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A Polymer-Bound Cavitand

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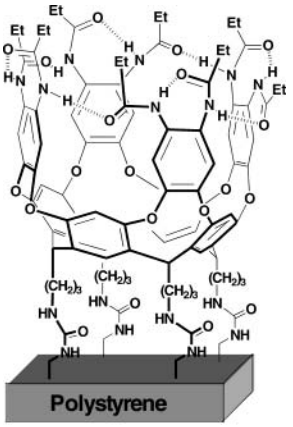
ABSTRACT



An amino-footed cavitand, 1, was attached to an insoluble polystyrene support, and the uptake of organic guest molecules by the resulting polymer 3 from xylene or toluene solutions was achieved.

Polymeric reagents and scavengers are enjoying a renaissance through the advantages they offer for solution phase combinatorial synthesis. Reversible interactions, as in molecular recognition, are also available in polymeric forms: cyclodextrins[1] and crown ethers[2] are widely used as stationary phases in chromatographic separations or in extractions. Calixarenes have likewise given materials with a wide array of properties; their platforms have been used for the attachment of various functional and polymerizable groups.[3,4] All the same, their cavity-forming properties have not been exploited, and neither have cavitands, the open-ended container molecules,[5] been involved. Their low binding affinities, modest dimensions, and difficult chemical modifications limit the applications. We have recently extended the depth of cavitands to the nanoscale and achieved high kinetic stability of their complexes, the caviplexes,[6,7] especially in the self-folding cavitands (e.g., **1**). Intramolecular hydrogen bonding and solvent effects control this host's

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(3) Recent references: (a) Crawford, K. B.; Goldfinger, M. B.; Swager, T. M. *J. Am. Chem. Soc.* **1998**, *120*, 5187−5192. (b) Dondoni, A.; Ghiglione, C.; Marra, A.; Scoponi, M. *J. Org. Chem.* **1998**, *63*, 9535−9539. (c) Blanda, M. T.; Adou, E. *J. Chem. Soc., Chem. Comunun.* **1998**, 139−140. (d) Kenis, P. J. A.; Noordman, O. F. J.; Van Hulst, N. F.; Engbersen, J. F. J.; Reinhoudt, D. N.; Hams, B. H. M.; Van den Vorst, C. P. J. M. *Chem. Mater.* **1997**, *9*, 596−601. (e) Klok, H.-A.; Eibeck, P.; Moeller, M.; Reinhoudt, D. N. *Macromolecules* **1997**, *30*, 795−802. (f) Deligöz, H.; Yilmaz, M. *React. Funct. Polym.* **1996**, *31*, 81−88. (g) Kawabata, H.; Aoki, M.; Murata, K.; Shinkai, S. *Supramol. Chem.* **1993**, *2*, 33−39. (h) Shinkai, S.; Kawaguchi, H.; Manabe, O. *J. Polym. Sci. Part C: Polym. Lett.* **1988**, *26*, 391−396.

(4) Resorcinarenes on a polymeric support: Pfeiffer, J.; Schurig, V. *J. Chromatogr., A* **1999**, *840*, 145−150.

(5) Cram, D. J.; Cram, J. M. *Container Molecules and their Guests*; Royal Society of Chemistry: Cambridge, 1994; pp 85−130.

(6) For a review from this laboratory, see: Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991−2005.

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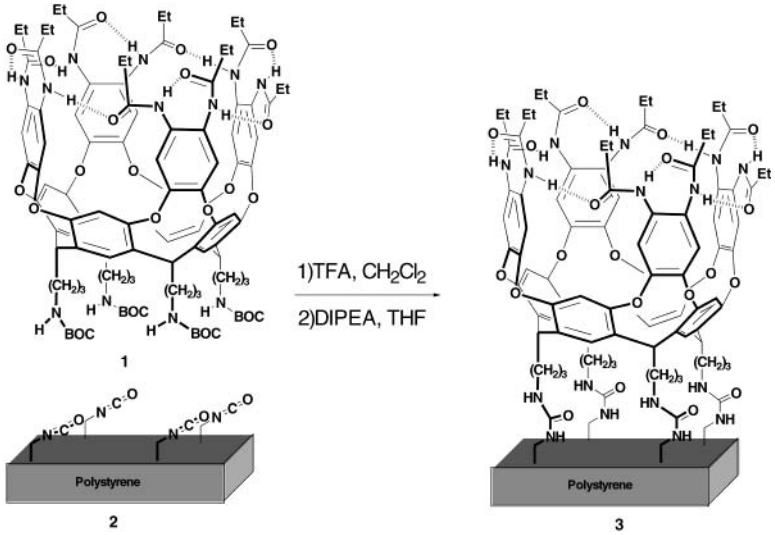
Scheme 1. Attachment of the Cavitand to a Polystyrene Support



conformational dynamics and rates of guest exchange: these rates are slow on the NMR time scale (300−600 MHz, ambient temperatures) even though the binding affinities are quite modest (1−3 kcal/mol). These effects have been amplified in porphyrin-cavitands,[8a] Kemp's triacid cavitands,[8b] and much larger, semicapsular structures.[8c,d] In this Letter, host **1** is introduced to a solid support and shown to complex guests from organic solutions.

For the attachment, the Boc groups were removed from the amines of **1**[9] (CH_2Cl_2, TFA) and the free tetraamine was treated with the polymer-bound isocyanate **2**[10] (THF, DIPEA), a popular amine scavenger (Scheme 1). The stoichiometry of this reaction, in which only a slight excess of **1** was used, ensured that the cavitand is predominantly attached to the polymer, bound via all four amines.

This was confirmed by the disappearance of the isocyanate band in the IR spectrum, by the expected weight gain of the polymer, by elemental analyses (see Supporting Information), and also by the reduced swelling of the polymer in aromatic solvents expected from increased cross-linking.[11]

Binding of molecules to solid supports can be monitored through the decrease of absorbance or fluorescence of the free molecule in solution,[12] and we used this tactic to characterize the complexing abilities of polymer **3**. Guests **4** and **5a** bearing quinone and pyrene chromophores and adamantyl or cyclohexyl groups were employed. These alicyclics are known[7] for their affinities for cavitand interiors (Figure 1). The disappearance of the amides **4** and **5a** from

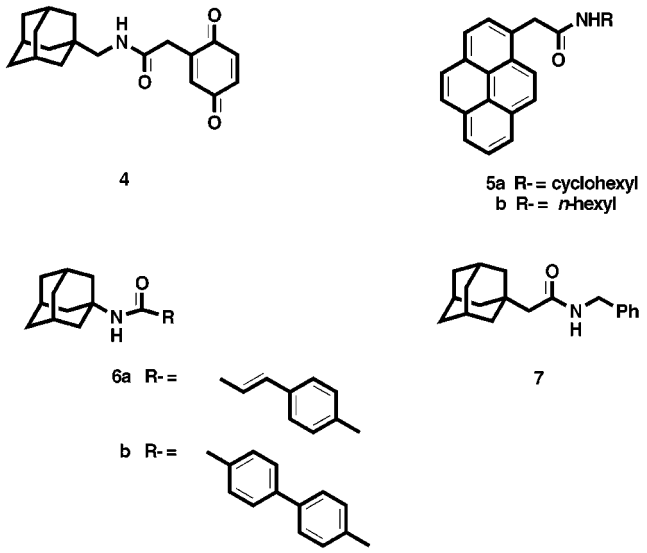


Figure 1. Amide guests **4**−**7**.

a toluene solution corresponded with the amount of polymer used (Figure 2). For example, by varying the weight of **3** from 0 to 35 mg, we found a linear decrease from 1.48 to 1.32 in the absorbance at $\lambda = 320$ nm of amide **4** (∼1 mM solution). With amide **5a**, the absorbance at $\lambda = 377$ nm

(7) (a) Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 12216−12225. (b) Shivanyuk, A.; Rissanen, K.; Förner, S. K.; Rudkevich, D. M.; Rebek, J., Jr. *Helv. Chim. Acta* **2000**, *83*, 1778−1790.

(8) For functionalized self-folding cavitands, see: (a) Starnes, S. D.; Rudkevich, D. M.; Rebek, J., Jr. *Org. Lett.* **2000**, *2*, 1995−1998. (b) Renslo, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 3281−3283. (c) Tucci, F. C.; Renslo, A. R.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 1076−1079. (d) Lücking, U.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 8880−8889.

(9) Haino, T.; Rudkevich, D. M.; Shivanyuk, A.; Rissanen, K.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 3797−3805.

(10) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882−4886.

(11) Technically, the main competition in the reaction of amines with isocyanates comes from hydrolysis. However, the sturdiness of this reaction on cross-linked polystyrene with cleavable linkers has been successfully demonstrated (see: Scialdone, M. A. *Tetrahedron Lett.* **1996**, *37*, 8141−8144 and Chong, P. Y.; Petillo, P. A. *Tetrahedron Lett.* **1999**, *40*, 4501−4504), giving products with high yields and high purities. Clearly this competition is not a major issue.

(12) (a) Yan, B.; Li, W. *J. Org. Chem.* **1997**, *62*, 9354−9357. (b) Yan, B. *Acc. Chem. Res.* **1998**, *31*, 621−630.

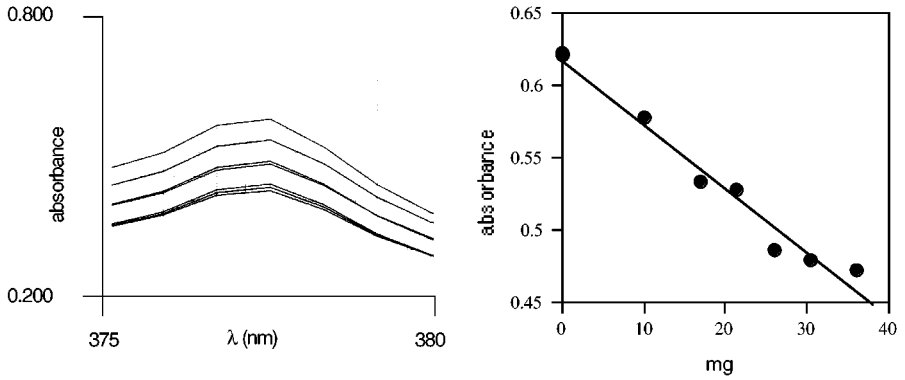


Figure 2. Direct UV traces and resulting relationship for the uptake of amide **5a** by polymer **3** in toluene at 25 °C.

decreased from 0.62 to 0.47 in a parallel experiment (∼1 mM solution).

The binding process with polymer **3** is a combination of three concomitant pathways: a host/guest interaction in the cavity, an unspecific, noncovalent attachment onto the polymer, and some preferential partitioning of the solute in the gel-phase over the solution phase. That the host/guest interaction is an important component for **3** was demonstrated in the following experiments. First, the extraction of amide **5b**, possessing a pyrene chromophore and *n*-hexyl fragment, was four times poorer than that for amide **5a**. Unlike the alicyclics, the *n*-hexyl group is not known to be a good guest for the cavitands.

Second, competition experiments with binary mixtures of guests with different binding affinities were performed. From the ^{1}H NMR measurements (Figure 3), the selectivity of monomeric cavitand **1** for the 1-adamantanamides **6a** and **6b** over amide **7** is high (> ∼20:1). When **3** was added to the NMR solutions of **6a** and **7** or **6b** and **7** in *p*-xylene-d_{10}, a ∼20−25% enrichment of the supernatant by amide **7** was detected. This enrichment—modest but reproducible—is with

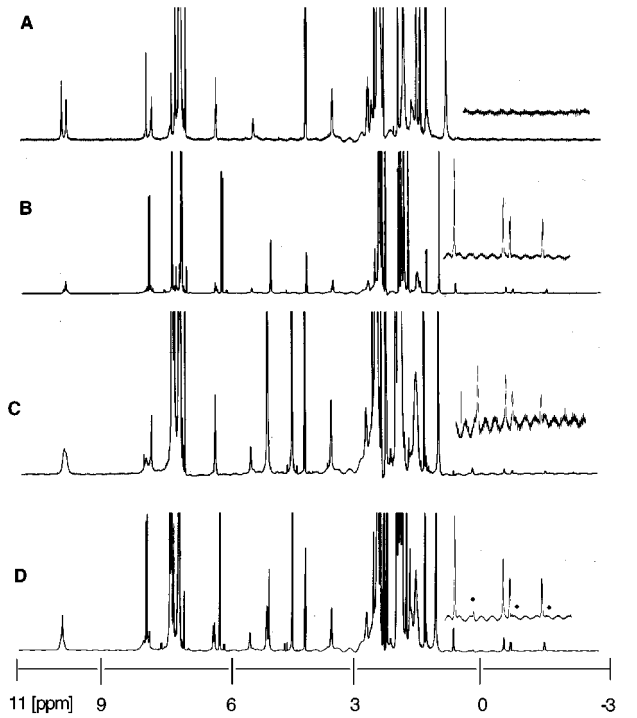


Figure 3. Competition experiments for binding of amide **6a** versus amide **7** by **1**. Complete NMR spectra (*p*-xylene-d_{10}, 295 K) and expanded upfield regions of **1** (A), **1** and amide **6a** (B), **1** and amide **7** (C), and **1** with a 1:1 mixture of amides **6a** and **7** (D). Signals pertaining to amide **7** in D have been marked (●).

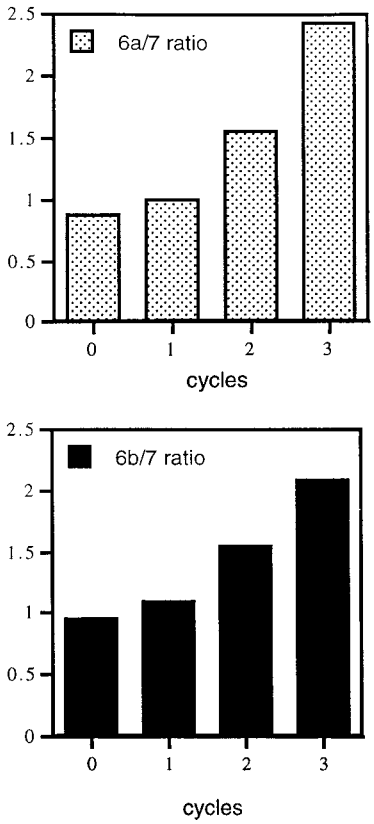


Figure 4. Enrichment of amides **6a** and **6b** versus amide **7** in the supernatant solution during release experiments.

respect to parallel experiments with equivalent amounts of unfunctionalized polystyrene.[13]

At first glance, these results imply that only a fraction of the solutes are bound through host/guest interactions and that nonspecific binding and partitioning also take place. Instead, we believe that the results are a consequence of the low binding affinities ($K_{ass.} < 100\ M^{-1}$, $-\Delta G \sim 2$ kcal/mol in *p*-xylene-d_{10}) between these hosts and their guests.[7] A better measure of selectivity of **3** was revealed through release experiments. The supernatant solution of the two guests was removed and then replaced with fresh solvent. This process was repeated several times (Figure 4) to determine which of the guests was preferentially bound.

The ratio of released amide **6a** to amide **7** increased from ~0.9:1 to ~2.5:1 and that of amide **6b** to amide **7** from ~0.9:1 to ~2.1:1. In each case more than a 2-fold increase was apparent in just three cycles. The enrichment of the solution phase in the better guest confirms that host/guest interactions take place on **3**.[14]

These preliminary binding studies show that molecular recognition occurs in the polymer-bound cavitand. The simplicity of the attachment augurs well for access to polymers functionalized with more elaborate container-molecules,[8] possibly even some carcerands. Applications in extractions and chromatographic separations are underway.

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Supporting Information Available: Experimental procedures and IR spectrum of **3**, UV/vis spectra of **4**, **5a**, and **5b** and representative NMR spectra of **1** and mixtures **6a·7**, **6a·1**, **7·1**, **6a·7·1**, **6a·7·3**, **6a·7·**polystyrene, **6b·7**, **6b·1**, **6b·7·1**, **6b·7·3**, and **6b·7·**polystyrene. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In practice a ~1: 1 mixture of the two guests (5−10 mg of each) was added to a known amount of polymer-bound cavitand **3** (~20 mg) or an equivalent amount of polystyrene and the resulting ratios compared.

(14) The effect is expected to be in fact higher, but this experiment is inherently flawed by the uncertainty associated with the removal of the supernatant and the necessity to leave the solvent in the gel-phase behind, as the rate of exchange of the guest is extremely fast (~2 s^{-1}).[7]