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Polymer-bound self-folding cavitands

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Abstract—The attachment of self-folding cavitands to polymeric supports has been successfully demonstrated. Crosslinked polystyrene and PEGA were used. The synthesis of cavitands properly functionalized for this purpose is reported. The uptake of guest molecules by the resulting materials and the formation of inclusion complexes on the supports was demonstrated.

1. Introduction

Cavitands are synthetic host molecules with open-ended enforced cavities large enough to accomodate guest molecules or ions.[1] The first cavitands were shallow—barely a meniscus on the molecular surface—and they held their miniscule guests only fleetingly. Deeper cavitands such as **1**[2] followed, through addition of walls made of flat aromatic surfaces (Fig. 1). This allowed the inclusion of larger molecules, such as aromatic guests. Recently, intramolecular hydrogen bonds were added to stabilize cavitand conformation and these more rigid containers **2** form complexes (caviplexes) of relatively high kinetic stability:[3,4] guest exchange rates are slow on the NMR timescale ($k \sim 2\ s^{-1}$) and separate signals are seen for free and bound guests. These resonances of the latter are shifted to higher field, typically upfield of TMS, where they report on the magnetic and steric environment of the cavity. These so-called self-folding cavitands have now been outfitted with functional groups, a step that makes them further resemble the binding pockets of biological receptors: porphyrin-cavitands,[5a] cavitands with an introverted carboxylic acid,[3,5b] and even larger, nanoscale container structures are accessible.[5c–e] Approaches towards water-soluble cavities have also been developed.[6]

Practical applications of cavitands are now in sight. In this paper, we describe strategies for the attachment of cavitands to polymeric supports, and establish their binding behavior (Fig. 2).[7] To our knowledge, such an attachment to insoluble supports has not been reported,[8] while other hosts involved in molecular recognition—cyclodextrins,[9] crown ethers,[10] porphyrins[11] and even calixarenes[12]—have been so immobilized. The immobilized cavitands promise roles in chromatographic separations[13] and eventually as catalysts, but for the initial applications, they take their place along side of the polymeric reagents and scavengers useful in solution phase combinatorial synthesis. Before these can be realistically applied, the challenges of synthesis, and issues of recovery and recycling must be resolved, and we address them here.

2. Results and discussion

2.1. Attachment strategies; preparation of polymers 5–9 (Fig. 3)

The preparation of monofunctionalized cavitands for site-selective reactions is a difficult process. In contrast, identical functional groups on all four 'feet' of a resorcinarene are readily available. Immobilizing the cavitands on a polymer through the feet in an unselective fashion is possible. In other words, functional groups on all four feet are allowed to react with up to four complementary groups on the polymer. This necessarily adds crosslinks in the polymer and decreases its ability to swell, but this strategy appeared justified by its simplicity. Accordingly, we used cavitands **10**–**12** (Fig. 4) as precursors for attachment.

For the preparation of polymer-bound cavitand **5**, the BOC groups of amino-footed cavitand **10**[6] were removed with TFA and the resulting tetra-amine was treated with the polymer-bound isocyanate **13** (a popular and commercially-available amine scavenger[14]) in a mixture of THF and Hünig's base (Scheme 1). The stoichiometry of the functional groups involved was held at four isocyanate groups per cavitand, and the structure of the resulting material **5** was confirmed by the disappearance of the isocyanate signal in the IR spectrum, the increased weight of

Keywords: cavitands; polymer; polystyrene; PEGA; crosslinking.

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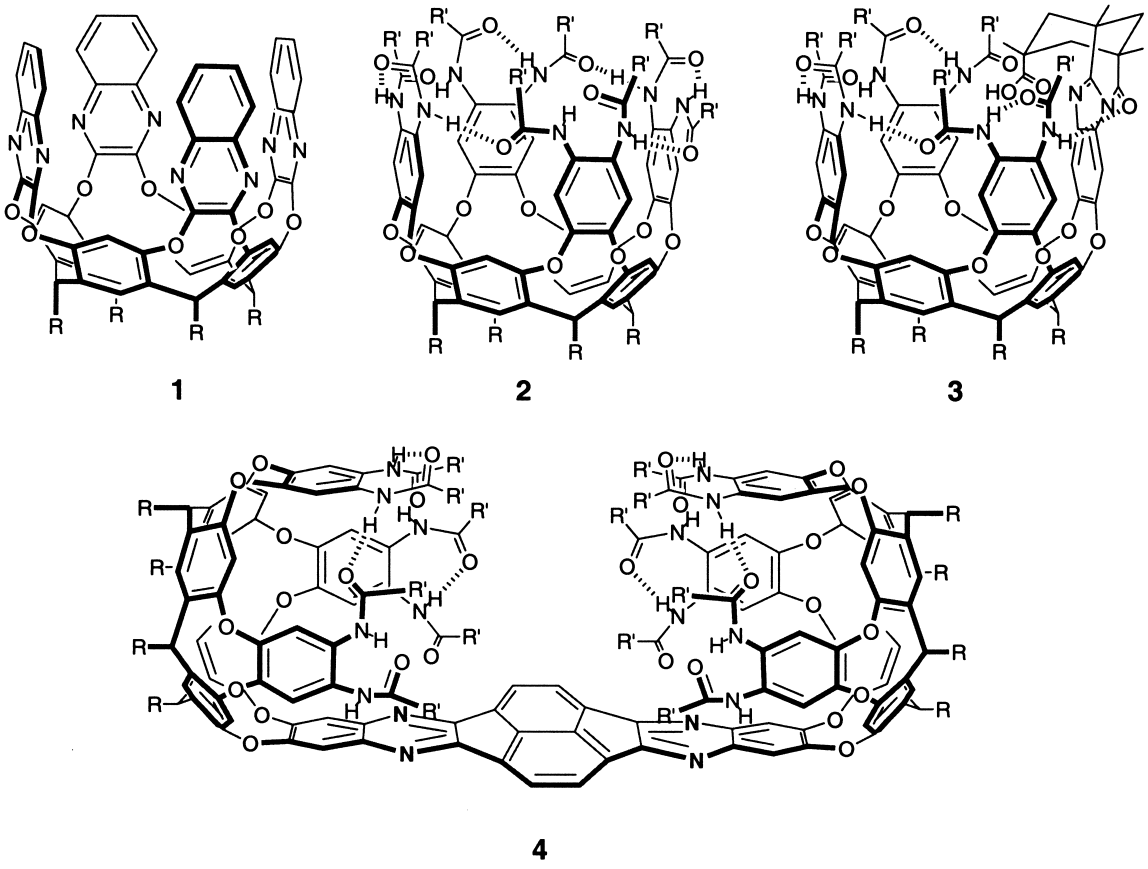


Figure 1. Selected cavitands: (1): deepened cavitand;[2] (2): self-folding cavitand;[3,4] (3): introverted functionality;[5b] (4): semi-capsular structure[5c,d] (R, R′=alkyl).

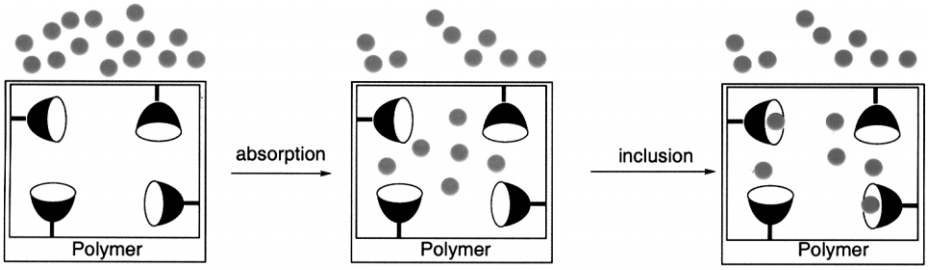


Figure 2. Schematic representation of the formation of polymer-bound caviplexes.

the polymer and elemental analysis. As expected decreased swelling of the polymer in organic solvents was observed.

Hydroxy-footed cavitand **11** was used in a similar fashion. Here, the attachment was to polymeric support **14**, through the formation of tetrahydropyranyl ethers in the presence of *p*-toluenesulfonic acid, a well-established method for the immobilization of alcohols.[15] The result was polymer-bound cavitand **6** (Scheme 2), and the 4:1 stoichiometry was confirmed by the resulting weight gain in the product polymer and its elemental analysis.

Given the increased crosslinking and the reduced swelling of the resulting materials and their potential effects on the properties of the polymers, alternative methods were devised to reduce crosslinking. One such approach relied on the conversion of **11** into self-folding cavitand **15** containing polymerizable feet,[16] simply by treatment with 4-vinylbenzoyl chloride in the presence of triethylamine and DMAP (Scheme 3). This cavitand, divinylbenzene and styrene were used in suspension polymerization to produce the polymer-bound cavitand **7**, keeping the amount of **15** low enough to maintain a targeted 5% crosslinking. Although this value is still high, the advantage of this approach is the ability to vary crosslinking at will.

Another method relied on the selectively functionalized cavitand **12** to keep crosslinking at its original level. In similar fashion to cavitand **10**, this container molecule was deprotected and coupled with isocyanate **13** to give the desired polymer-bound cavitand **8** (Scheme 4).

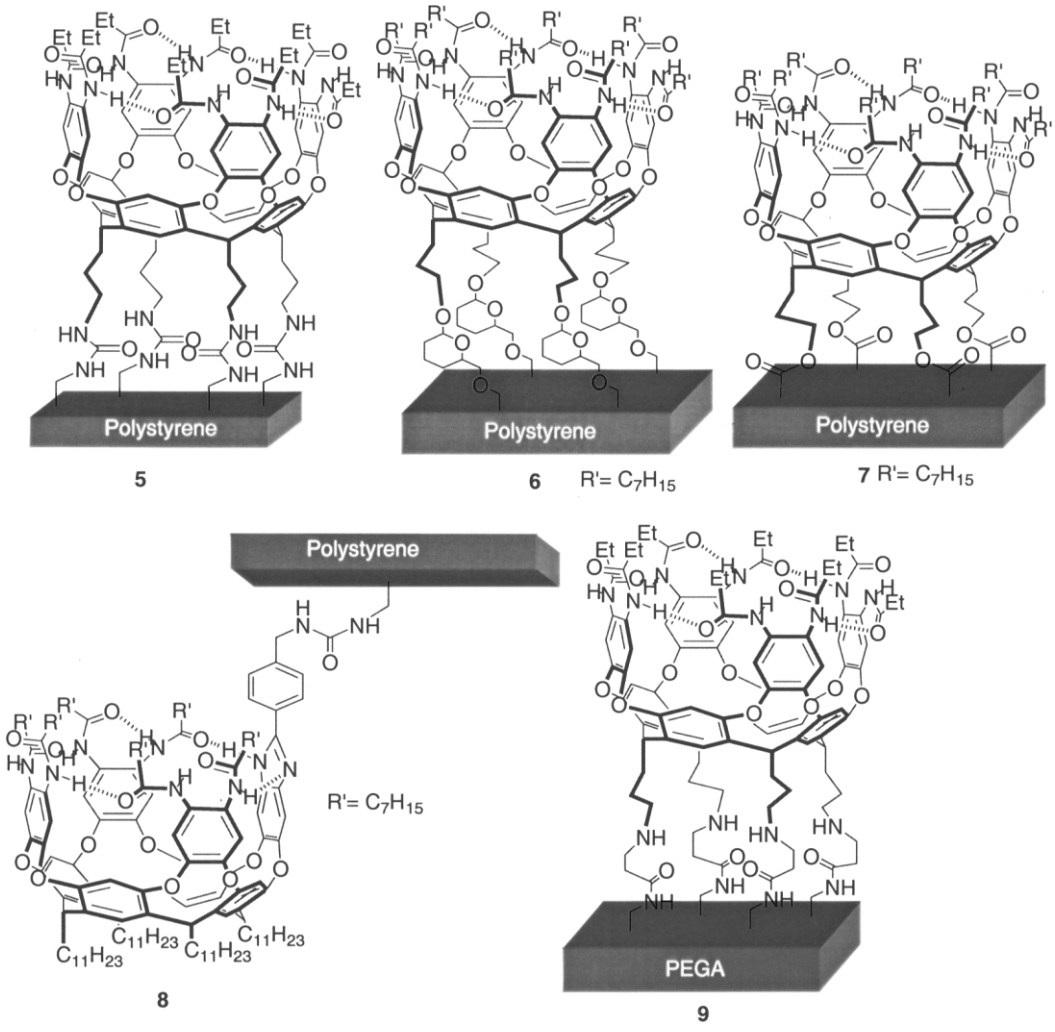


Figure 3. Polymer-bound cavitands **5**–**9**.

Recently, we found that with proper solubilizing appendages, self-folding cavitands can be employed in water to form kinetically stable caviplexes.[6] In these cases, the presence of the guest induces the conformation necessary for binding through hydrophobic effects. In principle, the replacement of the hydrophobic polymeric support by one that can swell in water should allow for guest uptake in aqueous media. We chose the highly

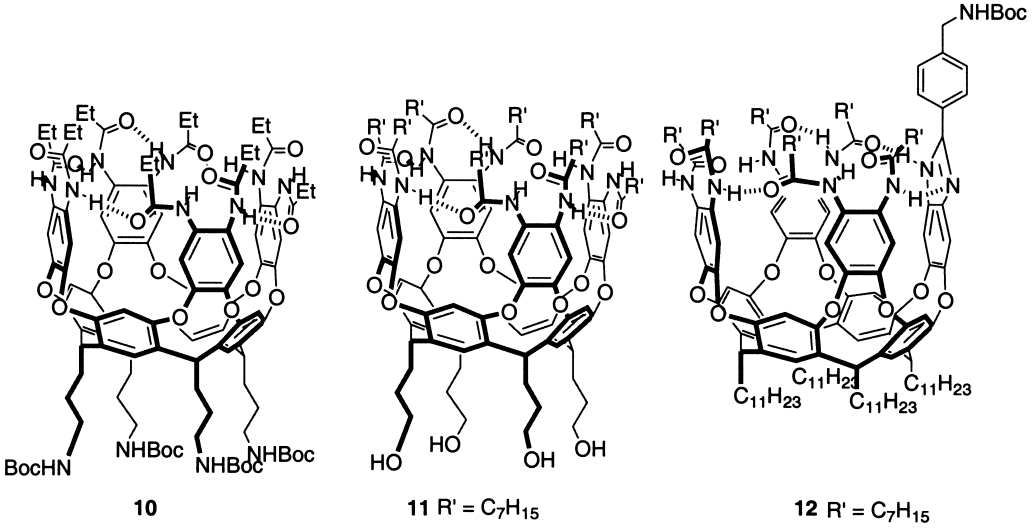
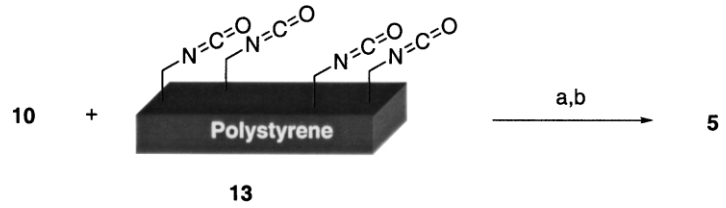
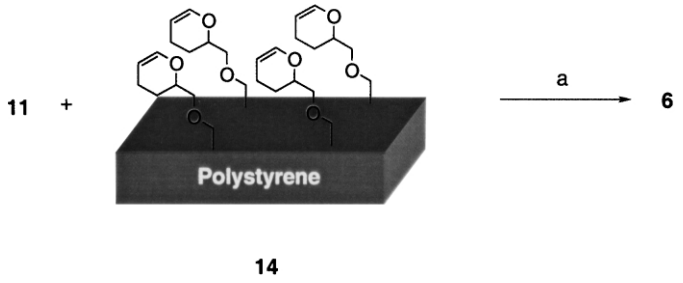


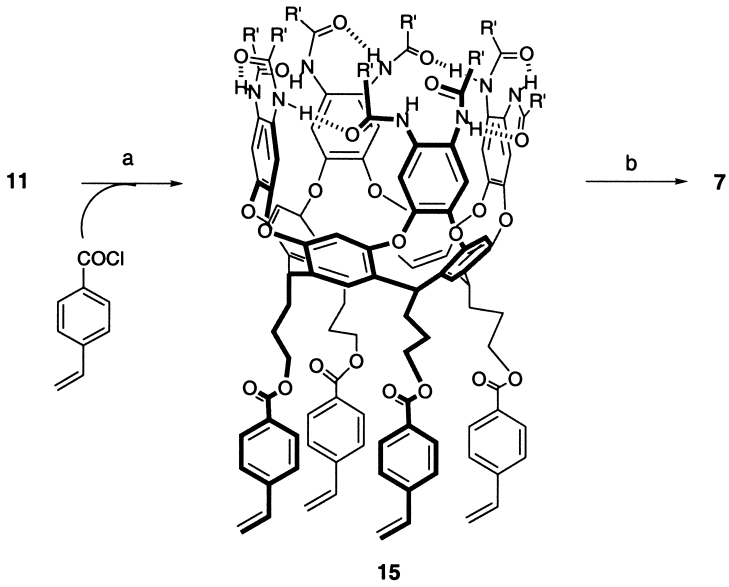
Figure 4. Cavitands **10**–**12** used for attachment.



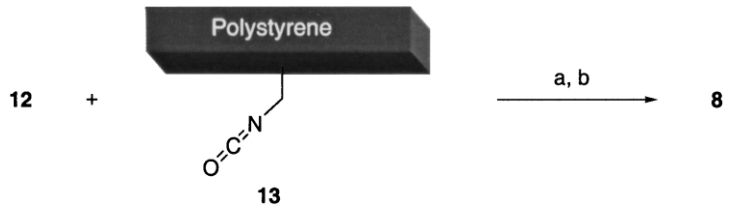
Scheme 1. (a) TFA, CH_2Cl_2. (b) **13**, DIPEA, THF.



Scheme 2. *p*-TsOH, CH_2Cl_2, 0°C.



Scheme 3. (a) DMAP, TEA, CH_2Cl_2. (b) Styrene, 5% DVB, Benzoyl peroxide, PhCl, H_2O, 85°C.

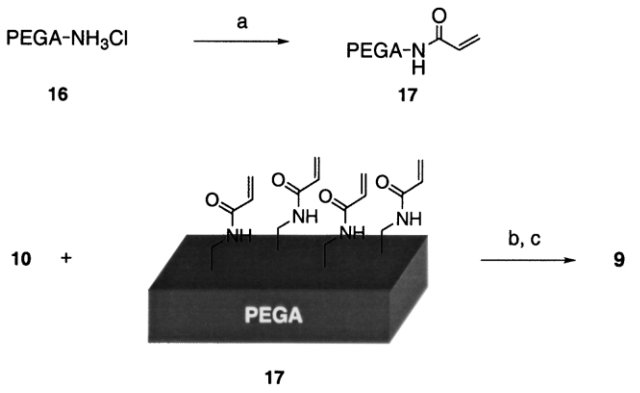


Scheme 4. (a) TFA, CH_2Cl_2. (b) **13**, DIPEA, THF, reflux.

hydrophilic PEGA[17] **16** (Scheme 5). This polymer was converted to its acrylamide **17**, and, similarly to the REM resin,[18] used to attach amino footed cavitand **10**. This gave the polymer-bound cavitand **9** by sequential treatment with TFA in CH_2Cl_2 and DIPEA in DMF.

2.2. Preparation of cavitands 10–12 for attachment

We reported the preparation of the amino-footed cavitand **10** elsewhere.[6] This host molecule is produced from the hydroxy footed resorcinarene **18**[19] and this affords a shorter



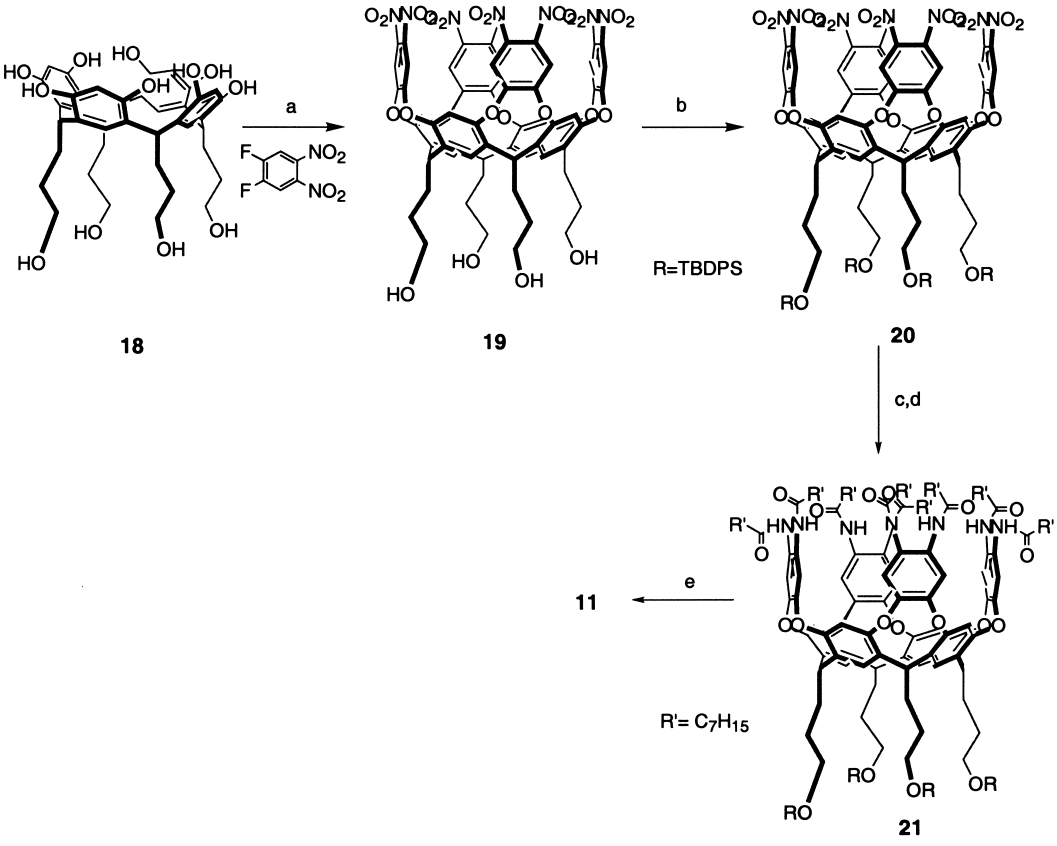
Scheme 5. (a) acryloyl chloride, DMF, DIPEA. (b) TFA, CH_2Cl_2. (c) **17**, DIPEA, DMF, 70°C.

route to polymer-bound cavitands, through the preparation of **11** (Scheme 6). Treatment of **18** with four equivalents of 1,2-difluoro-4,5-dinitrobenzene in the presence of triethylamine yields octanitrocavitand **19**. Obviously the reaction takes place at the phenolic hydroxyls rather than the aliphatic ones. The feet were treated with *t*-butyldiphenylsilyl chloride and imidazole in DMF, for protection and enhanced solubility. The resulting octanitro **20** was reduced with hydrogen and Raney Ni, and the crude octaamine was acylated with octanoyl chloride under Schotten–Baumann conditions. The product **21** was desilylated to provide the desired hydroxy-footed **11**.

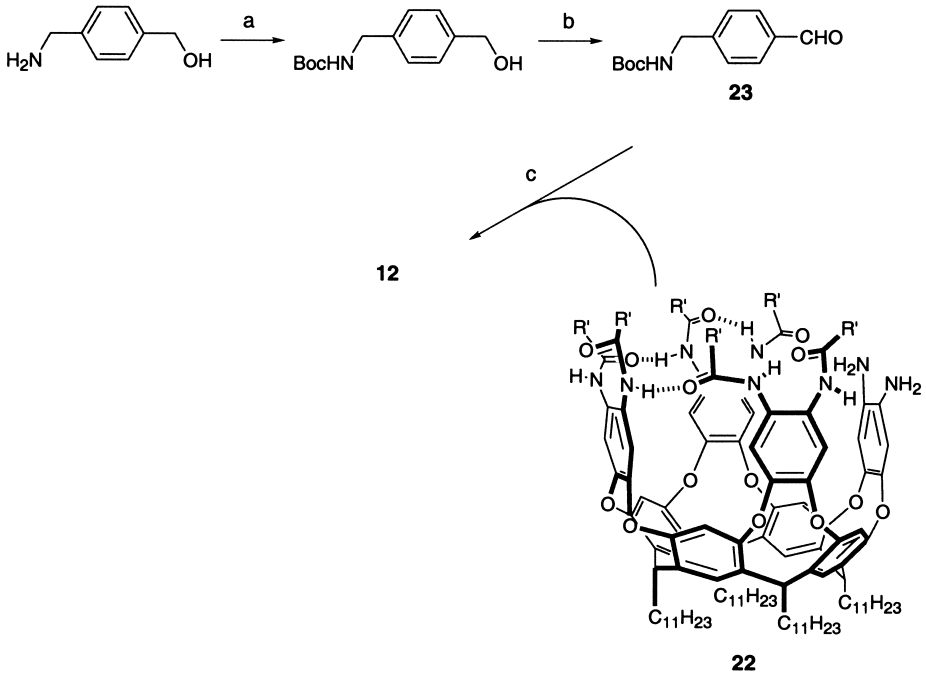
The selectively functionalized cavitand **12** arises from diaminocavitand **22**,[5] through reaction with aldehydes in nitrobenzene, acting simultaneously as solvent and mild oxidant. The benzimidazole function of the product participates in the seam of hydrogen bonds.[5d] The appropriately substituted benzaldehyde **23** was prepared by BOC protection of (4-aminomethyl)benzyl alcohol followed by oxidation with PCC (Scheme 7). Condensation with diaminocavitand **22** in nitrobenzene gave the desired product **12**, although only in moderate yield (20%).

2.3. Guest uptake and inclusion studies

Binding of molecules to solid supports can be monitored through the associated decrease in absorbance or fluorescence of the free molecules in solution.[20] With **5**–**9** this results in a clear relationship between the inverse of the absorbance of the guest molecule and increasing amounts of polymer (Fig. 5). The affinity of self-folding cavitands for alicyclics such as those possessing cyclohexyl or adamantyl groups, is known.[4] Using guest molecules **24** (which can form a caviplex with **10**) and **25**, (which is not known to do so) we tested binding to polymer **5**. This clearly showed the uptake of guests by polymer **5**, and that this uptake was five times higher for **24** than for **25**. Interestingly, the resulting binding constants were large ($K_{ass}\sim10^4$–10^5 equiv.$^{-1}$), when compared to those of the corresponding soluble caviplexes ($K_{ass}\sim10^2\ M^{-1}$). It is, therefore, unlikely that inclusion alone is responsible for the uptake, and stronger evidence of selective molecular recognition is clearly needed.



Scheme 6. (a) DMF, TEA. (b) DMF, TBDPSCl, imidazole. (c) PhMe, MeOH, H_2, Raney Ni. (d) $C_7H_{15}COCl$, K_2CO_3, EtOAc, H_2O. (e) TBAF, AcOH, THF.



Scheme 7. (a) Boc_2O, KOH, THF, H_2O, 45 min. (b) PCC, NaOAc, CH_2Cl_2, overnight. (c) $PhNO_2$, 130°C, 24 h.

The high kinetic stability of the inclusion complexes proved to be an asset.[4] Through ^{1}H NMR measurements (Fig. 6), the selectivity of monomeric cavitand **10** for the *N*-adamantylamides **26** and **27** over amide **28** was determined to be high (>∼20:1) in *p*-xylene-d_{10}. When **5** was added to equimolar NMR solutions of **26** and **28** or **27** and **28**, a modest (∼20%) enrichment of the supernatant in amide **28** was detected. This enrichment—modest but reproducible—is with respect to parallel experiments with equivalent amounts of unfunctionalized polystyrene, and confirms that only a fraction of the solutes are bound through host/guest interactions. In addition, these results could be a consequence of the low binding affinities (K_{ass}∼10^2, $-\Delta G$∼2 kcal mol^{-1} in *p*-xylene-d_{10})[4] between these hosts and their guests. A better measure of selectivity of **5** was obtained by the release of the bound guests (Fig. 7). The supernatant solution of the two guests was removed then replaced with fresh solvent, followed by NMR determination of the guest ratio. This process was repeated several times to determine which of the guests were preferentially bound.

The ratio of released amide **26** to amide **28** increased from ∼0.9:1 to ∼2.5:1 and that of amide **27** to amide **28** from ∼0.9:1 to ∼2.1:1 in just three cycles. The enrichment of the solution phase in the preferred guest provides clear evidence that host/guest interactions take place on material **5**.

Attachment of the cavitand to a *soluble* polystyrene support[21] would give direct evidence of the inclusion, by allowing the use of solution ^{1}H NMR experiments. This,

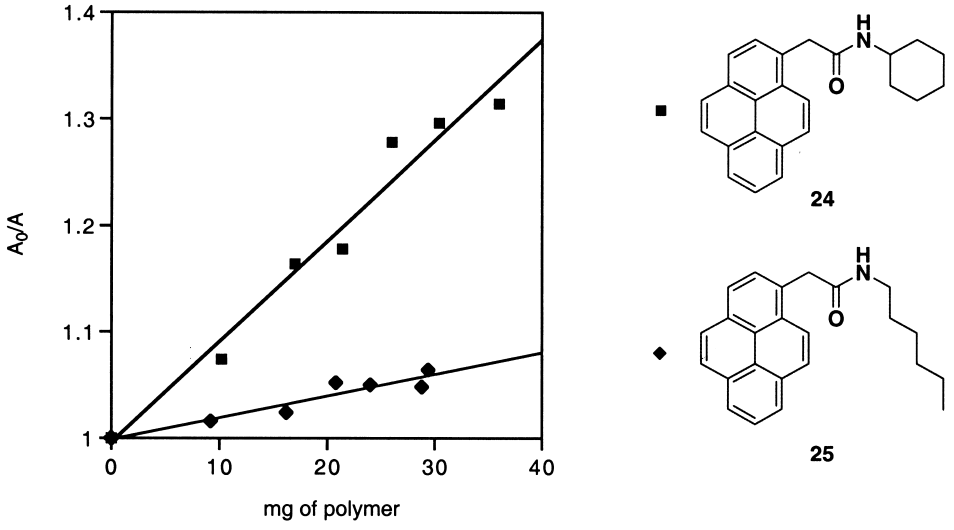


Figure 5. Uptake of guest molecules **24** and **25** (∼1 mM) by polymer **5** in toluene as measured by the decrease in absorbance at 298 K.

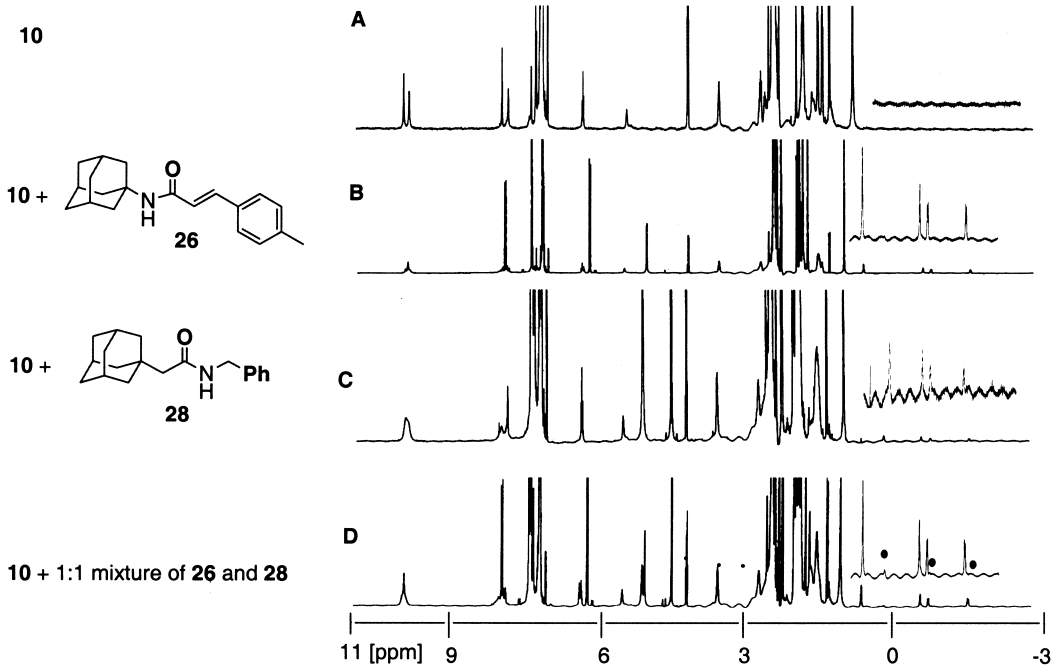


Figure 6. ^{1}H NMR spectra of **10** and guests in *p*-xylene-d_{10} at 295 K. Signals of included guests are in the −3–0 ppm region. ● indicates the minor guest.

however, required a selectively functionalized cavitand and **29**[5d] (Scheme 8) was an ideal candidate for this purpose. Soluble chloromethylated polystyrene **30** was converted to the diethylphosphonoacetate **31**, by treatment with the cesium salt of diethylphosphonoacetic acid in DMF. This polymer was in turn used for a Horner–Wadsworth–Emmons olefination,[22] using lithium bromide/triethylamine as promoters, providing polymer-bound cavitand **32** (Scheme 8). Being freely soluble in *p*-xylene-d_{10}, this polymer gave NMR spectra of guests included in the cavitands, and confirmed that inclusion does take place on the polymer. The same guests (**26** and **27**) used in the earlier competition studies were used in these NMR experiments (Fig. 8) and gave direct evidence of inclusion.

2.4. On the role of the polymer

In most cases, polymeric supports are not solid states.[23] Rather, they are softer gel-like supports to allow extended contact between soluble and insoluble components, while managing higher loadings and easier preparations. In the case of the peptide coupling reagent P-EDC, an interesting

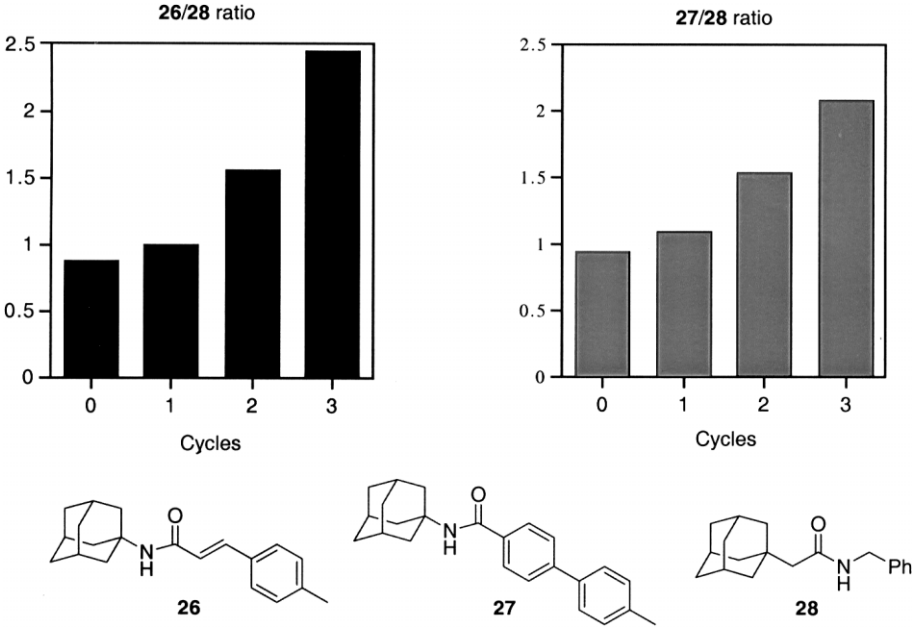
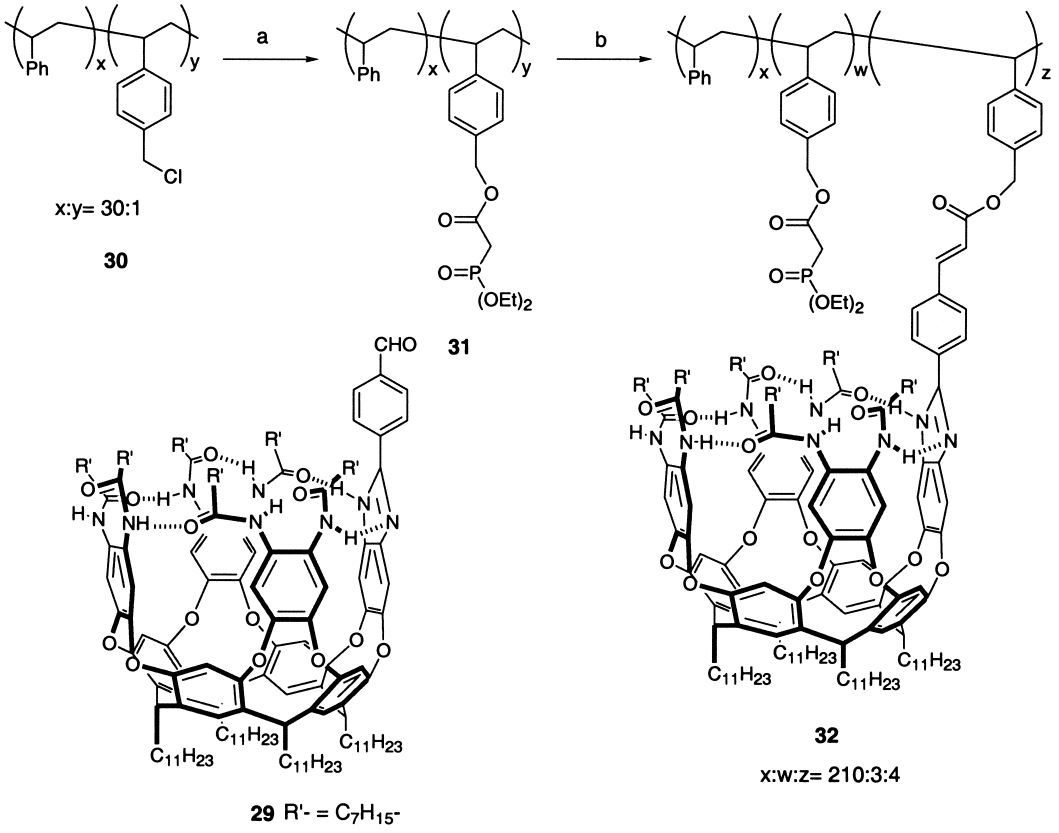


Figure 7. Enrichment resulting from the release by **5**, in the supernatant solution, of guests **26** and **27** versus **28**.



Scheme 8. (a) Diethylphosphonoacetic acid, Cs_2CO_3, DMF, 70°C. (b) **29**, LiBr, Et_3N, THF.

study of the effect of the support over the function of the reagent has been reported.[24] The efficiency of the reagent was shown to depend on both loading (in particular very high loading was detrimental) and crosslinking. Given the importance of solvents to the proper conformation, and hence function, of our container molecules, the role of the polymeric 'phase' is of more than routine interest, since the swollen polymer may be a good guest for proper inclusion, and competing with host–guest contact. Polystyrene initially represented an ideal choice: being non-polar and able to swell in non-polar solvents, it is suspected not to interfere with the seam of H-bonds. As we have already related, a number of the guest molecules bind the polymer through unspecific interactions. Another description of this

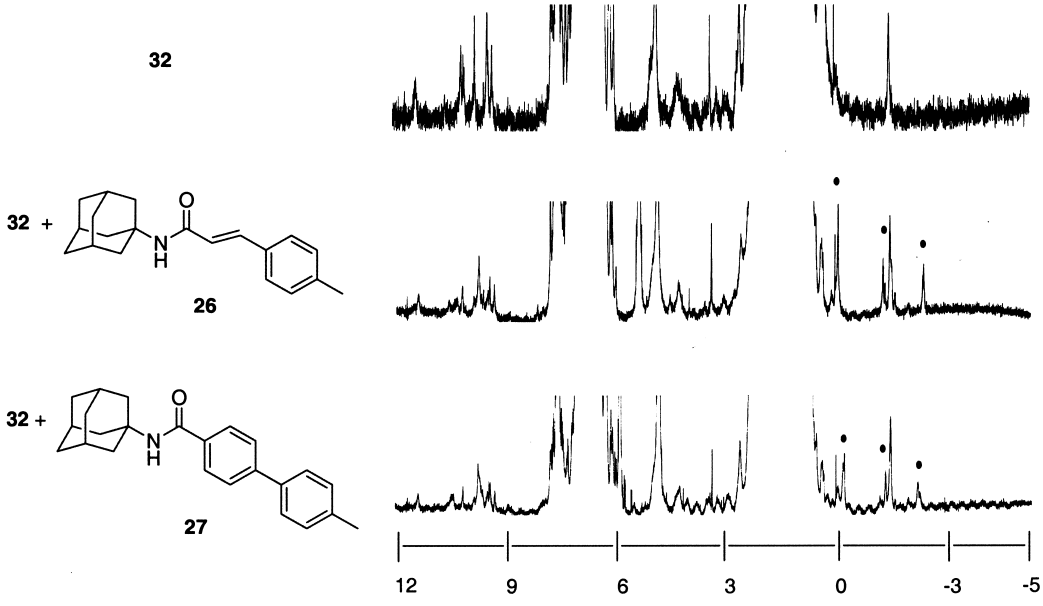


Figure 8. ^{1}H NMR of soluble polymer-bound cavitand **32** alone or in the presence of 30 equiv. of guest **26** and guest **27** in *p*-xylene-d_{10} at 295 K. with the telltale signals in the −3–0 ppm region. ● indicates the signals of the included guest.

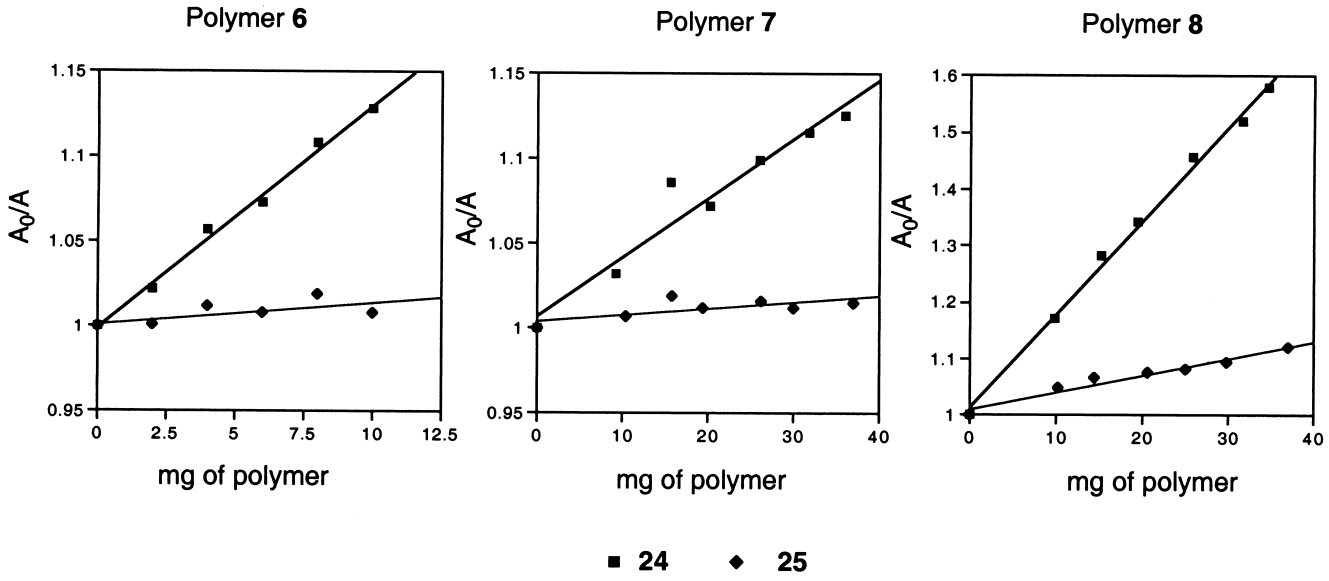


Figure 9. Uptake of guest molecules **24** and **25** (~1 mM) by polymers **6–8** in toluene as measured by the decrease in absorbance at 298 K.

phenomenon is that the soluble molecules like to 'dissolve' in the gel-phase, or, in other words, partition favorably between gel-phase and solution-phase. If most of the guest molecules are absorbed this way, then the volume associated with the gel-phase—the swelling volume—and hence the extent of crosslinking is crucial to the extent of absorption. Since general methods for the attachment of cavitands with highly (**5–7**) and slightly (**8**) crosslinked resins were at hand, a comparison was feasible.

The uptake by polymers **6–8** of guests **24** and **25**, is shown by the relationships in Fig. 9. The 5–10-fold greater uptake of guest **24** can be, in part, attributed to its inclusion. Translating these relationships based on polymer weight to ones based on equivalents of cavitand provides an interesting comparison of the different resins (Fig. 10). These clearly show the greater uptake of the guest in the low crosslinked polymer **8**, as opposed to the higher crosslinked **5–7**. This is true for both **24** and **25**, clearly indicating the importance of the swelling volume on the uptake.

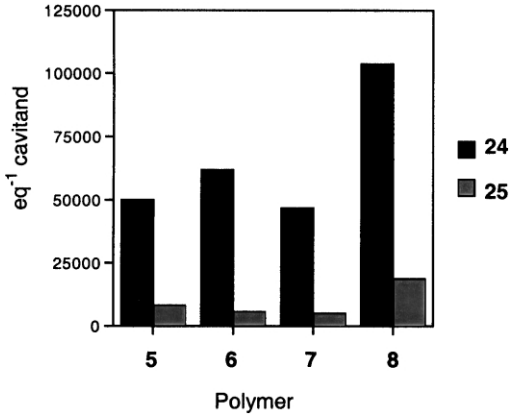


Figure 10. The relative uptake of guests **24** and **25** (~1 mM) by polymer-bound cavitands **5–9** at 298 K.

In short, the cavitands in **8** are exposed to more guest molecules than in the other polymers. However, given the moderate differences in the values, we prefer the more synthetically accessible polymers **5–7**.

The role of the support is further highlighted in polymer-bound cavitand **9**, attached to the hydrophilic PEG-A. Using water-soluble guests **33** and **34**, known to be included in our water-soluble cavitands,[6] the same binding studies were performed as before (Fig. 11). Whereas **33** was taken up as expected and to a greater extent by **9** than by its cavitand free precursor **17**, the trend shown by **34** told another tale. The higher the amount of polymer, the higher becomes the absorbance. This is probably due to deprotonation of **34** by the groups present on the polymer.

2.5. Future prospects

The described experiments clearly show that the decreased swelling resulting from multiple attachments of the cavitands to their polymeric supports is of only modest effect to the desirable properties of the material. Moreover, the practicality of this simple synthesis is undeniable. This is further demonstrated with the preparation of selectively functionalized cavitand **38** (Scheme 9). This direct precursor to many immobilized or water-soluble and functional host molecules was prepared from amino-footed resorcinarene **35**. The treatment of this compound with 3 equiv. of 1,2-difluoro-4,5-dinitrobenzene lead to the selectively functionalized hexanitro cavitand **36** in 30% yield. Reduction of the nitro groups with Raney Ni, is followed by acetylation leads to the hexaamide **37**, on which a fourth bridge is added to give **38**. This cavitand was further deprotected and attached to polymer **13**, in a fashion similar to **5**, and yield the model system **39**. Compounds **38** and **39** represent extremely useful precursors for the synthesis of immobilized cavitands with introverted functionalities, cavitand–porphyrin hybrids and larger host molecules.[3–5]

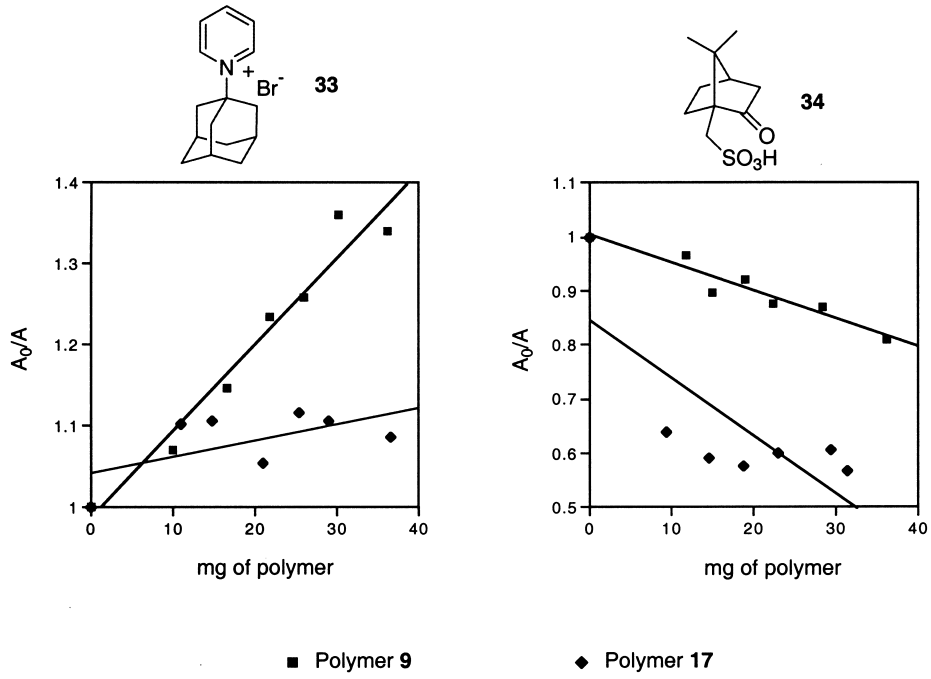
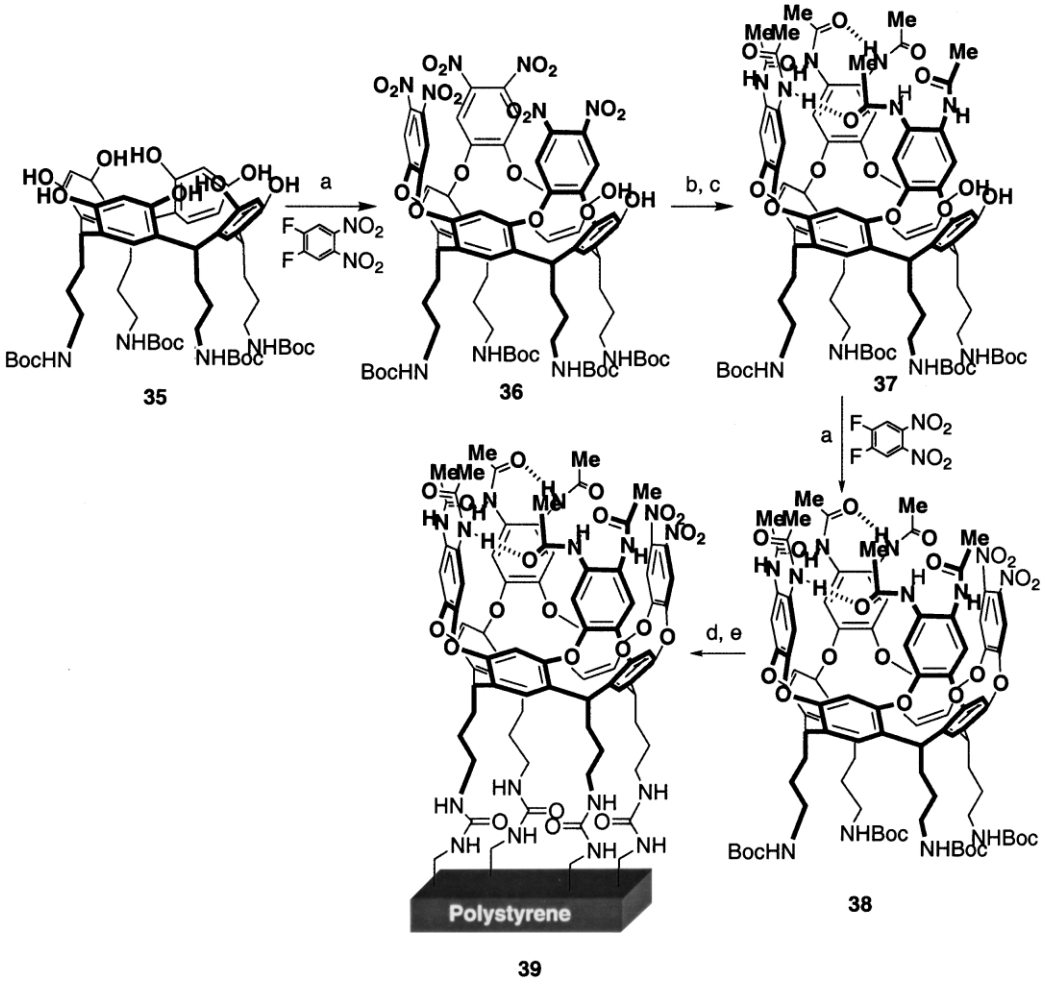


Figure 11. Uptake of guest molecules **33** and **34** (~1.5 mM) by polymer-bound cavitand **9** and by PEGA acrylamide **17** in water as measured by the absorbance at 298 K.



Scheme 9. (a) DMF, TEA. (b) PhMe, MeOH, H_2 Raney Ni. (c) Ac_2O, TEA, DMAP, CH_2Cl_2, then $NH_2NH_2{\cdot}H_2O$, EtOH. (d) TFA, CH_2Cl_2. (e) **13**, DIPEA, THF, reflux.

3. Conclusions

Our experiments indicate that immobilized cavitands effectively perform their duties on polymeric supports. The simplicity of the unselective attachments and the fact that increased crosslinking is not a true hindrance to proper function, augurs well for further developments in the chemistry of polymer-bound cavitands. The decreased swelling caused by the unselective attachments affects the extent of uptake but not inclusion itself. With the preparation of selectively functionalized aminofooted cavitand **38**, the development of more functional materials is within reach. In addition, the use of unselective attachments to a polymeric support is a promising approach for the immobilization of other related host molecules such as (hemi)carcerands.

4. Experimental

4.1. General methods

CH_2Cl_2 and DIPEA were kept over 4 Å molecular sieves for at least 24 h prior to use. THF was distilled through a drying column. Amides **24**–**28** were obtained as solids in 65–90% yield after crystallization, using textbook procedures of peptide chemistry. All other reagents were used as commercially available. Silica gel chromatography was performed with silica gel 60 (EM Science or Bodman, 230–400 mesh). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under a nitrogen atmosphere. ^{1}H NMR spectra were recorded on a Bruker DRX-600 spectrometer using solvent residues as reference. FTIR spectra were recorded on a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer. UV spectra were recorded on a Perkin–Elmer lambda12 UV/Vis spectrometer. High-resolution matrix-assisted laser desorption/ionization (HR MALDI FTMS) mass spectrometry experiments were performed on an IonSpec HiRes-MALDI Fourier transform mass spectrometer; DHB was used as a matrix. For high-resolution mass spectral data, for compounds with molecular weight of ≥2000, lower than 10 ppm resolution was achieved. Electrospray ionization (ESI) mass spectra were recorded on an API III Perkin–Elmer SCIEX triple quadrupole mass spectrometer. Elemental analyses were performed by NuMega, Inc. (San Diego, CA).

4.1.1. Polymer-bound cavitand 5. A solution of *N*-BOC footed cavitand **10**[6] (140 mg, 7.1×10^{-5} mol) in CH_2Cl_2 (26 mL) and TFA (18 mL) was stirred at rt for 1 h. The solvents were then removed in vacuo, and the resulting residue was dissolved in a mixture of dry THF (1.8 mL) and DIPEA (0.6 mL). This mixture was added to 200 mg (~0.22 mequiv.) of polymer-bound isocyanate **13**. The flask containing the cavitand was further rinsed with THF (2×0.4 mL) and DIPEA (0.4 mL), and the rinsings were added to the polymer suspension. The mixture was gently stirred at rt for 20 h, before 80 μL (0.63 mmol) of *p*-tolyl isocyanate was added, and the mixture further stirred for 3 h. The resulting resin was filtered, and washed with CH_2Cl_2 (3×2 mL). The resin was resuspended in CH_2Cl_2 (3 mL) and Et_2NH (1 mL) was added. The mixture was stirred for 1 h, and the resin was filtered and washed with 5×2 mL of each of CH_2Cl_2, THF, CH_2Cl_2 in this order. The polymer-bound cavitand **5** (286 mg, 99% yield, $\sim1.9\times10^{-4}$ equiv. g^{-1}) was obtained after drying in vacuo at 80°C for 3 h, and at rt for 24 h: IR (KBr disc): 1654 cm^{-1} (broad signal); elemental analysis (with a loading of 1.9×10^{-4} equiv. g^{-1}) calcd C 82.5%, H 7.1%, N 4.3%, found C 81.5%, H 7.3%, N 4.1%.

4.1.2. Polymer-bound cavitand 6. The resin **14** (50 mg, 0.049 mmol) is stirred in CH_2Cl_2 (2 mL) at rt for 15 min. The hydroxy-footed cavitand **11** (105 mg, 0.049 mmol) is then added and the mixture is chilled to 0°C followed by addition of *p*-TsOH (14.8 mg, 0.049 mmol) in one portion. The resulting suspension is stirred at 0°C for 48 h. The resin was then washed with CH_2Cl_2 (1×), 1:1 DMF/water (4×), DMF (3×), and CH_2Cl_2 (3×) and dried in vacuo (yield: 77.2 mg): IR (KBr disc): 3253, 3060, 3026, 2925, 2854, 1655, 1601, 1403, 1269 cm^{-1}; elemental analysis (with a loading of 2.1×10^{-4} equiv. g^{-1}) calcd C 80.0%, H 7.8%, N 2.4%, found C 78.4%, H 7.8%, N 2.4%.

4.1.3. Polymerizable cavitand 15. To a solution of 4-vinylbenzoic acid (111.2 mg, 7.51×10^{-4} mol) in CH_2Cl_2 (8 mL) cooled in an ice bath, was added oxalyl chloride (0.8 mL, 9.17×10^{-3} mol), dropwise. The mixture was stirred at the same temperature for 15 min and at rt for 20 h. The solvents were removed in vacuo and the resulting residue used as such.

To the crude hydroxyfooted self-folding cavitand **11** (170.8 mg, 7.96×10^{-5} mol) DMAP and (10.6 mg, 8.68×10^{-5} mol) in dry CH_2Cl_2 (2 mL), cooled in an ice bath, was added the previously prepared 4-vinyl benzoyl chloride in CH_2Cl_2 (1 mL). The acid chloride flask was further rinsed with 2×1 mL of dry CH_2Cl_2 and the rinsings added to the reaction mixture. After the dropwise addition of dry TEA (100 μL, 7.17×10^{-4} mol), the mixture was kept on ice for 2 h, and then left to come to rt on its own and stir there for a total of 16 h. The solvents were removed in vacuo and the residue was triturated with MeOH. The solid was collected and purified by chromatography (30% EtOAc in hexanes gave one fraction and 10% MeOH in CH_2Cl_2 gave the other), to give after trituration with MeOH 144.4 mg (5.41×10^{-5} mol, 64%) of product **15**: mp 156–158°C; IR (KBr disc): 3449, 3250, 2927, 2856, 1719, 1662, 1608, 1514, 1484, 1404, 1274 cm^{-1}; ^{1}H NMR(600 MHz, $CDCl_3$) δ 0.87 (6H, m), 1.16–1.45 and 1.55–1.90 (22H, m), 2.15–2.53 (6H, m), 4.43 (2H, t, J=6.7 Hz), 5.32 (1H, d, J=10.9 Hz), 5.79 (1H, d, J=17.6 Hz), 5.88 (1H, t, J=8.2 Hz), 6.67 (1H, dd, J=10.9, 17.5 Hz), 7.21 (1H, s), 7.30 (1H, s), 7.37 (2H, d, J=8.2 Hz), 7.74 (1H, s), 7.97 (2H, d, J=8.0 Hz), 9.08 (1H, s), 9.87 (1H, s); ESI-MS *m*/*z* 2664 ($M-H^+$), 2666 ($M+H^+$); HRMS-MALDI-FTMS calcd for $C_{164}H_{200}N_8O_{24}Na$ ($M+Na^+$) 2688.4567, found 2688.4710.

4.1.4. Polymer-bound cavitand 7. To a mixture of cavitand **15** (49 mg, 1.84×10^{-5} mol), benzoyl peroxide (14.8 mg, 6.11×10^{-5} mol), styrene (550 μL, 4.80×10^{-3} mol) and divinylbenzene (80% technical grade, 40 μL, 2.81×10^{-4} mol) in chlorobenzene (1 mL) was added 10 mL of a mixture of water (300 mL), polyvinyl alcohol (2 g) and NaCl (7.5 g). The mixture was stirred vigorously

to generate a good suspension and the reaction vessel was evacuated and filled with N_2 repeatedly. The mixture was stirred under N_2 at 85°C for 40 h. The resulting resin was washed with water, MeOH, acetone, acetone/MeOH (1:1), THF and CH_2Cl_2 (2×10 mL each). The material was then washed in a continuous extractor for 6 h with THF. It was dried in vacuo to a constant weight of 406.8 mg (68%): IR (KBr disc): 1719, 1656, 1592, 1492 cm^{-1}; elemental analysis (with a loading of 7.3×10^{-5} equiv. g^{-1}) calcd C 88.4%, H 7.7%, N 0.82% found C 86.6%, H 8.0%, N 0.82%.

4.1.5. Polymer-bound cavitand 8. The cavitand **12** (238 mg, 9.5×10^{-5} mol) was dissolved in CH_2Cl_2 (15 mL) and TFA (10 mL). After stirring for 1.5 h at rt, the solvents were removed in vacuo. The residue was taken up in a mixture of dry THF (0.5 mL) and dry DIPEA (0.3 mL) and added to (199 mg, $\sim2.2\times10^{-4}$ equiv.) of polymer-bound isocyanate **13**. The flask containing the cavitand was further rinsed with 3×0.5 mL of dry THF and the rinsings were added to the polymer suspension. This mixture was heated to reflux for 24 h. The resin was filtered and washed with 4×5 mL of each of acetone and CH_2Cl_2. It was resuspended in dry CH_2Cl_2 (2 mL) and *p*-tolyl isocyanate (150 μL, 1.2 mmol) was added. The mixture was stirred at rt for 2 h before Et_2NH (0.5 mL) was added. After another 2 h of stirring, the resin was filtered, washed with 4×5 mL of each of CH_2Cl_2, THF, THF/MeOH (1:1), MeOH, THF/MeOH (1:1), THF and CH_2Cl_2, and dried in vacuo. Yield: 326 mg (95%): IR (KBr disc): 3245, 3025, 2924, 1654, 1600, 1480, 1449 cm^{-1}; elemental analysis (with a loading of 1.6×10^{-4} equiv. g^{-1}) calcd C 83.5%, H 8.2%, N 3.5%, found C 82.5%, H 8.5%, N 3.2%.

4.1.6. PEGA acrylamide 17. A mixture of PEGA **16**[17] (248.4 mg, $\sim5\times10^{-5}$ equiv.) in dry DMF (3 mL) with DIPEA (370 μL, 2.12 mmol) was stirred at rt for 30 min before of acryloyl chloride (170 μL, 2.09 mmol) was added. The mixture was stirred at rt for 15 h, before another portion of DIPEA (370 μL) and acryloyl chloride (170 μL) were added. The mixture was stirred for another 3 h, it was filtered and washed with acetone, MeOH, acetone and CH_2Cl_2 (4×5 mL each). It was then dried in vacuo to give 308 mg of resin, used as such in the next step.

For the binding studies, the polymer was further purified by loading onto a continuous extractor and washing with MeOH for 24 h and with water for 24 h: IR (KBr disc): 2922, 1654, 1452, 1406, 1307, 1098 cm^{-1}; elemental analysis (with a loading of 2.0×10^{-4} equiv. g^{-1} and 7.5% by weight of water) calcd C 49.8%, H 7.2%, N 9.7%, found C 50.0%, H 7.8%, N 9.8%.

4.1.7. Polymer-bound cavitand 9. A solution of *N*-BOC footed cavitand **10**[6] (31.6 mg, 1.59×10^{-5} mol) in CH_2Cl_2 (7.5 mL) and TFA (5 mL) was stirred at rt for 1 h. The solvents were then removed in vacuo, and the resulting residue was dissolved in a mixture of dry DMF (2 mL) and DIPEA (0.6 mL). This mixture was added to PEGA acrylamide **17** (240.2 mg, $\sim4.8\times10^{-5}$ mequiv.). The mixture was gently stirred at 65°C for 20 h, under a N_2 atmosphere. The resulting resin was filtered, and washed with acetone (10×2 mL), MeOH (4×2 mL), acetone (10×2 mL), CH_2Cl_2 (4×2 mL). The polymer-bound cavitand **10** (242 mg, 90% yield) was obtained after drying in vacuo at rt for 24 h.

For the binding studies, the polymer was further purified by loading onto a continuous extractor and washing with MeOH for 24 h and with water for 24 h: IR (KBr disc): 2924, 1654, 1508, 1384, 1096 cm^{-1}; elemental analysis (with a loading of 4.6×10^{-5} equiv. g^{-1} and 7% by weight of water) calcd C 51.2%, H 7.3%, N 9.4%, found C 53.3%, H 7.3%, N 9.5%.

4.1.8. Hydroxy footed octanitrocavitand 19. To a solution of resorcinarene **18**[19] (776.4 mg, 1.08 mmol) and difluorodinitrobenzene (891.4 mg, 4.36 mmol) in DMF (50 mL) was added triethylamine (2.3 mL, 17.6 mmol), dropwise. The mixture was heated to 70°C for 18 h. The solvents were removed in vacuo. The resulting material was triturated with CH_2Cl_2, and the resulting precipitate was filtered and washed with 3×10 mL of CH_2Cl_2. It was then suspended in MeOH (10 mL) and sonicated for 5 min, before being filtered, and rinsed with 3×5 mL of MeOH. Finally after drying in vacuo at 60°C for 2 h, the desired cavitand **19** (964.2 g, 0.7 mmol, 65%) was obtained: mp >250°C; IR (KBr disc): 3396, 2938, 2874, 1594, 1541, 1402, 1364, 1286 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 330 K) δ 1.46 (2H, quintet, J=6.8 Hz), 2.44 (2H, d, J=6.8 Hz), 3.53 (2H, t, J=5.8 Hz), 4.31 (1H, broad s), 5.40 (1H, broad s), 7.79 (1H, broad s), 8.07 (1H, broad s), 8.71 (2H, s); ESI-MS m/z 1375 ($M-H^+$), 1399 ($M+Na^+$), 1411 ($M+Cl^-$).

4.1.9. Silyl protected octanitro cavitand 20. To a mixture of cavitand **19** (501.6 mg, 3.64×10^{-4} mol) and imidazole (141.8 mg, 2.08×10^{-3} mol) in dry DMF (5 mL) was added TBDPS-chloride (500 μL, 1.92×10^{-3} mol), and the mixture was stirred under N_2 for 20 h. The solvent was removed in vacuo and the residue was triturated in MeOH (10 mL) and the precipitate was collected and rinsed with 3×10 mL of MeOH. The solid was taken up in CH_2Cl_2 (50 mL) and was washed with 3% HCl and saturated $NaHCO_3$ solution, each time back extracting the aqueous layer with 2×20 mL of CH_2Cl_2. The organics were dried over $MgSO_4$, and concentrated in vacuo. The residue was triturated with 10 mL of MeOH, the precipitate filtered, washed with 3×5 mL of MeOH and dried in vacuo, to give of the product **20** (603.4 mg, 2.59×10^{-4} mol, 71%). The material was used as such but purer product can be obtained by chromatography of the solid in 1:1 hexanes/EtOAc: mp 236–239°C. IR (KBr disc): 3448, 3072, 2931, 2858, 1591, 1543, 1485, 1361, 1286 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 330 K) δ 0.97 (9H, s), 1.54 (2H, broad s), 2.02 (1H, broad s), 2.14 (1H, broad s), 3.62 (2H, t, J=6.2 Hz), 3.91 (1H, t, J=7.5 Hz), 7.24 (6H, broad m), 7.34 (3H, broad m), 7.57 (5H, m).

4.1.10. Silyloxyfooted self-folding cavitand 21. A catalytic amount of Raney Ni, washed with MeOH (4×5 mL) and EtOAc (2×5 mL), and suspended in 10 mL of MeOH, was added to a solution of cavitand **20** (1.0088 g, 4.33×10^{-4} mol) in THF (10 mL, added first to dissolve), toluene (140 mL) and MeOH (40 mL). The flask was evacuated and refilled with H_2 and this was repeated four times. The mixture was then stirred at 40°C under an

atmosphere of H_2 for 18 h. From this point all the solvents used were degassed by bubbling N_2 through for at least 20 min. The Raney Ni was then filtered under nitrogen and rinsed with 3×30 mL of degassed 1:1 THF/EtOH. The filtrate was reduced in vacuo, and redissolved in degassed EtOAc (30 mL). Under vigorous stirring, a solution of K_2CO_3 (1.8504 g, 1.02×10^{-2} mol) in water (30 mL) was added, followed by the dropwise addition of octanoyl chloride (1.75 mL, 5.85×10^{-4} mol). From this point on the solvents need not be degassed. After 4 h stirring at rt under nitrogen, the ethyl acetate layer was separated, and the aqueous layer was extracted with EtOAc (50 mL). The combined organics were washed with saturated $NaHCO_3$ solution (100 mL), which was in turn extracted with CH_2Cl_2 (50 mL). The organic layers were dried over $MgSO_4$ and reduced in vacuo. The residue was triturated with MeOH, and the solids were collected. They were purified by silica gel chromatography (CH_2Cl_2/toluene 1:1 to 3:1 with 2% TEA) to give product **21** (901 mg, 2.91×10^{-4} mol, 67%): mp 223–226°C. IR (KBr disc): 3424, 2927, 2855, 1662, 1599, 1516, 1483, 1404, 1273 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.86 (6H, m), 1.00 (9H, s), 1.27–1.32 and 1.49–1.75 (22H, m), 2.15–2.52 (6H, m), 3.68 (2H, m), 5.80 (1H, m), 7.13–7.33 (9H, m), 7.61 (4H, m), 7.74 (1H, s), 9.08 (1H, s), 9.87 (1H, s).

4.1.11. Hydroxyfooted self-folding cavitand 11. To a solution of cavitand **21** (302 mg, 9.74×10^{-5} mol) in THF (6 mL), was added acetic acid (250 μL) and 1 M TBAF in THF (6 mL), and the mixture was stirred at rt for 24 h. It was then concentrated in vacuo. The residue was triturated with ~5 mL of MeOH, filtered and rinsed with 3×2 mL of MeOH. After drying, this gave crude hydroxyfooted cavitand **11** (172.4 mg, 8.03×10^{-5} mol, 82%), which can be used as such. Purer material can be obtained by flash chromatography (3–5% MeOH in CH_2Cl_2): IR (KBr disc): 3247, 2928, 2856, 1663, 1600, 1404, 1274 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.86 (6H, t, J=5.6 Hz), 1.13–1.45 and 1.50–1.80 (22H, m), 2.15–2.55 (6H, m), 3.83 (2H, s), 5.76 (1H, t, J=8.2 Hz), 7.22 (2H, s), 7.53 (1H, s), 7.75 (1H, s), 9.06 (1H, s), 9.88 (1H, s); ESI-MS m/z 2144 ($M-H^+$), 2146 ($M+H^+$), 2168 ($M+Na^+$), 2180 ($M+Cl^-$); HRMS-MALDI-FTMS calcd for $C_{128}H_{176}O_{20}N_8Na$ ($M+Na^+$) 2168.2892, found 2168.3001.

4.1.12. *N*-BOC-(aminomethyl)benzaldehyde (23). (Aminomethyl)benzyl alcohol[25] (383 mg, 2.79 mmol) and potassium hydroxide (160 mg, 2.85 mmol) were dissolved in THF (11 mL) and water (3 mL). After dissolution is complete, di-*t*-butyl dicarbonate (756 mg, 3.46 mmol) was added, and the mixture was stirred for 45 min at rt. The mixture was added to water (50 mL) and CH_2Cl_2 (80 mL) and the organic layer was separated. The aqueous layer was extracted once more with CH_2Cl_2 (80 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to the crude BOC protected amino alcohol as a solid. This was dissolved in CH_2Cl_2 (10 mL) and added to a mixture of PCC (518 mg, 2.4 mmol) and sodium acetate (46 mg, 0.56 mmol). The mixture was stirred in the dark for 15 h. Then ether (60 mL) was added, and the mixture was triturated and filtered through celite. The filtrate was washed with water (60 mL), and this resulting aqueous layer was extracted with ether (60 mL). The combined extracts were dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by flash chromatoraphy (SiO_2, 20% to 40% EtOAc and 5% triethylamine in hexanes) to give product **23** (496 mg, 2.11 mmol, 76%) as an oil which solidifies on standing: mp 82–84°C; IR (KBr disc): 3351, 2983, 2927, 2740, 1712, 1676, 1610, 1508, 1366 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.44 (9H, s), 4.38 (2H, d, J=5.6 Hz), 5.00 (1H, broad s), 7.42 (2H, d, J=7.8 Hz), 7.82 (2H, d, J=7.9 Hz), 9.96 (1H, s); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 28.33, 44.32, 79.86, 127.67, 130.06, 135.49, 146.09, 148.74, 155.87, 191.86; ESI-MS m/z 236 ($M+H^+$); HRMS-MALDI-FTMS: calcd for $C_{13}H_{17}NO_3Na$ ($M+Na^+$) 258.1101, found 258.1093.

4.1.13. Self folding cavitand 12. A flask containing the crude diaminocavitand **22**, produced by the reduction of 548 mg (2.3×10^{-4} mol) of the dinitro precursor,[5d] nitrobenzene (5 mL) and the aldehyde **23** (76 mg, 3.2×10^{-4} mol) was evacuated and filled with nitrogen four times. It was then heated under N_2 to 135°C for 24 h. The nitrobenzene was removed in vacuo and the resulting residue was triturated with MeOH (5 mL) and the precipitate was filtered. This solid was purified by careful chromatography (SiO_2, 10–30% EtOAc and 2% triethylamine in hexanes) to afford the desired product **12** as a solid after trituration with MeOH (103 mg, 4.1×10^{-5} mol, 18%): mp 155–160°C; IR (KBr disc): 3243, 2925, 2854, 1663, 1600, 1514, 1484, 1274 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 0.6–1.9 (168H, m), 1.9–2.6 (20H, m), 4.31 (2H, s), 4.87 (1H, broad s), 5.66–5.75 (4H, m), 7.18–7.87 (20H, m), 8.30 (1H, broad s), 8.83 (1H, s), 9.11 (1H, s), 9.49 (1H, s), 9.69 (1H, s), 9.99 (2H, s), 11.68 (1H, s); MALDI-TOF MS m/z 2494 (M_{ave}).

4.1.14. Polymer-bound diethylphosphonoacetate 31. To a mixture of chloromethylated polystyrene **30**[21f] (1 g, ~0.33 mequiv.) and cesium carbonate (248 mg, 0.76 mmol) in dry DMF (5 mL) was added diethylphosphonoacetic acid (250 μL, 1.56 mmol). The mixture was stirred at 70°C under nitrogen for 6 h. The mixture was poured into water (20 mL), 3% HCl (3 mL) and CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer was extracted again with CH_2Cl_2 (20 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate and concentrated in vacuo. The residue was taken up in 3×1.5 mL of THF and added to vigorously stirring MeOH (100 mL) in an MeCN/dry ice bath. The precipitated polymer was filtered and washed with 3×15 mL of MeOH. This resulted, after drying in vacuo, in product **31** (954 mg, ~0.29 mequiv., 87%): ^1H NMR (600 MHz, $CDCl_3$) δ 0.87–2.22 (107H, m), 2.96 (2H, m), 4.11 (4H, s), 5.05 (2H, s), 6.35–7.27 (154H, m).

4.1.15. Soluble polymer-bound cavitand 32. A mixture of LiBr (58 mg, 0.67 mmol), cavitand **29**[5d] (49 mg, 2×10^{-5} mol), polymer-bound phosphonate **31** (99 mg, ~3×10^{-5} mequiv.), dry THF (500 μL) and triethylamine (78 μL, 0.56 mmol) was stirred at rt for 24 h, under N_2. The solution was added to vigorously stirring MeOH (75 mL) in an MeCN/dry ice bath. The precipitated polymer was filtered and washed with 3×10 mL of MeOH. This resulted, after drying in vacuo, in of product **32** (114 mg, ~1.4×10^{-5} equiv., 70%): ^1H NMR (600 MHz, $CDCl_3$) δ

0.82–2.49 (551H, m), 3.10 (2H, m), 3.73 (1H, m), 4.40+4.50 (4H, two overlapping s), 5.13 (2H, s), 5.70 (4H, two overlapping m), 6.25–7.71 (348H, m), 7.83 (1H, s), 8.51 (1H, s), 8.75 (1H, s), 8.94 (1H, s), 9.09 (1H, s), 9.76 (1H, s), 9.89 (1H, s), 11.73 (1H, s).

4.1.16. Hexanitro cavitand 36. Triethylamine (1.7 mL) was added to a solution of *N*-BOC-aminofooted resorcinarene **35**[6] (1.93 g, 1.73 mmol) and difluorodinitrobenzene (1.06 g, 5.20 mmol) in DMF (50 mL) in an ice bath and the reaction mixture was stirred at 60°C for 10 h. The reaction mixture was cooled and concentrated in vacuo. The resulting solid was purified by column chromatography to obtain the desired product as yellow solid (837 mg, 0.52 mmol, 30%): ^{1}H NMR (600 MHz, acetone-d_6, 320 K) δ 1.42–1.36 (36H, m), 1.51–1.46 (8H, m), 2.26–2.22 (8H, m), 3.15–3.09 (8H, m), 4.36 (1H, t, J=7.7 Hz), 4.49–4.45 (2H, m), 4.53 (1H, t, J=7.8 Hz), 5.84 (4H, br s), 6.76 (2H, s), 7.09 (2H, s), 7.25 (2H, s), 7.31 (2H, s), 7.97 (2H, s), 8.05 (2H, s), 8.08 (2H, s), 8.09 (1H, s), 8.38 (1H, s); ESI-MS m/z 1633 ($M+Na^+$), 1609 ($M-H^-$).

4.1.17. Hexaamide cavitand 37. To a suspended solution of Raney Ni in toluene (30 mL) and MeOH (10 mL) was added hexanitro cavitand **37** (0.50 g, 0.31 mmol) and the mixture was stirred under a H_2 atmosphere at 40°C. After 24 h, the solution was cooled, filtered through a pad of celite, and washed with CH_2Cl_2 and MeOH. The filtrate was concentrated to afford the corresponding hexaamine as a pale brown solid. This was dissolved in CH_2Cl_2 (20 mL), and acetic anhydride (0.22 mL), triethylamine (0.35 mL) and DMAP (50 mg) were added and the mixture was stirred at rt overnight. The reaction mixture was washed with water and dried over $MgSO_4$ and then concentrated in vacuo. A solution of the resulting in toluene (20 mL) and EtOH (20 mL), to which was added hydrazine (0.2 mL), was heated to 80°C for 3 h. The resulting solution was concentrated and purified by column chromatography to obtain hexaamide **37** as brown solid (122 mg, 7.3×10^{-5} mol, 23%): ^{1}H NMR (600 MHz, acetone-d_6) δ 1.42 (36H, s), 1.58–1.52 (8H, m), 2.24–2.21 (18H, m), 2.47–2.37 (8H, m), 3.15–3.10 (8H, m), 5.84–5.73 (4H, m), 6.02 (4H, broad s), 6.74 (2H, s), 7.67 (2H, s), 7.53 (4H, s), 7.70 (2H, s), 7.74 (2H, s), 7.78 (2H, s), 7.89 (4H, s), 8.84 (1H, s), 8.98 (1H, s), 9.57 (1H, s), 9.67 (1H, s); MALDI-TOF MS m/z 1705 ($M+Na^+$), 1721 ($M+K^+$).

4.1.18. Hexaamide-dinitro cavitand 38. Triethylamine (0.1 mL) was added to a solution of hexaamide cavitand **14** (122 mg, 7.3×10^{-5} mol) and difluorodinitrobenzene (30 mg) in DMF (10 mL) in an ice bath and the reaction mixture was stirred at 60°C for 20 h. The reaction mixture was cooled and the solvent was evaporated. The resulting solid was dissolved in EtOAc, washed with water, dried over $MgSO_4$, concentrated in vacuo and purified by column chromatography to obtain the desired product **38** as yellow solid (100 mg, 5.4×10^{-5} mol, 77%): ^{1}H NMR (600 MHz, acetone-d_6) δ 1.42 (36H, s), 1.60–1.51 (8H, m), 2.24–2.22 (18H, m), 2.40–2.37 (8H, m), 3.20–3.17 (8H, m), 5.87–5.64 (4H, m), 6.13 (4H, broad s), 7.54 (2H, s), 7.67 (2H, s), 7.73 (4H, s), 7.89 (2H, s), 7.92 (2H, s), 8.07 (2H, s), 8.48 (2H, s), 8.53 (2H, s), 9.50 (2H, s), 9.59 (2H, s); MALDI-TOF MS m/z 1868 ($M+Na^+$).

4.1.19. Polymer-bound cavitand 39. The procedure for polymer-bound cavitand **5** was applied to cavitand **38** (3 mg, 1.6×10^{-6} mol) and polymer-bound isocyanate **13** (17.8 mg, $\sim1.8\times10^{-5}$ equiv.) but the second reaction was run for 48 h at reflux. Yield 17.2 mg (83%): IR (KBr disc): 1634 (broad signal), 1600, 1506, 1488 cm^{-1}.

4.2. Determination of binding by UV spectroscopy

A solution of guest in toluene or water (~1 mM) was added in 2 mL aliquots to vials containing increasing amounts (10–35 mg) of polymer-bound cavitand. The resulting suspensions were sonicated for 0.5 h, before 1 mL aliquots of the supernatants were taken out and their absorbance measured.

The binding constant can be determined by a least squares analysis of the data fitted to the equation:

$$A_0/A = 1 + KW$$

where A is the absorbance, A_0 is the absorbance in the absence of polymer, K is a constant and W is the weight of polymer. The corresponding plots are presented in Figs. 5, 9 and 11.

4.3. Competition studies for amides 26 and 27 versus 28

4.3.1. Binding of amides 26 and 27 versus 28. A 1:1 mixture of the two amides (~5–10 mg of each) was dissolved in 3.2 mL of *p*-xylene-d_{10} and 0.8 mL aliquots were added to NMR tubes containing nothing (a bank), ~20 mg of polymer-bound cavitand **5**, ~14 mg of polystyrene, ~2.5 mg of cavitand **10**, respectively. The tubes were sonicated for 2 h, and their respective ^{1}H NMR spectra were measured.

4.3.2. Release experiments of amides 26 and 27 versus 28. 1:1 solutions of the two amides were prepared as for the previous competition experiments and a 0.8 mL aliquot was added to ~20 mg of polymer. A blank was also prepared. The resulting tubes were sonicated for 2 h, and their ^{1}H NMR spectra measured. The supernatant of the tubes containing the polymer were pipetted out, and 0.6 mL of fresh *p*-xylene-d_{10} were added. The tubes were manually shaken for 4–5 min and the spectra measured once more. The same procedure was repeated for the second and third releases.

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