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Lower Rim Functionalized Resorcinarenes: Useful Modules for Supramolecular Chemistry

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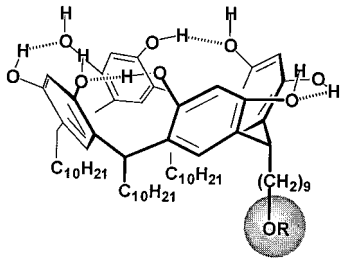
ABSTRACT



A synthetic scheme for the selective functionalization of all-cis (rccc) resorcinarene platform at the "lower rim" was developed. Self-folding and self-complementary cavitands were prepared for molecular recognition and self-assembly, bearing functionality at remote sites. These molecules promise applications on solid support and as polymeric capsules.

Resorcinarenes such as **1** (Figure 1) are cyclic tetramers obtained from the condensation of resorcinol with appropriate aldehydes.[1] They are enormously popular platforms for studying molecular recognition phenomena.[2] Broad applications exist in the direct complexation of cations and other polar organic molecules (e.g., carbohydrates, nucleosides, etc.):[3] they are starting materials for the syntheses of various open-ended cavitands,[4] they are the subunits for the original closed-surface carcerands,[5] they serve as platforms for large molecular cavities,[6] and they even self-assemble as large hydrogen-bonded structures—directly[7] or after simple modifications.[8] Their binding properties have been studied in the solid state, the gas phase, in solution, and even on a gold

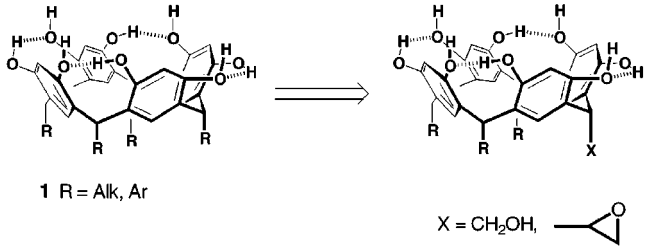


Figure 1. Resorcinarene platform **1** and its lower rim functionalized derivatives.

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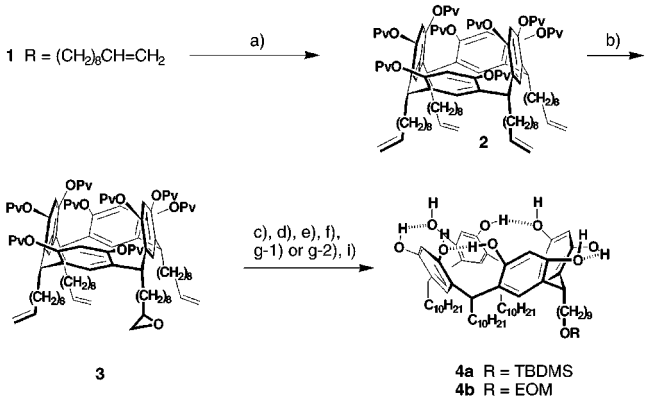
Scheme 1



(a) *t*-BuCOCl, $(i\text{-Pr})_2$NEt, DMAP, CH_2Cl_2 (56%); (b) *m*-CPBA(1.2eq), $CHCl_3$(34%); (c) H_2, Pd-C, AcOEt; (d) CF_3SO_3H, THF-H_2O (10:1)(65%, 2steps); (e) $NaIO_4$, MeOH; (f) $NaBH_3CN$, MeOH (85%, 2 steps); (g) 1) TBDMSOTf, $(i\text{-Pr})_2$NEt, CH_2Cl_2 (86%) ; 2) $EtOCH_2Cl$, $(i\text{-Pr})_2$NEt, CH_2Cl_2 (90%); (i) $LiAlH_4$, ether (quant)

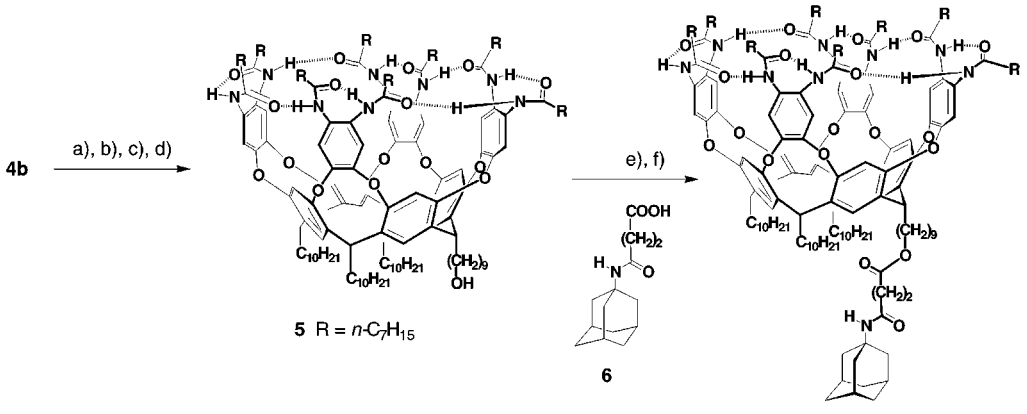
surface as self-assembled monolayers.[2−9] The cavities of the resorcinarene-based hosts are built only at their upper rims; the substituents at the lower rim are not involved in the complexation directly but offer a means to control solubility. In this Letter, we describe the selective functionalization of the lower rim (Figure 1) and demonstrate its use for the preparation of self-complementary cavitands. We believe this opens further applications of resorcinarenes and their derivatives as new polymers and as analytical devices through attachment to solid supports, silica gel, etc.

Partial functionalization of the resorcinarene lower rim is unknown. The (stepwise) condensation of resorcinol with two different aldehydes does give a mixture of resorcinarenes but the desired all-cis vase-like structure is not the major product.[10] Resorcinarene **1** (R = $(CH_2)_8CH{=}CH_2$), prepared as an all-cis (*rccc*) isomer in a high yield from resorcinol and 10-undecenal (Scheme 1),[11] was protected as its octapivalate **2** and then oxidized. We employed *m*-chloroperbenzoic acid in $CHCl_3$ at room temperature to control the oxidation of the four double bonds. Monoepoxide **3** was obtained in 34% yield along with the bis-epoxides (isolated in ca. 20% yield). The three remaining double bonds of **3** were hydrogenated by Pd/C in EtOAc; then the epoxide was hydrated under acidic conditions. Oxidative cleavage of the resulting diol removed the asymmetric center, and reduction to the corresponding alcohol was followed by protection with either TBDMS triflate or $EtOCH_2Cl$. Finally, the pivaloyl groups were cleaved with $LiAlH_4$ in ether, followed by basic workup, to give the desired resorcinarenes **4a**,**b** (Scheme 1).[12]

Self-folding[13] cavitands **5** and **9** were synthesized to demonstrate preparative applications of the monofunctionalized modules (Schemes 2 and 3). Functionalized resorcinarene **4b** was converted to cavitand **5** via coupling with 1,2-difluoro-4,5-dinitrobenzene in DMF in the presence of Et_3N, followed by the reduction with Raney Ni. The (unstable) octaamine was acylated with *n*-octanoyl chloride under Schotten−Baumann conditions in EtOAc−H_2O in the presence of K_2CO_3 and then deprotected. Alternatively, resorcinarene **1** (R = $(CH_2)_8CH{=}CH_2$) was coupled with 1,2-difluoro-4,5-dinitrobenzene with the formation of octanitro compound **8** in 70% yield. Reduction of the octanitro derivative with $SnCl_2{\cdot}2H_2O$ in boiling EtOH and concentrated HCl, acylation as described above, and then epoxidation with *m*- chloroperbenzoic acid gave octaamide **9** in 30% yield (Scheme 3). The sequence described for epoxide **3** gave cavitand **5**.

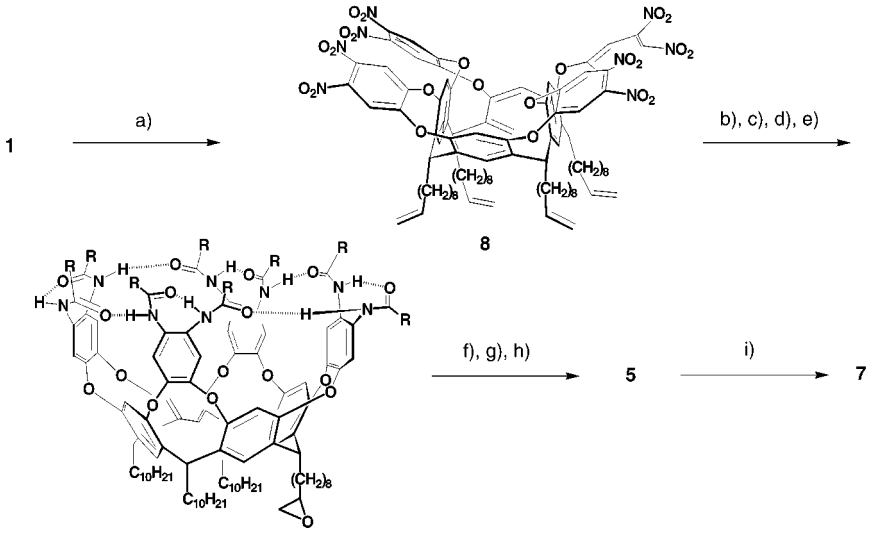
The ^{1}H NMR spectra of **5** and **9** in various nonpolar solvents showed the spectroscopic earmarks of self-folding cavitands.[13,14] The compounds have a "vase" conformation at room temperature, including the characteristic methine CH triplet at ∼6 ppm. The two N−H resonances are far downfield (9 ppm) and suggest strong intramolecular hydrogen bonding. The two amides present hydrogen bonds that bridge adjacent rings—interannular binding—and are held in place by the seven-membered intraannular hydrogen bonds. These cavitands are expected[13] to form kinetically

Scheme 2



(a) 1,2-difluoro-4,5-dinitro-benzene, Et_3N, DMF (70%); (b) Raney-Ni, H_2, toluene; (c) *n*-$C_7H_{15}COCl$, AcOEt-H_2O, K_2CO_3; (d) CF_3COOH, CH_2Cl_2; (e) K_2CO_3, MeOH (quant., 2steps); (f) DCC, DMAP, CH_2Cl_2 (40%)

Scheme 3



(a) 1,2-difluoro-4,5-dinitrobenzene, Et_3N, DMF (70%); (b) $SnCl_2$-$2H_2O$, EtOH-HCl; (c) n-$C_7H_{15}COCl$, $CHCl_3$-H_2O, NaOH (37%, 2 steps); (d) m-CPBA (1.2eq), $CHCl_3$ (29%); (e) H_2, Pd-C, AcOEt (quant.); (f) CF_3SO_3H, THF-H_2O; (g) $NaIO_4$, MeOH; (h) $NaBH_3CN$, MeOH (80%, 3 steps); (i) DCC, DMAP, CH_2Cl_2, **6** (40%)

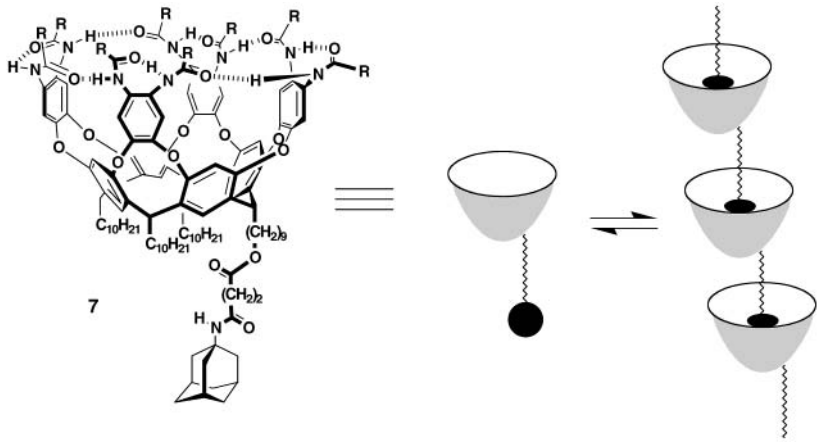


Figure 2. Self-complementary cavitand **7** and a cartoon representation of noncovalent polymer formation.

stable host−guest complexes with neutral molecules such as adamantane and cyclohexane derivatives. Accordingly, cavitand **5** was outfitted with its own adamantyl appendage: 1-aminoadamantane was treated with succinic anhydride and the resulting acid **6** was then linked to the terminal hydroxyl of **5** using DCC. The *self-complementary* cavitand **7** is

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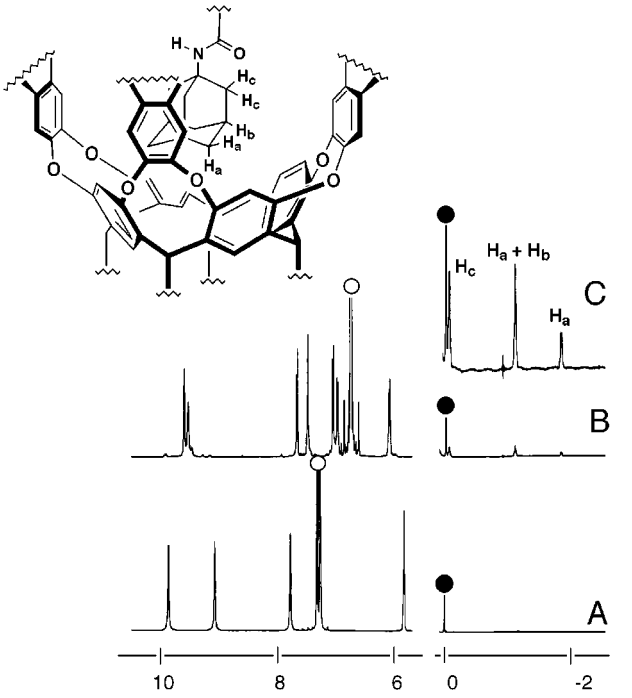

Figure 3. Downfield and upfield regions of the ^{1}H NMR spectra (600 MHz, 295 K, 2.9 mM) of cavitand **7**. (A) In $CDCl_3$. No adamantyl encapsulation is detected. (B) In *p*-xylene-d_{10}. (C) Expanded upfield region of B which shows the adamantyl encapsulation. The solvent signals and the internal standard singlet are designated as ○ and ●, respectively. The C(O)−NH signals are situated at 10−9 ppm; the methine CH triplet is at ∼6 ppm. The encapsulated adamantyl signals were assigned as in ref 13.

geometrically precluded from intramolecular complexation, but can easily do so in an intermolecular manner (Figure 2). The ^{1}H NMR spectrum of **7** in *p*-xylene-d_{10} solution clearly showed adamantane encapsulation (Figure 3). The CH signals for the adamantane fragment were observed *upfield* of 0 ppm, a feature characteristic of inclusion in a shielded environment.[13] The exchange between complexed and free guest species is slow on the NMR time scale, as two sets of signals—both for the cavitands and the corresponding oligomeric caviplexes—were observed (Figure 3). Because the association constant is not high (∼100 M^{-1}),[13] only ∼15−20% of the dimeric form is seen under these conditions and higher oligomers are expected to be present only at high concentrations. Even so, this is a rare example of a *kinetically* stable assembly which is held together by the weakest of intermolecular forces—van der Waals interacions and solvophobic effects. In $CDCl_3$, where the cavity−adamantyl association is known to be negligible,[13] no encapsulation was observed (Figure 3).

In conclusion, a resorcinarene platform with a lower rim attachment site is now available for additional applications in molecular recognition. We are currently exploring some of these and will report on them in due course.

Acknowledgment. We are grateful to the Skaggs Research Foundation and the National Institutes of Health for support. The Sankyo Co provided fellowship support to S.S.

Supporting Information Available: Spectral data for compounds **2**−**9** and their intermediates, representative ^{1}H NMR spectra. This material is available free of charge via Internet at http://pubs.acs.org.

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(12) All new compounds were characterized by high-resolution ^{1}H and ^{13}C NMR spectroscopy and high-resolution (HRMS-FAB) mass spectrometry. The detailed experimental description will be published in a full paper. The conformations depicted in Schemes 1−3 for compounds **2**−**9** were established by ^{1}H NMR spectroscopy.

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(14) Selected ^{1} H NMR (300 MHz, $CDCl_3$) spectroscopic data. Cavitand **5**: δ 9.88 (s, 4 H), 9.05 (s, 4 H), 7.74 (s, 4 H), 7.3−7.2 (m, 12 H), 5.74 (t, J = 8 Hz, 4 H), 3.65 (br t, J = 7 Hz, 2 H), 2.6−0.8 (m, 199 H). Cavitand **9**: δ 9.89 (s, 4 H), 9.06 (s, 4 H), 7.74 (s, 4 H), 7.4−7.1 (m, 12 H), 5.72 (t, J = 8 Hz, 4 H), 2.9 (m, 1 H), 2.7 (br t, J = 4.6 Hz, 1 H), 2.5−0.8 (m, 200 H).