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Synthesis and Applications of a Deep, Asymmetric Cavitand on a Solid Support

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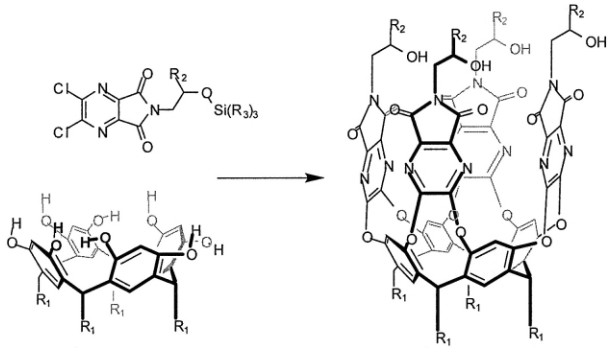
Abstract—The synthesis of an optically active cavitand and its attachment to a polystyrene support are described. The cavitand is used for selective recognition based on size and shape of guest molecules in solution.

We have been concerned with the synthesis and characterization of receptors that reversibly, but more or less completely, surround their targets. The resulting host–guest complexes represent a special form of molecular recognition: molecules within molecules.[1] We recently introduced a new structural motif[2] based on Högberg's resorcinarenes,[3] and showed that asymmetric microenvironments can be achieved within their vase-like cavities. Here we describe new receptors within this series, and explore their recognition properties when attached to a solid support.[4]

The molecules are made by condensing the octol[2] with activated dihalides of substituted aromatic imides[5] as shown in Scheme 1. Unmasking of the alcohol function attached to the imide nitrogens then leads to the hydrogen bond donors involved in stabilizing the receptor's conformation. Two means of stabilization are available, those that involve a cooperative seam of hydrogen bonds involving only the alcohols as donors and acceptors, and those involving alcohols as donors and the amide carbonyls as acceptors (Fig. 1). In either case, the seemingly remote chiral centers on these side chains impart an unusual folding arrangement of the walls of the cavity. This induced asymmetry then allows the cavity to assume shapes capable of enantioselective recognition.

For attachment to a conventional solid support we chose the phenyl ethanolamine derivative (Scheme 2) described previously. The synthesis began with the octapivalate derivative which was oxidized with *m*-chloroperbenzoic acid in chloroform at room temperature.[6] Hydrogenation of the alkenes with concomitant hydrogenolysis of the epoxide gave mostly the secondary alcohol, contaminated with a small amount of the primary alcohol from which it could not be separated. Removal of the pivalates by lithium aluminum hydride in ether restored the eight phenol functions. The latter were condensed with the appropriate dichloropyrazene derivative to give the fully protected, monofunctionalized cavitand.

The silyl-blocking groups were removed with the anticipation that the intramolecular seam of hydrogen bonds at the top of the vase, as well as at the bulk of the nearby phenyl groups would protect the four alcohols from further reactions with electrophiles. This expectation was borne out during model reactions of the remaining lower rim alcohol with dihydropyran. Accordingly, when the intact cavitand was treated with



Scheme 1. General synthetic scheme for constructing the chiral cavitand.

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the polymer-bound dihydropyran derivative we were able to anchor it to a commercial[7] solid phase and characterize it by IR spectroscopy. The loading level as judged from the weight gain was approximately 40 mg of cavitand/200 mg of the commercial resin.

In the first application, the selective extraction of norbornene from solutions of it and adamantane were explored. A simple pipette was loaded with the solid support and an approximately equimolar mixture of norbornene and adamantane in deuterated *p*-xylene was dripped through. After one rinse with additional *p*-xylene, the solid phase was treated with a mixture of deuterated methanol and chloroform and this solution phase was examined directly by NMR. The spectrum is shown in Figure 2 and reveals a very large selectivity of the polymer-bound cavitand for norbornene over adamantane (>100:1; Fig. 3). The small peak for adamantane was confirmed by adding adamantane to that solution as shown in the inset of the lower NMR spectrum.

A second application involved the resolution of 1,2-*trans*-cyclohexane-diol. Equilibration of the solid phase

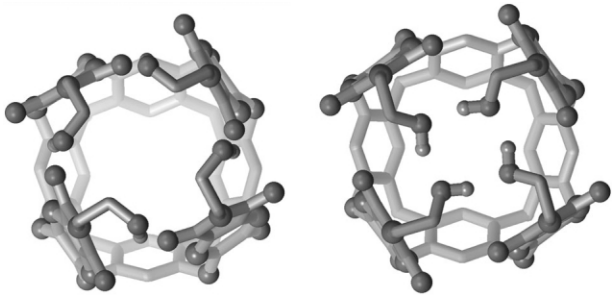
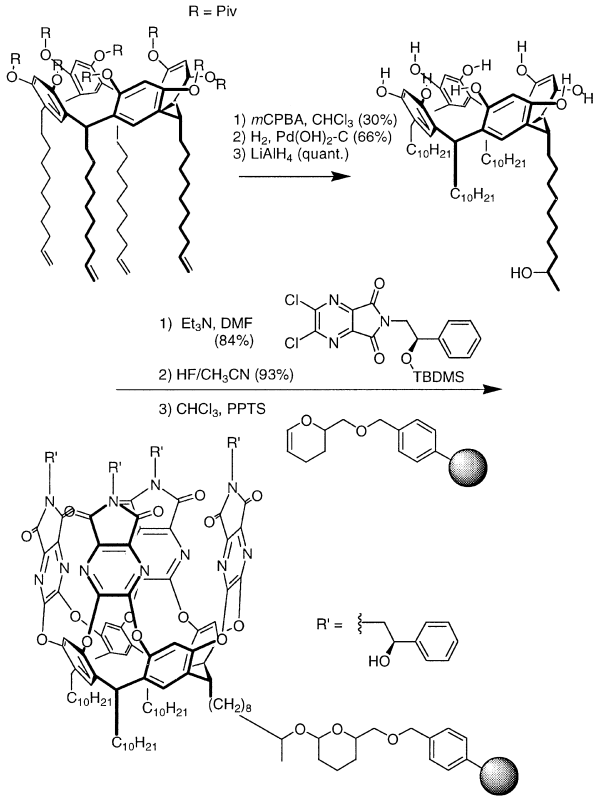


Figure 1. Two possible arrangements of intramolecular hydrogen bonds: (a) between alcohol and carbonyl; (b) between alcohols. The peripheral alkyl groups have been removed for viewing clarity.



Scheme 2. Synthesis of the cavitand and its attachment to the solid

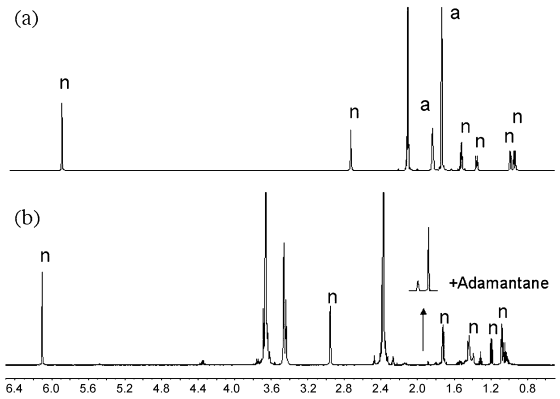


Figure 2. Selective extraction: ^{1}H NMR spectrum of norbornene (n) and adamantane (a) are shown. (a) Loading solution (d_{10}-*p*-xylene) ([n]:[a] = 1:0.94). (b) Extract ($CDCl_3$–CD_3OD) from the resin. ([n]:[a] >100:1), the inset locates the signals for added adamantane in the solvent mixture.

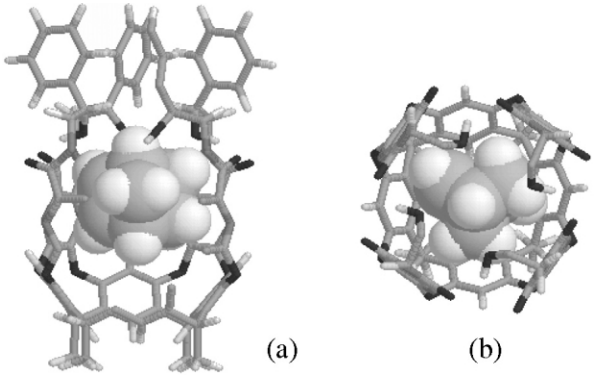


Figure 3. Model for norbornene in the cavitand. (a) Side view; (b) top view. Some atoms have been removed for viewing clarity.

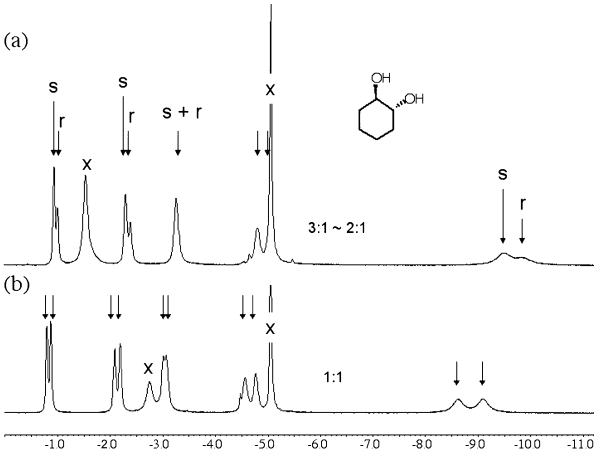


Figure 4. Resolution: ^{1}H NMR spectrum of 1,2-*trans*-cyclohexane-diols (solvent: $CDCl_3$) are shown. (s: (1*S*,2*S*)-isomer, r: (1*R*,2*R*)-isomer): (a) Extract from the resin; (b) racemic mixture. Both spectra have X (praseodymium tris [3-(hepta-fluoropropylhydroxy methylene)-(+)-camphorate]) added as the shift reagent.

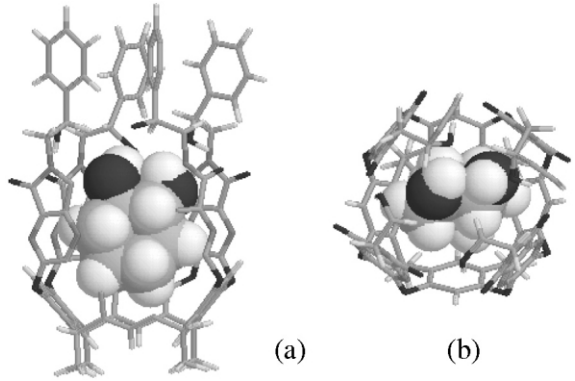


Figure 5. Models of 1,2-*trans*-cyclohexane-diol in the cavitand: (a) side view; (b) top view. Some peripheral atoms are removed for viewing clarity.

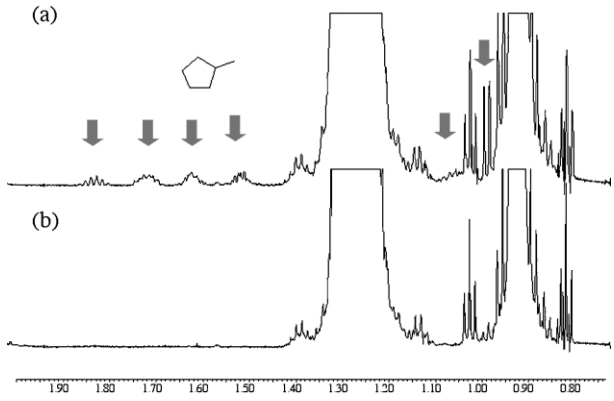


Figure 6. Purification of *n*-hexane. *n*-Hexane (solvent: d_{10}-*p*-xylene) are shown. (a) Commercially available 99+ % *n*-hexane. Indicated peaks are from contaminating methylcyclopentane; (b) *n*-hexane after treatment with the polymer-bound cavitand.

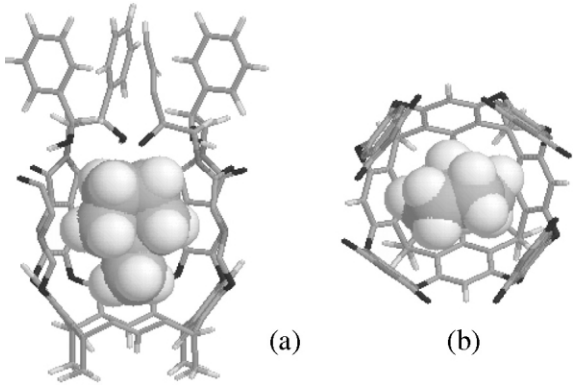


Figure 7. Model for methylcyclopentane in the cavitand. (a) Side view; (b) top view. Some atoms are removed for viewing clarity.

with the racemic solution was followed by a rinse with *p*-xylene as described before. Again, extraction with chloroform/methanol gave a sample that was subjected to NMR study with a chiral shift reagent (praseodymium tris [3-(hepta-fluoropropylhydroxy methylene)-(+)-camphorate]). The analysis showed between a 2:1 and 3:1 selectivity for the appropriate enantiomer (Figs. 4 and 5).

Finally, an application involving the purification of the solvent *n*-hexane was accomplished. The commercially available material (99+%) has as the principal impurity (<1%) methylcyclopentane, an excellent guest for the parent cavitand. The NMR spectrum of the commercial solvent at high amplitude is shown in Figure 6, where the methylcyclopentane resonances are identified. We used the pipette loaded solid support as described above, and compared the NMR spectra of the solution (deuterated *p*-xylene) phases before and after treatment with the polymer. As apparent in the spectrum, the methylcyclopentane content is now undetectable.

In summary, the utility of the polymer-bound cavitand has been established for highly selective binding of norbornene and methylcyclopentane (Fig. 7). The diastereo selectivity observed to date is only modest. Even so, the transmission of asymmetry from the peripheral groups to the shape of the cavity promises applications of these cavitands as reaction chambers for selective processes.

Acknowledgements

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