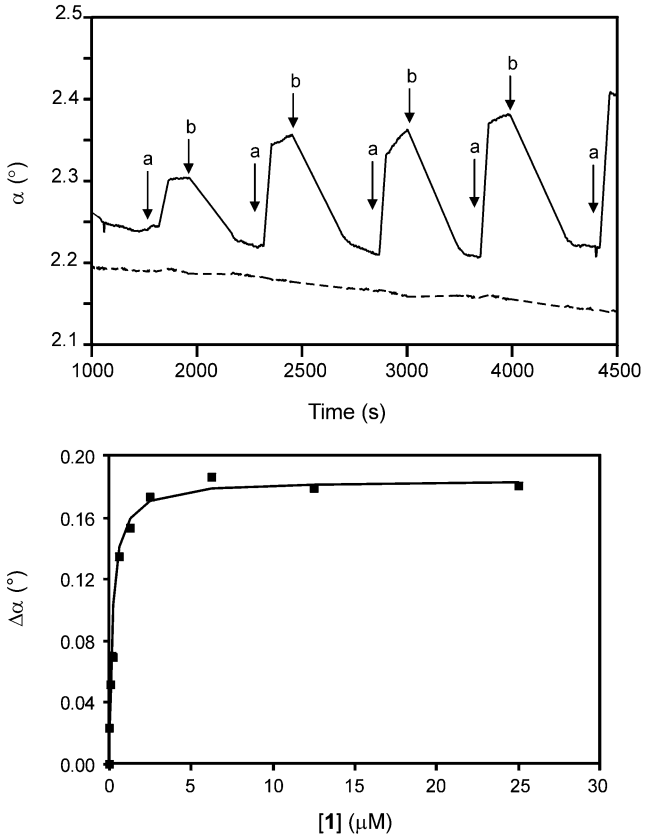


Figure 6. (Top) Part of the SPR sensogram for the titration of increasing amounts of **1** to a β-CD SAM saturated with **2** (solid line) and to a β-CD SAM (dashed line). Additions of increasing amounts of a 1×10^{-5} M solution of **1** are depicted. (All solutions in 1×10^{-2} M aqueous KCl.) (a) **1**. (b) 1 M KCl followed by 1×10^{-2} M KCl. (Bottom) Data points (markers) and best fit (line) for the change in SPR angle of the monolayer of **2@**β-CD SAM as a function of the concentration of **1**.

the SPR signal accounting for the adsorption of the calix[4]-arene derivative **2** onto the molecular printboard.[27] Upon addition of **1**, a further increase in the SPR angle was observed as the result of the formation of the molecular capsule through the specific binding between the tetrasulfonate and tetraguanidinium moieties of the calix[4]arenes.[27] Afterward, the surface was extensively rinsed with a 1 M KCl solution, which was expected to lead to the dissociation of half of the capsule from the surface (see Figure 6). The drop in the angular shift to a value similar to that observed prior to the addition of **1** to the surface accounts for the removal of the tetrasulfonate calix[4]-arene **1**. Subsequently, the surface was rinsed with 2-propanol, which caused the desorption of **2** from the β-CD SAM, as indicated by the restoration of the angular shift to its initial level. The SPR sensogram clearly indicates that, starting from a bare β-CD SAM, it is possible to assemble and disassemble the molecular capsule in a stepwise, controlled manner. The disassembly of the molecular capsule is achieved by rinsing the surface with media that weaken the noncovalent forces, that is, ionic interactions and hydrophobic interactions responsible for the binding of **1** to **2** and of **2** onto the molecular printboard, respectively. In aqueous solution, the hydrophobic interactions between the β-CD and adamantyl moieties ensure a stable binding of tetraguanidinium calix[4]arene **2** onto the surface. Therefore, after washing off the tetrasulfonate calix[4]arene **1**, the tetraguanidinium calix[4]arene **2** remains adsorbed at the β-CD SAM. Its full desorption is achieved only upon rinsing with a solvent (2-propanol) that competes with the hydrophobic interactions responsible for the anchoring to the surface.

Experimental Section

General Information and Instrumentation. All moisture-sensitive reactions were carried out under nitrogen atmosphere. Most of the solvents and all reagents were obtained from commercial sources and used without further purification. All dry solvents were prepared according to standard procedures and stored over molecular sieves. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC300 and Bruker AMX400 spectrometers. Spectra are reported in parts per million downfield from TMS as internal standard. Mass spectra by ESI and chemical ionization (CI) methods were recorded on a Micromass ZMD (or a Micromass LCT time-of-flight mass spectrometer) and on a Finnigan Mat SSQ710 spectrometer, respectively. MALDI-MS spectra were recorded with a PerSpective Biosystems Voyager-De-RP spectrometer. Elemental analyses were performed using a Carlo Erba EA1106. Analytical TLC was performed using Merck prepared plates (silica gel 60 F-254 on aluminum). Merck silica gel (40−63 μm) was used for flash chromatography.

Monolayer Preparation. Gold substrate was obtained from Ssens B. V. (Hengelo, The Netherlands). SAMs of β-CD heptathioether were prepared as reported previously.[20]

Binding Studies. Calorimetric Measurements. The titration experiments were carried out using a Microcal VP-ITC microcalorimeter with a cell volume of 1.4115 mL. The formation of the assemblies **1·2** has been studied adding aliquots of a 0.5 mM solution of **1**, in the buret, to a 0.05 mM solution of **2**, in the calorimetric cell, and monitoring the heat change after each addition. Dilution experiments showed that at the experimental concentrations employed here none of the species showed any detectable aggregation in water. The thermodynamic parameters given above are based on three independent calorimetric titrations. Titration curves were fitted with a 1:1 model using a least-squares fitting procedure and the association constant and enthalpy of binding as independent fitting parameters

SPR. SPR measurements were performed in a two-channel vibrating mirror angle scan setup based on the Kretschmann configuration, described by Kooyman and co-workers.[28] Light from a 2 mW HeNe laser was directed onto a prism surface by means of a vibrating mirror. The intensity of the light was measured by means of a large-area photodiode. This setup allowed the determination of changes in plasmon angle with an accuracy of 0.0028. The gold substrate with the monolayer

(27) The small drop in the SPR signal upon restoration of the 4 mM β-CD + 10 mM KCl solution is attributed to the change in refractive index. The fact the SPR signal remains elevated with respect to the starting positions rules out desorption of the building block.

(28) Lenferink, A. T. M.; Kooyman, R. P. H.; Greve, J. *Sens. Act. B* **1991**, 261−265.

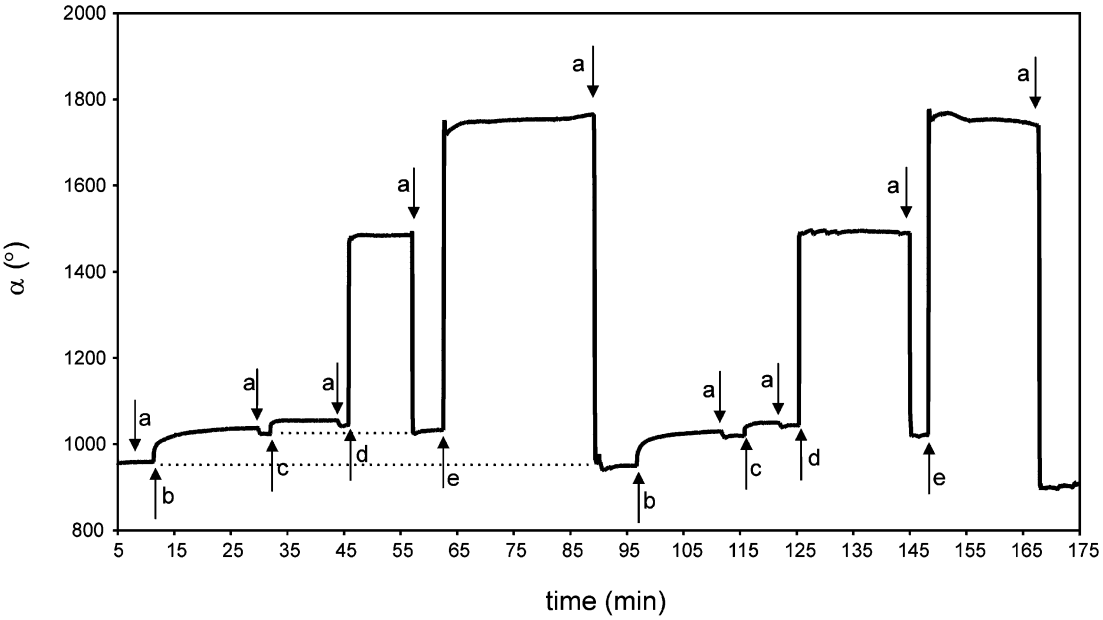


Figure 7. SPR sensogram for the stepwise assembly followed by the stepwise disassembly of the molecular capsule **1·2** over a β-CD SAM on a gold. (a) 4 mM β-CD + 10 mM KCl. (b) Addition of **2** (0.1 mM in 4.0 mM β-CD + 10 mM KCl). (c) Addition of **1** (0.1 mM in 4 mM β-CD + 10 mM KCl). (d) 1 M KCl. (e) 2-Propanol. All the solutions are in H_2O. The cycle was repeated two times.

was optically matched to the prism using an index matching oil. All solutions were made using Millipore water, and all solutions were filtered through nanopore filters prior to use.

In a typical experiment, a cell placed on top of a β-CD monolayer was filled with 800 μL of a 10 mM KCl solution. After stabilization of the SPR signals, the β-CD monolayer in one of the cells was saturated with **2** by replacing 720 μL of the buffer solution with a 10 mM KCl buffer solution containing 0.1 mM of **2** and 5 mM of β-CD. The system was equilibrated while monitoring the SPR angle change. After stabilization of the SPR signal (typically 30 min), both cells were rinsed with a 10 mM KCl solution by repeatedly replacing 720 μL of the cell solutions with 720 μL of the buffer solution (seven times). Titrations with **1** were performed by systematically replacing an increasing amount of buffer solution with of **1** (1−100 μM) in 10 mM KCl for both cells. Between additions, the cells were rinsed by repeatedly replacing 720 μL of the cell solution with 720 μL of a 1 M KCl solution (seven times). The initial KCl concentration was restored by replacing 720 μL of the cell solutions with 720 μL Millipore water and subsequent rinsing with 10 mM KCl using the procedure outlined above. Binding constants given above are based on three independent SPR titrations.

Synthesis. 5,11,17,23-*p-tert*-Butyl-25,26,27,28-tetrakis(2-(2-(2-(2-(adamantyl-1-oxy)ethoxy)ethoxy)ethoxy)ethoxy)-calix[4]arene (4). *p-tert*-Butyl calix[4]arene (2.5 g, 3.85 mmol) was dissolved in 60 mL of dry DMF, and NaH (0.46 g, 19.3 mmol) was added. The solution, kept under N_2 atmosphere, was stirred for 10 min before the addition of the Ad-tetraethylene glycol tosylate **3** (13.0 g, 27 mmol). The mixture was heated at 75 °C for 2 days, and then more alkylating agent was added (2 g, 4.2 mmol). The solution was heated at 75 °C for another 3 days and then poured in 150 mL of 1 N HCl solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried over Na_2SO_4, and filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography: a first column (Et_2O:EtOAc, 1/1) was necessary to purify the product (R_f = 0.2) from the partial substituted calixarenes ($R_f \approx 0.3$), a second column (Et_2O:MeOH, 15/0.4) was needed to remove the byproducts of the alkylating chain. Compound **4** was obtained as pale yellow oil. Yield: 23%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.75 (s, 8H, ArH), 4.42 (d, 4H, $ArCH_2Ar$ ax, J = 12.5 Hz), 4.10 (t, 8H, $ArOCH_2$), 3.93 (t, 8H, $ArOCH_2CH_2$), 3.74−3.57 (m, 48H, $AdO(CH_2CH_2O)_3$), 3.09 (d, 4H, $ArCH_2Ar$ eq, J = 12.5 Hz), 2.14 (bs, 12H, $Ad[CH_2CHCH_2]$), 1.74 (d, 24H, $Ad[CHCH_2C]$ J = 2.4 Hz), 1.61 (m, 24H, $Ad[CHCH_2CH]$), 1.07 (s, 36H, $ArC(CH_3)_3$). ^{13}C NMR (75 MHz; $CDCl_3$): δ 153.3 (s, Ar ipso), 144.5 (s, Ar para), 133.7 (s, Ar ortho), 124.9 (d, Ar meta), 72.8 (t, $ArOCH_2$), 72.2 (s, $Ad[CH_2CCH_2]$), 71.3, 70.64, 70.59, 70.4, 70.3 (t, $ArOCH_2(CH_2OCH_2)_3R$), 59.2 (t, $AdOCH_2$), 41.5 (t, $Ad[CCH_2CH]$), 36.5 (t, $Ad[CHCH_2CH]$), 33.8 (s, $ArC(CH_3)_3$), 31.4 (q, $ArC(CH_3)_3$), 31.0 (t, $ArCH_2Ar$), 30.5 (d, $Ad[CH_2CHCH_2]$). MS (MALDI-TOF) m/z (%): 1914.5 (100) $[M(^{13}C) + Na]^+$, 1913.5 (85) $[M + Na]^+$. Anal. Calcd for $C_{116}H_{176}O_{20}$ (1890.67): C, 73.69; H, 9.38. Found: C, 73.81; H, 9.44.

5,11,17,23-Tetranitro-25,26,27,28-tetrakis(2-(2-(2-(2-(adamantyl-1-oxy)ethoxy)ethoxy)ethoxy)ethoxy)calix[4]arene (5). Calix[4]arene **4** (0.536 g, 0.283 mmol) was dissolved in 5 mL of CH_2Cl_2 dry, and the solution was kept under N_2 and cooled to 0 °C. Glacial CH_3COOH (2.6 mL, 45.4 mmol) and HNO_3 100% (0.91 mL, 22.7 mmol) were added. The solution was stirred for 1 h at 0 °C and for 30 min at room temperature. The reaction mixture was slowly poured in 80 mL of $NaHCO_3$ saturated aqueous solution and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (Et_2O:MeOH, 10/0.9) to give **5** as a pale yellow oil. Yield: 43%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.58 (s, 8H, ArH), 4.66 (d, 4H, $ArCH_2Ar$ ax, J = 14.1 Hz), 4.24 (t, 8H, $ArOCH_2$, J = 4 Hz), 3.81 (t, 8H, $ArOCH_2CH_2$, J = 4 Hz), 3.65−3.55 (m, 48H, $AdO(CH_2CH_2O)_3$), 3.38 (d, 4H, $ArCH_2Ar$ eq, J = 14.1 Hz), 2.12 (bs, 12H, $Ad[CH_2CHCH_2]$), 1.73 (d, 24H, $Ad[CHCH_2C]$, J = 2.9 Hz), 1.60 (m, 24H, $Ad[CHCH_2CH]$). ^{13}C NMR (75 MHz; $CDCl_3$): 161.6 (s, Ar ipso), 143.0 (s, Ar para), 135.7 (s, Ar ortho), 123.9 (d, Ar meta), 74.3 (t, $ArOCH_2$), 72.2 (s, $Ad[CH_2CCH_2]$), 71.3, 70.6, 70.5, 70.4 (t, $ArOCH_2(CH_2OCH_2)_3R$), 59.2 (t, $AdOCH_2$), 41.5 (t, $Ad[CCH_2CH]$), 36.4 (t, $Ad[CHCH_2CH]$), 31.1 (t, $ArCH_2Ar$), 30.5 (d, $Ad[CH_2CHCH_2]$). MS (ES+) m/z (%): 961.6 (65) $[M + 2K]^{2+}$, 953.4 (100) $[M + Na + K]^{2+}$. Anal. Calcd for $C_{100}H_{140}O_{28}N_4$ (1846.23): C, 65.06; H, 7.64; N, 3.03. Found: C, 65.18; H, 7.55; N, 3.09.

5,11,17,23-Tetramino-25,26,27,28-tetrakis(2-(2-(2-(2-(adamantyl-1-oxy)ethoxy)ethoxy)ethoxy)ethoxy)calix[4]arene (6). Hydrazine monohydrate (0.37 mL, 12 mmol) and a catalytic amount of Pd/C were added to a solution of calix[4]arene **5** (0.277 g, 0.15 mmol) in 10 mL of absolute EtOH. The solution was stirred at 80 °C overnight. The mixture was cooled to room temperature, filtered, and evaporated to dryness.

The residue was dissolved in 50 mL of ethyl acetate and washed with a $NaHCO_3$ saturated aqueous solution. The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure, obtaining calix[4]arene **6** as a pale brown oil in a quantitative yield. ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.04 (s, 8H, ArH), 4.31 (d, 4H, $ArCH_2$-Ar ax, J = 13.2 Hz), 3.98 (t, 8H, $ArOCH_2$, J = 5.8 Hz), 3.81 (t, 8H, $ArOCH_2CH_2$, J = 5.8 Hz), 3.66−3.57 (m, 48H, $AdO(CH_2CH_2O)_3$), 2.89 (d, 4H, $ArCH_2Ar$ eq, J = 13.2 Hz), 2.13 (bs, 12H, $Ad[CH_2CHCH_2]$), 1.74 (d, 24H, $Ad[CHCH_2C]$ J = 2.7 Hz), 1.58 (m, 24H, $Ad[CHCH_2CH]$). ^{13}C NMR (75 MHz; $CDCl_3$): δ 150.2 (s, Ar ipso), 140.5 (s, Ar para), 135.9 (s, Ar ortho), 116.3 (d, Ar meta), 73.2 (t, $ArOCH_2$), 72.6 (s, $Ad[CH_2CCH_2]$), 71.7, 71.0, 70.8 (t, ArOCH2$(CH_2OCH_2)_3$R), 59.6 (t, $AdOCH_2$), 41.9 (t, $Ad[CCH_2CH]$), 36.9 (t, $Ad[CHCH_2CH]$), 31.4 (t, $ArCH_2Ar$), 30.9 (d, $Ad[CH_2CHCH_2]$). MS (ES+) m/z (%): 1747.8 (25) $[M + Na]^+$, 885.3 (100) $[M + 2Na]^{2+}$. Anal. Calcd for $C_{100}H_{148}O_{20}N_4$ (1726.30): C, 69.57; H, 8.64; N, 3.24. Found: C, 69.47; H, 8.47; N, 3.20.

5,11,17,23-Tetrakis[*N*′,*N*″-bis-(*tert*-butyloxycarbonyl)guanidyl]-25,26,27,28-tetrakis(2-(2-(2-(2-(adamantyl-1-oxy)ethoxy)ethoxy)-ethoxy)ethoxy)calix[4]arene (7). To a solution of tetramine calix[4]-arene **6** (0.089 g, 0.05 mmol) in 3 mL of dry DMF, kept under N_2, were added bis-Boc-thiourea (0.063 g, 0.23 mmol) and Et_3N (0.085 mL, 0.61 mmol). The solution was cooled to 0 °C with an ice bath, and $HgCl_2$ (0.062 g, 0.23 mmol) was added. The reaction was quenched after 4 h by pouring Et_2O in the flask and filtering the solution to remove the mercury salts. The solvent was removed under vacuum, and the residue was purified by column chromatography (Et_2O:EtOAc 1/1) to give **7** as a colorless oil. Yield: 61%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 11.58 (bs, 4H, NHBoc), 9.82 (s, 4H, ArNH), 6.93 (s, 8H, ArH), 4.44 (d, 4H, $ArCH_2Ar$ ax, J = 13.0 Hz), 4.09 (t, 8H, $ArOCH_2$, J = 5.6 Hz), 3.86 (t, 8H, $ArOCH_2CH_2$, J = 5.6 Hz), 3.63−3.53 (m, 48H, AdO-(CH_2CH_2O)3), 3.15 (d, 4H, $ArCH_2Ar$ eq, J = 13.0 Hz), 2.13 (bs, 12H, $Ad[CH_2CHCH_2]$), 1.76 (d, 24H, $Ad[CHCH_2C]$, J = 2.7 Hz), 1.60−1.45 (m, 24H, $Ad[CHCH_2CH]$ + 72H, Boc). ^{13}C NMR (75 MHz; CDCl3): δ 163.4 (s, C═O), 153.5 (s, Ar ipso), 152.5 (s, ArNHC), 134.6 (s, Ar para), 130.9 (s, Ar ortho), 123.1 (d, Ar meta), 79.1 (s, $C(CH_3)_3$), 73.0 (t, $ArOCH_2$), 72.1 (s, $Ad[CH_2CCH_2]$), 71.2, 70.6, 70.3, 70.0 (t, $ArOCH_2(CH_2OCH_2)_3$R), 59.2 (t, $AdOCH_2$), 41.4 (t, $Ad[CHCH_2$-$CH]$), 36.4 (t, $Ad[CHCH_2CH]$), 31.2 (t, $ArCH_2Ar$), 30.5 (d, $Ad[CH_2$-$CHCH_2]$), 30.2, 28.1 (q, $R(CH_3)_3$). MS (ES+) m/z (%): 1369.7 (100) $[M + 2Na]^{2+}$, 1358.7 (85) $[M + H + Na]^{2+}$, 1348.7 (70) $[M + 2H]^{2+}$. Anal. Calcd for $C_{144}H_{220}O_{36}N_{12}$ (2695.40): C, 64.17; H, 8.22; N, 6.24. Found: C, 64.28; H, 8.16; N, 6.14.

5,11,17,23-Tetraguanidinium-25,26,27,28-tetrakis(2-(2-(2-(2-(ada-mantyl-1-oxy)ethoxy)ethoxy)ethoxy)ethoxy)calix[4]arene, Tetra-chloride (2). Calix[4]arene **7** (0.053 g, 0.02 mmol) was dissolved in diethyl ether (2 mL), and 2 M HCl solution in dioxane was added (0.34 mL, 0.7 mmol). The solution was stirred overnight at room temperature and then evaporated under reduced pressure, giving the compound **2** in quantitative yield. Compound **2** was obtained as a white solid upon recrystallization from CH_2Cl_2/hexane solution. ^{1}H NMR (300 MHz; CD_3OD): δ 6.72 (s, 8H, ArH), 4.66 (d, 4H, $ArCH_2Ar$ ax, J = 13.4 Hz), 4.26 (t, 8H, $ArOCH_2$, J = 4.5 Hz), 3.99 (t, 8H, $ArOCH_2CH_2$, J = 4.5 Hz), 3.70−3.57 (m, 48H, $AdO(CH_2CH_2O)_3$), 3.32 (d, 4H, $ArCH_2$-Ar eq, J = 13.4 Hz), 2.04 (bs, 12H, $Ad[CH_2CHCH_2]$), 1.67 (d, 24H, $Ad[CHCH_2C]$, J = 2.7 Hz), 1.55 (m, 24H, $Ad[CHCH_2CH]$). ^{13}C NMR (75 MHz; CD_3OD): δ 158.2 (s, C═N), 157.6 (s, Ar ipso), 138.1 (s, Ar ortho), 130.2 (s, Ar para), 127.1 (d, Ar meta), 75.5 (t, $ArOCH_2$), 74.0 (s, $Ad[CH_2CCH_2]$), 72.6, 72.3, 72.1, 72.0, 71.9 (t, $ArOCH_2(CH_2$-$OCH_2)_3$), 60.8 (t, $AdOCH_2$), 42.3 (t, $Ad[CHCH_2CH]$), 37.8 (t, $Ad[CCH_2$-$CH]$), 32.3 (d, $Ad[CH_2CHCH_2]$), 32.2 (t, $ArCH_2Ar$). MS (ES+) m/z (%): 632.8 (100) $[M - H - 4Cl^-]^{3+}$. Anal. Calcd for $C_{104}H_{160}O_{20}N_{12}$-$Cl_4$ (2040.30): C, 61.22; H, 7.90; N, 8.24. Found: C, 61.33; H, 7.87; N, 8.15.

Conclusions

The results obtained indicate that the concept of building noncovalent molecular capsules based on ionic interactions, investigated thus far only in the bulk solution, can be successfully extended to the surface. This approach opens the possibility to build a large variety of molecular capsules on molecular printboards by simply functionalizing one of the building blocks with adamantyl units.

The immobilization of the molecular capsule at the surface relies on three different noncovalent interactions, that is, the thiol-gold interactions, the hydrophobic β-CD−Ad interactions, and the ionic interactions between the sulfonate and guanidinium groups of the calix[4]arene derivatives. This feature enables full control over the attachment/detachment of the adamantyl derivative onto the surface as well as over the binding of the second building block at the interface. Because of the possibility to control chemically the stepwise assembly and disassembly of the supramolecular capsule, promising applications, such as the transfer of molecular patterns from one surface to another, can be envisioned.

Acknowledgment. This work was financially supported by the Council for the Chemical Sciences of The Netherlands Organization for Scientific Research (CW-NWO; F.C.: Project JC 9953; A.M.: Project 700.98.305; M.J.W.L.: Vidi Vernieuwingsimpuls Grant 700.52.423 to J.H.) and by the Ministero dell'Istruzione, Università, Ricerca (MIUR) (FIRB Project RBNEO19H9K: Manipolazione molecolare per macchine nanometriche).

JA046780J