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Chiral recognition by hemicarcerand-like host in aqueous solution

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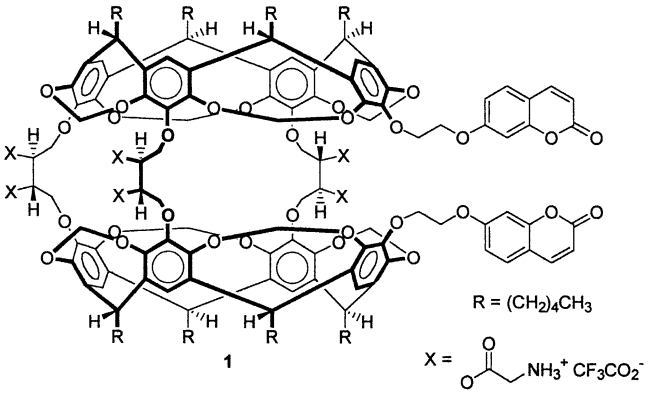
Abstract—The synthesis and binding properties of a hydrophilic hemicarcerand-like host with three chiral linker groups and one enlarged opening, that is partially blocked by two appending coumarin moieties, are reported. The complexation behavior towards three achiral and eight chiral guests were investigated. For those guests, in which binding was observed, guest exchange was slow on the NMR time scale and allowed the observation of free and complexed guest signals. At 22°C, binding affinities ranged from 1.4 to 370 mol^{-1}. Guest binding is driven by enthalpy. In binding studies with racemic guests, the highest diastereomeric excess of complexation (de=20%) was observed for racemic 3-methylcyclohex-1-ene. The much lower de for racemic 3-methylpent-1-ene suggests that guest rigidity is important to achieve selectivity.

1. Introduction

Hemicarcerands are an exceptional class of host molecules that bind a single guest molecule with high selectivity that depends mainly on the guest's size and shape.[1] Despite the application of hemicarcerands in the stabilization of reactive intermediates,[2] and for molecular delivery,[3] little effort has been undertaken to modify them for specific applications that might profit from their superb binding properties. Possible applications include the molecular sensing of biomolecules and also their use as catalysts for asymmetric induction.[4] For these applications a large difference in the affinity for the two enantiomeric ground states or transition states, respectively is desired. The latter might translate into different reaction rates for the formation of both enantiomeric products. In this work, we focus on answering the question whether chiral recognition is possible inside the inner phase of a chiral hemicarcerand with one extended equatorially located portal?[5,6] The expected fast guest exchange through the extended portal might be desirable for the above mentioned applications.

For our investigations, we have designed the chiral tris-bridged hemicarcerand **1** with six attached glycine units to achieve solubility in hydroxylic polar solvents.[7] In addition, hemicarcerand **1** has two coumarin groups, which are attached via flexible ethylene-dioxy linking groups. We envisioned that these groups might provide the hemicarcerand with two novel properties:



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(a) *An optical sensor for complexation events*. In polar solvents, one coumarin unit might occupy the inner phase (equilibrium 1, Scheme 1). Upon binding of a guest, this coumarin unit would be expelled from the hydrophobic inner phase to the polar bulk phase leading to an environment-induced fluorescence emission change (equilibrium 3, Scheme 1).[8] For example, the emission of **2** increases by about two orders of magnitude upon changing the solvent from ethyl acetate to water. Such a medium induced modulation of the fluorescence properties has earlier been utilized in the design of cyclodextrin based molecular sensors.[9]

(b) *Gating*.[10] Alternatively to the above described sensing of guest-binding events, both coumarin units might π-stack in a polar medium which could increase the barrier for guest exchange.

Keywords: hemicarcerand; chiral recognition; host–guest chemistry.

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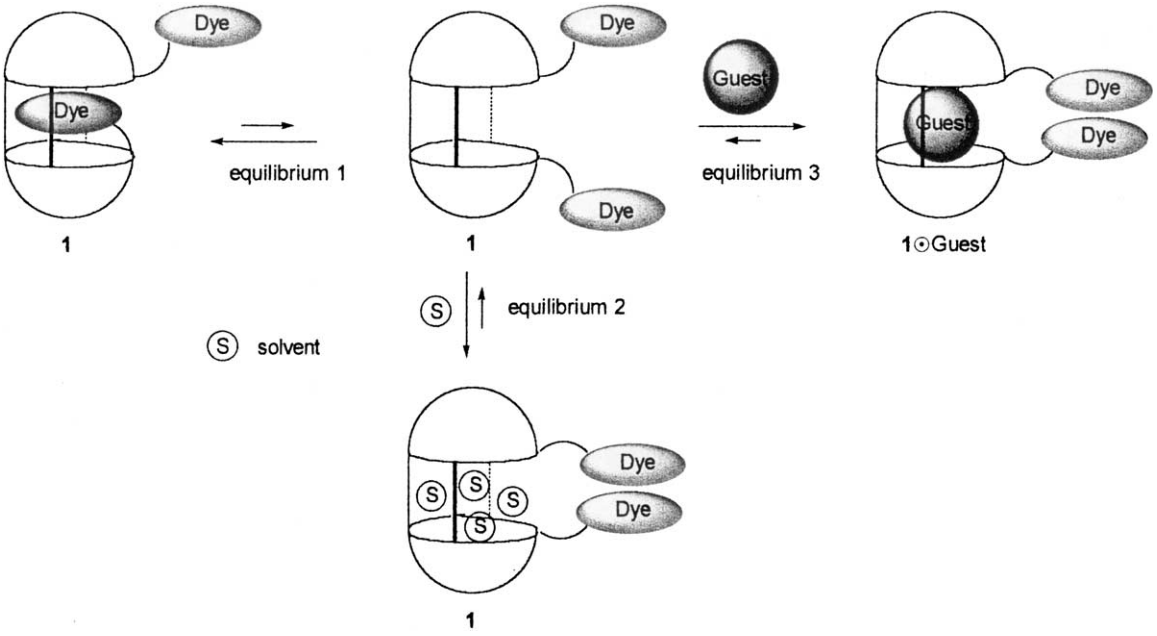


Scheme 1.

Here, we wish to report the synthesis of hemicarcerand **1** and its binding properties. Our results suggest, that the coumarins do not function as temporary 'host-cavity-fillers' in the absence of guests but are still able to sense binding of a chiral guest.

2. Results and discussion

2.1. Synthesis of chiral hemicarcerands

We prepared the chiral hemicarcerand-like diol host **3**

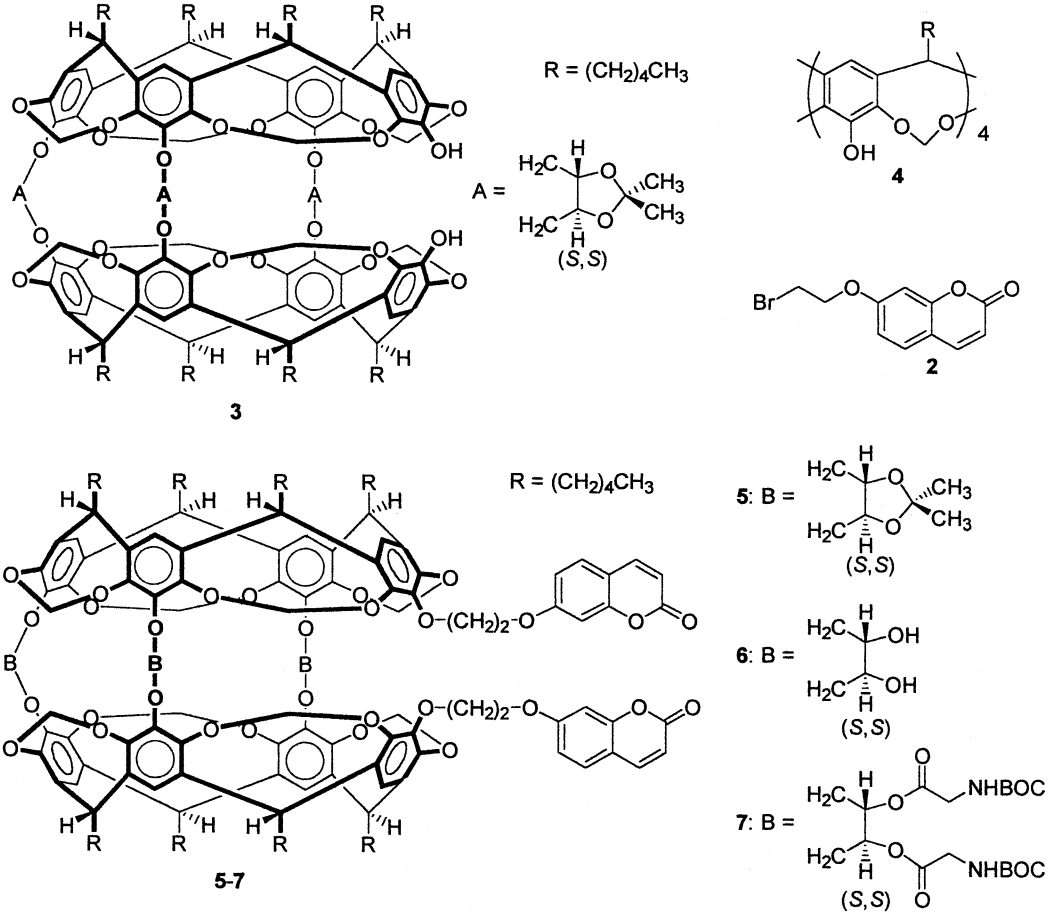


Chart 1.

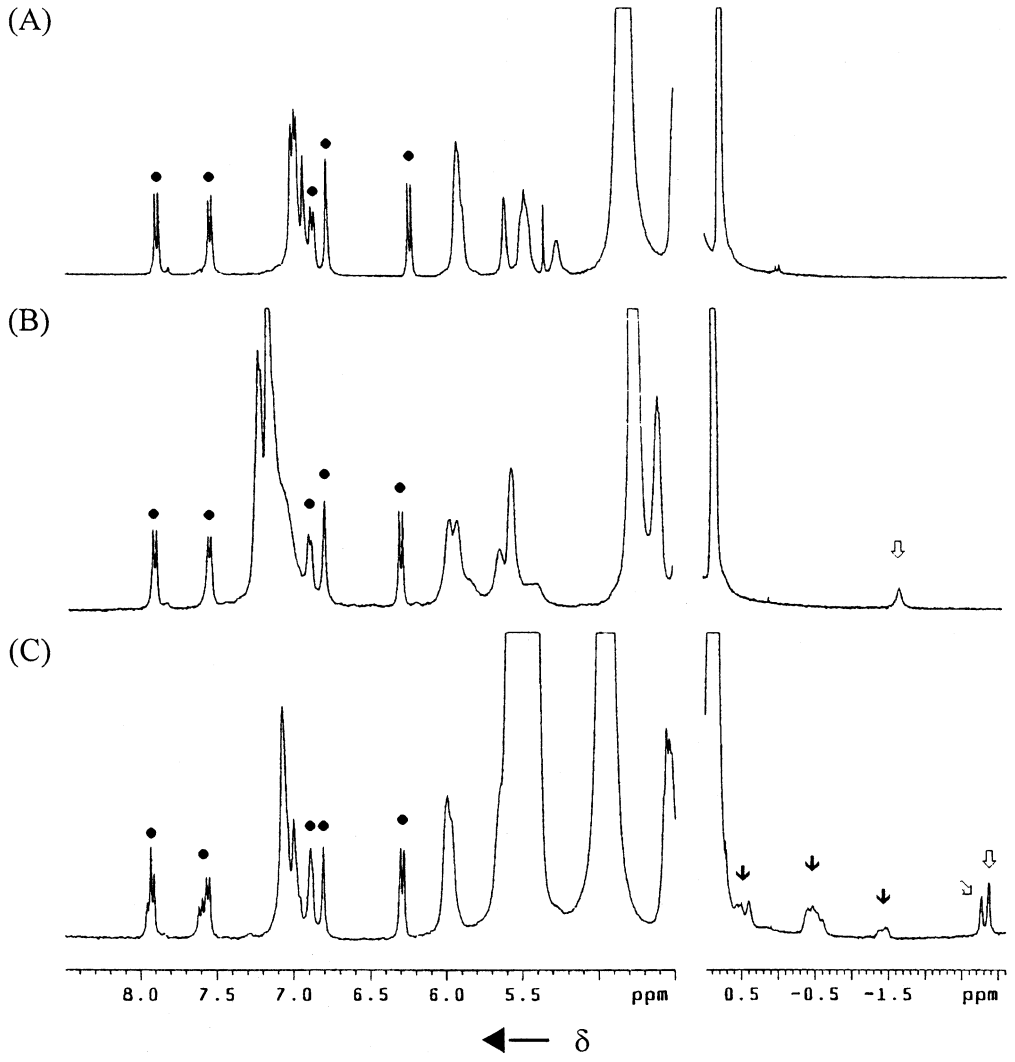


Figure 1. Partial ^{1}H NMR spectra (400 MHz; $D_2O/CD_3OD/CD_3COOD$ (10:5:1) at 22°C (A, C) and 40°C (B)) of **1** in the absence (A) and in the presence of excess toluene (B) or (+/−)-**12** (C). Multiplets marked with black dots (●) indicate the protons of the coumarin moieties of **1**. The singlet (B) and the doublets (C) marked with open arrows (⇩) indicate the guest methyl protons of **1**⊙toluene (B) or of the diastereomeric complexes **1**⊙(+)-**12** and **1**⊙(−)-**12** (C). Filled arrows (⬇) indicate methylene and methine protons of complexed **12** (C).

according to a modified procedure published by Cram and coworkers for the related phenethyl-footed diol-host (Chart 1).[5c] The slow addition of 2 equiv. of cavitand **4**[11] and 8 equiv. of (*S*,*S*)-(−)-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol to a suspension of Rb_2CO_3 in DMA afforded **3** in 15% yield. Diol **3** was further modified by attaching two coumarins units to its shell. First, the coumarin linker group **2** was prepared by reacting 7-hydroxycoumarin with excess 1,2-dibromoethane in DMF in the presence of K_2CO_3.[12] The reaction of 3 equiv. of **2** with **3** and K_2CO_3 in DMF for 8 days afforded **5** in 50% yield.

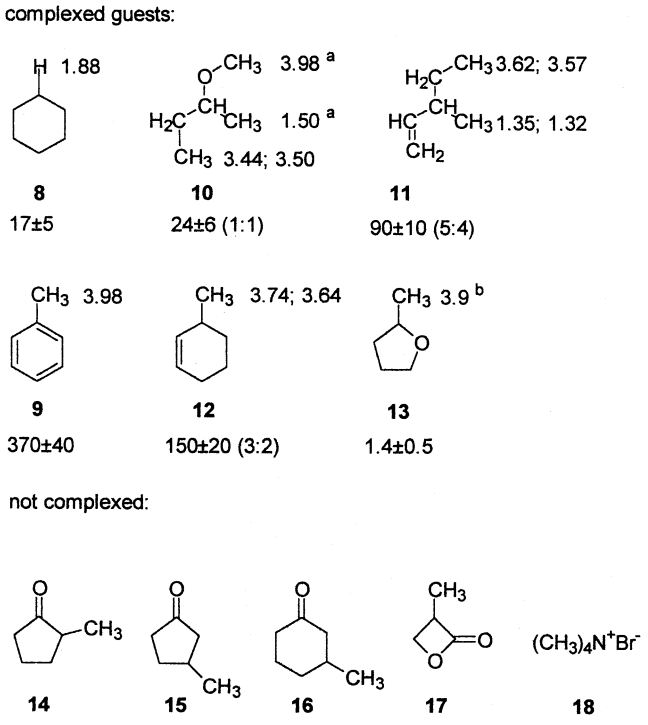
The subsequent acid-catalyzed deprotection of **5** in $CHCl_3$/CH_3OH/H_2O/TFA (6:1:1:2; 10 days at 60°C) yielded quantitatively **6**, whose six hydroxyl groups are expected to increase its solubility in hydrophilic solvents. Host **6** is soluble in CH_2Cl_2/CH_3OH mixtures (2:3 (v/v)) however not in pure methanol. In order to increase its hydrophilicity, we reacted **6** with excess N-BOC-glycine in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide and catalytic amounts of DMAP to afford host **7**. Deprotection of the six protected glycines of **7** with cold trifluoroacetic acid gave the protonated host **1**, which is soluble in water/methanol/acetic acid mixtures (10:5:1) in millimolar concentrations.

2.2. Fluorescence properties

Addition of potential guests to a dilute solution of **1** in water/methanol/acetic acid 95:4:1 (v:v) unfortunately did not enhance the fluorescence emission spectrum of the appended coumarins. Thus, the equilibriums in Scheme 1 are shifted towards the solvent filled host with both dyes bulk phase exposed. This interpretation is consistent with the absence of large upfield shifts for the coumarin protons in the NMR spectrum of **1** in aqueous solution prior to and after the addition of a guest (Fig. 1(A) and (B)).

2.3. Guest binding studies

Even though the emission and nuclear magnetic properties and of **1** are essentially unchanged upon the addition of



Scheme 2. Complexed and not complexed achiral and chiral guests. The binding constants (in mol^{-1} at 22°C) and diastereomeric ratio (in parentheses) are given underneath the compound number. Host induced upfield shifts of the ^1H NMR signals of selected guest protons are written next to the guest protons. (a) Both diastereomeric complexes had identical chemical shifts, (b) signal was too broad to allow a determination of the diastereomeric ratio.

small non-polar organic molecules to a solution of **1**, the observed large characteristic upfield shifts for the complexed guest protons in the ^1H NMR spectrum indicate the formation of 1:1 complexes **1**⊙Guest (Fig. 1).

For example, the addition of toluene (5.4 mM) to a solution of **1** in $D_2O/CD_3OD/CD_3COOD$ (10:5:1) instantaneously led to the appearance of a broad singlet at δ −1.65, which we assign to the three methyl protons of complexed toluene.[13] No further changes are observed if a ^1H NMR spectrum is recorded at later times indicating that equilibrium is reached. The methyl protons of complexed toluene are upfield shifted by 3.98 ppm relative to the methyl protons of uncomplexed toluene. Thus, free and complexed guest slowly exchange on the NMR time scale

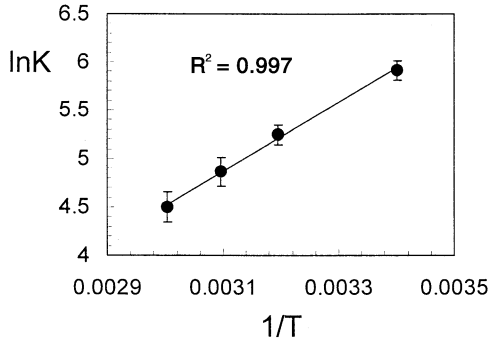
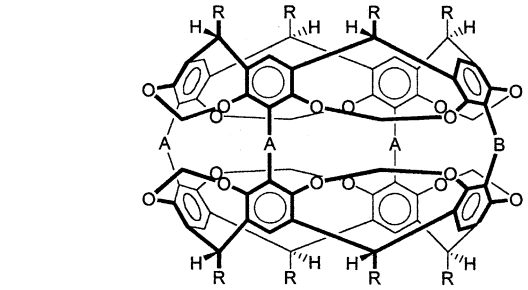


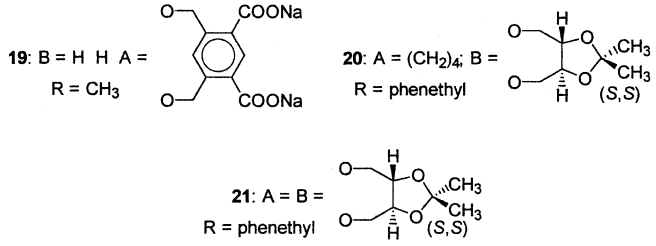
Figure 2. Temperature dependence of the toluene binding constant K (in mol^{-1}) of host **1** in $D_2O/CD_3OD/CD_3COOD$ (10:5:1).

at room temperature despite the large extended portal of **1**. This novel behavior was earlier observed by Piatnitski et al., for a related water-soluble tris-bridged hemicarcerand,[7b] and by Rebek et al., for a water-soluble extended cavitand.[14]

The simultaneous observation of free and complexed guest allowed for the determination of binding constants K from the relative integration of **1**⊙Guest and free **1** at a given total guest concentration. Binding constants ranged between K=1.4 and 370 M^{-1} (Scheme 2). A van't Hoff plot of the temperature dependence of the toluene binding constant (Fig. 2) yielded ΔH^0=7.3±0.8 kcal/mol and $T\Delta S^0$=3.8±0.8 kcal/mol from ΔG^0=3.5±0.1 kcal/mol, and shows that binding is enthalpy-driven in agreement with earlier observation by Piatnitski et al., for the complexation properties of **19**.[7b]

The observation of binding of achiral guests lured us to test whether chiral recognition would be possible in the twisted inner cavity of **1**. Indeed, the addition of racemic mixtures of chiral **10**–**12** led to the formation of diastereomeric complexes, which are characterized by different host-induced upfield shifts of the protons of both enantiomers. The absence of hemicarceplex formation with **14**–**18** is due to their greater polarity as compared to **8**–**13**. The highest diastereomeric excess de=20% was observed for 3-methylcyclohex-1-ene **12** (Fig. 1(C), Scheme 2). This moderate enantiomeric selectivity is consistent with earlier results by Cram and coworkers for binding studies involving the related hemicarcerands **20** and **21**.[5b,c] Larger enantioselectivity was observed for hemicarcerands that contain binaphthyl groups as chiral elements.[5a,b]





Though in the present chiral recognition studies the largest difference in host–guest interaction energy $\Delta\Delta G$= 0.25 kcal/mol is moderate, it is interesting that diastereoselectivity was observed despite the very similar size and shape (+)-**12** and (−)-**12** as compared to the enantiomers of **10** and **11**. Consistent with the results of Piatnitski et al., and their interpretation of hemicarcerand–guest binding interactions in water,[7b] we believe that dispersive interactions between the C–H bonds of both enantiomers and the

electron-rich aryl units in the asymmetrically twisted inner phase of **1** are the main driving force for the observed asymmetric discrimination.[15] Both enantiomers of the more flexible **10** and **11** are able to change their conformation such as to maximize their interactions with the surrounding host. This is more difficult for the more rigid **12**. Thus rigidity and inner phase-guest shape-complementarity are important guest properties to achieve high enantioselectivity in molecular recognition by open-shell hemicarcerands.[2f,5b]

Very interesting, too is the observation of a measurable chemical shift difference for the coumarin protons H3 (δ 7.98 (minor diastereomer) and 7.95 (major diastereomer)) and H5 (δ 7.64 (minor diastereomer) and 7.59 (major diastereomer)) of the diastereomeric complexes **1**⊙(+)-**12** and **1**⊙(−)-**12** (Fig. 1(C)). We believe that this is a result of different conformational changes of **1** as it binds to either (+)-**12** or (−)-**12**. Both enantiomers interact differently with the inner surface of the asymmetrically twisted **1**. It is reasonable to assume, that the flexible **1** will have different degrees of twist in both diastereomeric complexes in order to maximize host–guest contacts. This will lead to a slight difference in the distance and/or orientation between both appending coumarin groups. We believe, that this would translate into a measurable chemical shift difference *only* if both coumarins interact with each other, e.g. through π–π-interactions. Thus, the coumarin units are not passive groups, but are able to sense slight geometrical changes of the host during guest complexation.

3. Conclusions

A new chiral, hydrophilic hemicarcerand-like host has been synthesized that binds small non-polar guests in aqueous solution. Binding constants are on the order of 10^2 mol^{-1} and increase with decreasing polarity of the guest. The enantioselectivity in binding studies using racemic guest is modest. Nevertheless, it is very promising that the highest enantioselectivity was observed for the cyclic 3-methylcyclohex-1-ene, which is similar in shape and size to the transition state of a simple Diels–Alder reaction or Cope rearrangement. The question whether the inner phase of hosts, like **1**, can be used as a chiral reaction environment for asymmetric pericyclic reactions is currently investigated in our laboratory.[2f]

4. Experimental

4.1. General

CH_2Cl_2 and THF were freshly distilled from CaH, or benzophenone ketyl, respectively, under an inert atmosphere. All other reagents were used without further purification. All reactions were conducted under an argon atmosphere unless otherwise stated. ^{1}H and ^{13}C NMR spectra were obtained using a 400 MHz Varian FT NMR spectrometer. Spectra were referenced to the residual $CHCl_3$ and CHD_2OD at δ 7.26 and 3.30, respectively. For variable temperature NMR studies, the temperature was calibrated using an ethylene glycol standard and a calibration curve that is implemented in the Varian NMR software. MALDI-TOF mass spectra were obtained on an IonSpec HiRes MALDI mass spectrometer. Fluorescence spectra were recorded on a Spex Fluoro Max-2 spectrofluorometer using a 1×1 cm^2 quartz cuvette. Elemental analyses were obtained from Desert Analytics, Tucson, Arizona. Gravity chromatography was performed on Bodman silica gel (70–230 mesh). Preparative TLC was performed with glass-backed silica gel plates (20×20×1 mm^3) from Alltech. HPLC was performed on Rainin Varian Dual Pump System. Melting points are uncorrected.

4.1.1. Compound 3. Tetrahydroxycavitand **4** (100 mg, 0.114 mmol) was dissolved under argon in degassed DMA (550 mL). Anhydrous Rb_2CO_3 (2 g) was added and the solution was thermally equilibrated at 60°C. Once a stable temperature was achieved, a solution of (*S*,*S*)-(−)-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol (418 mg, 0.91 mmol) in degassed DMA (50 mL) was added dropwise with a syringe pump over 8 h. The solution was stirred for further 4 days at 60°C. The solution was concentrated by evaporation. Water (100 mL) was added to the residual solid. The resulting suspension was extracted with $CHCl_3$ (3× 100 mL). The combined organic layers were concentrated to 4 mL. The product was precipitated with CH_3OH (20 mL) and filtered off and purified by preparative TLC (SiO_2, CH_2Cl_2 containing EtOAc (1% v/v). The product was eluted from the silica gel with CH_2Cl_2/EtOAc (19:5). Concentration of the product fraction and precipitation with methanol as described above gave **3** (20 mg, 15% yield) as a colorless solid. Yields of different runs varied between 10 and 15%; mp 350°C (decomp.); δ_H ($CDCl_3$) 6.81 (2H, s), 6.78 (4H, s), 6.57 (2H, s), 5.95 (2H, d, *J*=7.2 Hz), 5.91 (2H, d, *J*=7.2 Hz), 5.83 (2H, d, *J*=7.2 Hz), 5.81 (2H, d, *J*=7.2 Hz), 4.73–4.54 (14H, m), 4.30 (2H, dd, *J*=3.8, 7.8 Hz), 4.19 (2H, dd, *J*=3.6, 7.6 Hz), 4.17 (2H, dd, *J*=4.0, 8.0 Hz), 4.15–4.08 (8H, m), 3.58 (2H, dd, *J*=10.4, 6.8 Hz), 3.58 (2H, dd, *J*=10.4, 6.8 Hz), 3.58 (2H, dd, *J*=10.4, 7.6 Hz), 3.58 (2H, dd, *J*=10.8, 8.0 Hz), 2.22–2.06 (16H, m), 1.48–1.26 (48H, m), 1.36 (6H, s), 1.35 (12H, s), 0.95–0.88 (24H, m). δ_C ($CDCl_3$) 148.87, 148.70, 148.57, 148.35, 148.11, 144.18, 144.15, 143.94, 142.39, 142.35, 141.11, 139.74, 139.44, 139.37, 139.34, 139.19, 138.70, 138.44, 115.12, 115.01, 110.73, 110.36, 100.55, 100.13, 99.65, 78.81, 78.72, 78.61, 76.43, 75.77, 74.98, 37.29, 37.16, 32.42, 32.41, 32.37, 32.36, 30.09, 30.06, 30.03, 29.98, 29.80, 28.49, 28.02, 27.91, 27.87, 27.82, 22.96 22.94, 14.40. MALDI HRMS *m/z* 2162.079 (M+Na$^+$) (calcd for $C_{125}H_{158}NaO_{30}$, 2162.073).

4.1.2. 7-(2-Bromoethoxy)coumarin (2).[11] 7-Hydroxycoumarin (1 g, 6 mmol) and excess 1,2-dibromoethane (5 mL, 58 mmol) were dissolved in degassed DMF (25 mL) under argon. Anhydrous K_2CO_3 (8.1 g, 59 mmol) was added and the suspension was stirred at 60°C for 4 days. The solution was neutralized to pH 6 using HCl aq (1.0N). The precipitate was filtered off, washed with water (10 mL) and redissolved in the minimum volume of CH_2Cl_2 and was subjected to column chromatography on silica gel with CH_2Cl_2 as the mobile phase. The product eluted as the first fluorescing fraction (366 nm). Concentration of the product fraction gave **2** as a white solid (0.8 g, 50%

yield). Mp 130.5°C; δ_H ($CDCl_3$) 7.62 (1H, d, J=9.6 Hz), 7.37 (1H, d, J=8.4 Hz), 6.84 (1H, dd, J=8.4, 2.4 Hz), 6.77 (1H, d, J=2.4 Hz), 6.24 (1H, d, J=9.6 Hz), 4.33 (2H, t, J=6.0 Hz), 4.66 (2H, t, J=6.0 Hz); δ_C ($CDCl_3$) 161.39, 161.17, 143.50, 129.19, 113.73, 113.27, 113.106, 113.00, 101.91, 68.43, 28.72.

4.1.3. Compound 5. Host **3** (100 mg, 0.047 mmol) was dissolved under argon in degassed DMF (15 mL). Anhydrous K_2CO_3 (2 g) was added and the suspension was stirred for 1 h. Linker **2** (38 mg, 0.14 mmol) was added to the suspension and stirring was continued at room temperature for 3 days. The suspension was filtered and the filtrate poured into phosphate buffer (0.2 M, pH 6, 40 mL). The precipitated crude product was filtered off and washed with water (2×10 mL) and CH_3OH (2×10 mL). It was redissolved in the minimum amount of $CHCl_3$ and precipitated again by adding 10 volume equivalents of CH_3OH. After filtering off the crude product it was purified by column chromatography on silica gel using CH_2Cl_2 as the mobile phase. Concentration of the product fraction gave **5** as a white solid (57 mg, 50% yield). Mp 180–181°C; δ_H ($CDCl_3$) 7.63 (2H, d, J=9.6 Hz), 7.43 (2H, d, J=8.8 Hz), 7.00 (2H, dd, J=8.8, 1.6 Hz), 6.88 (2H, d, J=1.6 Hz), 6.80 (2H, s), 6.79 (4H, s), 6.77 (2H, s), 6.27 (2H, d, J=7.6 Hz), 6.24 (2H, d, J=9.6 Hz), 5.82 (2H, d, J=8.0 Hz), 5.80 (2H, d, J=8.0 Hz), 5.55 (2H, d, J=7.2 Hz), 4.82–4.72 (2H, m), 4.72–4.54 (12H, m), 4.52–4.46 (2H, m), 4.40–4.31 (2H, m), 4.30–4.07 (12H, m), 4.05–3.96 (6H, m), 3.52–3.40 (6H, m), 2.22–2.08 (16H, m), 1.48–1.26 (66H, m), 0.95–0.88 (24H, m). δ_C ($CDCl_3$) 162.20, 161.45, 156.23, 149.13, 149.05, 148.79, 148.68, 148.61, 148.42, 148.27, 148.14, 144.40, 144.35, 144.25, 143.67, 143.54, 139.42, 139.39, 139.25, 139.21, 139.13, 139.05, 138.99, 129.33, 115.19, 115.03, 114.94, 114.85, 113.48, 113.12, 113.01, 110.45, 110.35, 101.83, 100.69, 100.02, 99.77, 99.58, 78.81, 78.55, 78.37, 76.39, 75.97, 75.41, 72.16, 67.38, 37.34, 37.28, 32.48, 32.42, 30.61, 30.25, 29.88, 28.20, 28.12, 27.98, 22.99, 22.94, 14.43. MALDI HRMS m/z 2458.113 (20%) ($M-2\times H_2CCCH_2+Na^+$) (calcd for $C_{141}H_{166}NaO_{36}$, 2458.106); 2418.116 (100%) ($M-3\times H_2CCCH_2+Na^+$) (calcd for $C_{138}H_{162}NaO_{36}$, 2418.074). Anal. calcd for $C_{147}H_{174}O_{36}$: C, 70.15; H, 6.96. Found: C, 70.09; H, 6.67.

4.1.4. Compound 6. Host **5** (30 mg, 0.0123 mmol) was dissolved in a solvent mixture containing CD_3OD (300 μL), $CDCl_3$ (100 μL), D_2O (50 μL), and CF_3COOH (20 μL) in a NMR tube. The tube was sealed with a Teflon screw-cap and the solution was heated to 60°C in an oil bath. Periodically, the progress of the reaction was checked by recording a ^1H NMR spectrum. The reaction was complete after 10 days. The solvent was removed by evaporation to give **6** (29.5 mg, quantitative) as a colorless solid. Mp 268°C (decomp.); δ_H ($CDCl_3$) 7.64 (2H, d, J=9.6 Hz), 7.43 (2H, d, J=8.8 Hz), 7.00 (2H, dd, J=8.4, 2.0 Hz), 6.89 (2H, d, J=2.0 Hz), 6.80 (2H, s), 6.79 (4H, s), 6.77 (2H, s), 6.27 (2H, d, J=7.6 Hz), 6.24 (2H, d, J=9.6 Hz), 5.82 (2H, d, J=8.0 Hz), 5.80 (2H, d, J=8.0 Hz), 5.55 (2H, d, J=7.2 Hz), 4.82–4.72 (2H, m), 4.72–4.54 (12H, m), 4.52–4.46 (2H, m), 4.40–4.31 (2H, m), 4.30–4.07 (12H, m), 4.05–3.96 (6H, m), 3.52–3.40 (6H, m), 2.22–2.08 (16H, m), 1.48–1.26 (66H, m), 0.95–0.88 (24H, m). δ_C ($CDCl_3$) 162.08, 161.94, 156.05, 148.84, 148.18, 147.60, 147.29, 147.07, 146.89, 145.22, 144.89, 144.07, 143.62, 140.02, 139.67, 139.50, 139.39, 139.21, 139.37, 139.27, 139.17, 139.01, 129.43, 115.20, 114.84, 114.74, 114.66, 113.43, 113.31, 113.24, 101.75, 99.88, 99.44, 99.12, 74.67, 73.41, 72.53, 72.26, 72.13, 72.02, 67.70, 37.32, 37.21, 32.35, 32.29, 30.54, 30.05, 29.59, 27.90, 27.83, 27.79, 22.97, 22.95, 22.91, 14.39. MALDI HRMS m/z 2418.045 ($M+Na^+$) (calcd for $C_{138}H_{162}NaO_{36}$, 2418.074).

4.1.5. Compound 7. Host **6** (50 mg, 0.021 mol) was dissolved in dry THF (15 mL). Subsequently, N-BOC-glycine (63 mg, 0.624 mmol), *p*-dimethylaminopyridine (3 mg, 0.024 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (191 mg, 0.643 mmol) were added. The reaction mixture was stirred under argon at room temperature for 5 days. The formed precipitate was filtered off. The filtrate was concentrated under reduced pressure. The remaining crude product was washed with water (2×20 mL) and was purified via semi-preparative HPLC (Luna-SiO_2 column; 10μ, 10×250 mm^2 (Phenomenex); CH_2Cl_2/THF (95:5); flow rate 10 mL/min; detection at 254 nm; retention time of **7**=35 min). The product fractions were concentrated down to 1 mL. The product was precipitated by the addition of hexanes (10 mL) and was filtered and dried at high vacuum to yield **7** as a white solid (45 mg, 65% yield). Mp 183–184°C (decomp.); δ_H ($CDCl_3$; 333 K) 7.65 (2H, d, J=9.6 Hz, coumarin H3), 7.42 (2H, d, J=8.4 Hz, coumarin H5), 6.88 (2H, dd, J=8.4, 2.0 Hz, coumarin H6), 6.80 (4H, s, ArH), 6.79 (2H, s, ArH), 6.78 (2H, s, ArH), 6.76 (2H, d, J=2.0 Hz, coumarin H8), 6.22 (2H, d, J=9.6 Hz, coumarin H4), 6.24 (2H, d, J=9.6 Hz), 6.13–5.97 (4H, m, $OCH\mathit{H}_{outer}O$), 5.94 (2H, d, J=7.2 Hz, $OCH\mathit{H}_{outer}O$), 5.75 (2H, d, J=6.8 Hz, $OCH\mathit{H}_{outer}O$), 5.66–5.42 (6H, m, N*H*), 4.76–4.67 (6H, m, C*H*,CH_2,CH_2), 4.56 (2H, t, J=7.8 Hz, C*H*,CH_2,CH_2), 4.46–4.16 (24H, m, $OC\mathit{H}_2C\mathit{H}_2O$, $OCH\mathit{H}_{inner}O$, $OC\mathit{H}_2CH$), 4.14 (2H, d, J=7.2 Hz, $OCH\mathit{H}_{inner}O$), 4.13–4.02 (2H, m, $OC\mathit{H}_2CH$), 4.0–3.6 (12H, m, $NHC\mathit{H}_2$), 3.82, 3.73 (6H, AB-system, J=18.2 Hz, $OCH_2C\mathit{H}$), 2.25–2.08 (16H, m, $C\mathit{H}_2CH_2CH_2CH_2CH_3$), 1.48 (18H, s, $C(C\mathit{H}_3)_3$) 1.46 (36H, s $C(C\mathit{H}_3)_3$), 1.48–1.26 (48H, m, $CH_2C\mathit{H}_2C\mathit{H}_2C\mathit{H}_2CH_3$), 0.95–0.88 (24H, m, $CH_2CH_2CH_2CH_2C\mathit{H}_3$). δ_C ($CDCl_3$, 335 K) 169.97, 169.83, 169.75, 162.29, 161.17, 156.36, 156.16, 156.11, 155.97, 148.80, 148.60, 148.31, 148.20, 148.13, 148.04, 144.08, 143.55, 139.65, 139.39, 139.35, 139.23, 139.21, 139.15, 129.33, 115.14, 115.06, 114.95, 114.87, 113.63, 113.29, 113.15, 102.14, 99.68, 99.64, 99.54 (sb), 99.38, 80.48, 80.34, 80.24, 72.72, 71.74, 70.19, 70.11 (sb), 67.92, 43.11, 43.03, 37.37, 32.41, 32.37, 32.34, 30.49, 30.39, 30.32, 29.97, 28.73, 28.02, 27.98, 27.96, 27.93, 22.94, 22.95, 22.92, 14.27. MALDI HRMS m/z 3360.486 ($M+Na^+$) (calcd for $C_{180}H_{228}N_6NaO_{54}$, 3360.517). Anal. calcd for $C_{180}H_{228}N_6O_{54}$: C, 64.73; H, 6.88; N, 2.52. Found: C, 65.05; H, 6.97; N, 2.86.

4.1.6. Compound 1. Host **7** (5 mg) was placed into a 5 mL round bottom flask. Ice-cold CF_3COOH (0.2 mL) was added at 0°C. The suspension was stirred until all of **7** had dissolved and was left at 0°C for 30 min. The solvent was removed under vacuum. $CHCl_3$ (1 mL) was added and was evaporated to leave **1** as a white powder, which was dried at high vacuum. Mp 320°C (decomp.); δ_H (D_2O/CD_3OD/

CD_3COOD (10:5:1); 295 K) 7.98 (2H, d, J=9.2 Hz), 7.63 (2H, d, J=8.4 Hz), 7.11 (2H, s), 7.09 (2H, s), 7.07 (2H, s), 6.03 (2H, s), 6.97 (2H, d, J=8.4 Hz), 6.89 (2H, s), 6.33 (2H, d, J=9.2 Hz), 6.17–5.97 (6H, m), 5.71 (2H, sb), 5.62–5.52 (4H, m), 5.4–5.34 (2H, m), 4.64–4.54 (8H, m), 4.5–3.66 (8H, m), 2.37–2.1 (16H, m), 1.43–1.15 (48H, m), 0.92–0.80 (24H, m). δ_C (CD_3OD, 303 K) 168.38, 168.32, 167.97, 163.54, 163.35, 163.2–161.3 (m), 156.02, 150.05, 149.97, 149.42, 149.36, 149.19, 149.11, 148.96, 148.80, 145.80, 145.42, 144.88, 144.79, 144.64, 140.67, 140.46, 140.43, 140.38, 140.17, 140.14, 140.09, 140.08, 130.80, 116.65, 116.51, 114.50, 113.65, 113.08, 103.62, 101.00, 100.94, 100.54, 74.99, 74.96, 73.60, 73.55, 72.84, 71.61, 69.97, 69.30, 41.11, 41.08, 40.97, 38.35, 38.27, 38.19, 32.94, 32.90, 32.88, 30.86, 30.72, 30.47, 30.40, 28.93, 28.85, 28.79, 23.78, 23.74, 14.43, 14.40. MALDI HRMS m/z 2760.233 (5%) ($M+Na^+$) (calcd for $C_{150}H_{180}N_6NaO_{42}$, 2760.203); m/z 2703.209 (10%) ($M-NH_2CH{=}C{=}O+Na^+$) (calcd for $C_{148}H_{177}N_5NaO_{41}$, 2703.182); m/z 2646.202 (20%) ($M-2\times NH_2CH{=}C{=}O+Na^+$) (calcd for $C_{146}H_{174}N_4NaO_{40}$, 2646.160); m/z 2589.152 (58%) ($M-3\times NH_2CH{=}C{=}O+Na^+$) (calcd for $C_{144}H_{171}N_3NaO_{39}$, 2589.139); m/z 2532.112 (100%) ($M-4\times NH_2CH{=}C{=}O+Na^+$) (calcd for $C_{142}H_{168}N_2NaO_{38}$, 2532.117); m/z 2475.086 (36%) ($M-5\times NH_2CH{=}C{=}O+Na^+$) (calcd for $C_{140}H_{165}N_1NaO_{37}$, 2475.096).

4.2. ^{1}H NMR complexation studies

In a typical experiment, **7** (3 mg, 1.1 μmol) was placed in a 5 mm NMR tube with Teflon screw-cap seal. Ice-cold CF_3COOH (0.2 mL) was added and the solution was left at 0°C for 30 min. The NMR tube was connected to a vacuum manifold and the solvent was pumped off. $CHCl_3$ (0.2 mL) was added and pumped off once again. The remaining **1** was dried at high vacuum (0.05 mm) for 1 h at room temperature before it was dissolved in D_2O/CD_3OD/CD_3COOD (10:5:1) (0.560 mL). A spectrum was recorded. Either neat guest, or a solution of the guest in CD_3OD was added with a 10 μL Hamilton syringe (total volume added <15 μL). The solution was thermally equilibrated for about 10 min before a second ^{1}H NMR spectrum was recorded. The relative amount of guest-occupied hemicarcerand **1**⊙guest and free **1** was determined from the integrals of guest protons in the upfield region of the ^{1}H NMR spectrum and from the integrals of the coumarin protons H3 (δ 8.05–7.90), H4 (δ 6.40–6.25), and H5 (δ 7.70–7.52) (see also Chart 1). The absence of a change in the amount of **1**⊙guest in a third spectrum, recorded 20 min later, assured thermal equilibrium. The binding constants K was determined via the following equation: K=([**1**⊙guest]/[total **1**]−[**1**⊙guest])/[guest], with [guest] being the concentration of guest added minus the concentration of **1**⊙guest. The reported binding constants are averages of 2–6 guest additions.

The diastereomeric excesses reported in Scheme 2 were determined from the integrals of multiplets, that we assign to the following protons of both enantiomeric guests: multiplets at δ −2.58 and −2.65 (CH_2CH_3 of **10**), multiplets at δ −2.70 and −2.75 (CH_2CH_3 of **11**) and doublets at δ −2.73 and −2.83 (CH_3 of **12**).

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References

1. (a) Cram, D. J.; Cram, J. M. In *Container Molecules and Their Guests*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1994; pp 131–216. (b) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931–967. (c) Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, *34*, 95–105.
2. (a) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed.* **1991**, *30*, 1024–1027. (b) Warmuth, R. *Angew. Chem., Int. Ed.* **1997**, *37*, 1347–1350. (c) Warmuth, R. *J. Chem. Soc., Chem. Commun.* **1998**, 59–60. (d) Warmuth, R.; Marvel, M. A. *Angew. Chem., Int. Ed.* **2000**, *40*, 1117–1119. (e) Warmuth, R.; Marvel, M. A. *Chem. Eur. J.* **2001**, *7*, 1209. (f) Warmuth, R. *J. Am. Chem. Soc.* **2001**, *123*, 6955.
3. Piatnitski, E. L.; Deshayes, K. D. *Angew. Chem., Int. Ed.* **1998**, *38*, 970–972.
4. (a) Warmuth, R.; Kerdelhué, J.-L.; Sánchez Carrera, S.; Langenwalter, K. J.; Brown, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 96–99. (b) Kang, K.; Rebek, Jr., J. *Nature* **1997**, *385*, 50–52.
(c) Kang, J.; Santamaría, J.; Hilmersson, G.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1998**, *120*, 7389–7390.
5. For chiral recognition studies involving chiral hemicarcerands see: (a) Judice, J. K.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2790–2791. (b) Yoon, J.; Cram, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11796–11806. (c) Park, B. S.; Knobler, C. B.; Eid, Jr., C. N.; Warmuth, R.; Cram, D. *J. Chem. Commun.* **1998**, 55–56.
6. For recognition studies involving chiral self-assembled molecular capsules see: (a) Rivera, J. M.; Martín, T.; Rebek, Jr., J. *J. Am. Chem. Soc.* **2001**, *123*, 5213–5220. (b) Saito, S.; Nuckolls, C.; Rebek, Jr., J. *J. Am. Chem. Soc.* **2000**, *122*, 9628–9630. (c) Rivera, J. M.; Rebek, Jr., J. *J. Am. Chem. Soc.* **2000**, *122*, 7811–7812. (d) Nuckolls, C.; Hof, F.; Martín, T.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1999**, *121*, 10281–10285. (e) Castellano, R. K.; Hyean Kim, B.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1997**, *119*, 12671–12672.
7. For binding studies involving achiral water-soluble hemicarcerands see: (a) Yoon, J.; Cram, D. J. *Chem. Commun.* **1998**, 497–498. (b) Piatnitski, E. L.; Flowers, II, R. A.; Deshayes, K. *Chem. Eur. J.* **2000**, *6*, 999–1006.
8. (a) Ikeda, H.; Ise, N.; Oguma, N.; Nakamura, M.; Nakamura, A.; Ikeda, T.; Toda, F.; Ueno, A.; Suzuki, I.; Osa, T. *J. Am. Chem. Soc.* **1996**, *118*, 10980–10988. (b) McAlpine, S. R.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 2750–2751.
9. For a fluorescence resonance energy transfer approach to sense binding events by self-assembled molecular capsules see: Castellano, R. K.; Craig, S. L.; Nuckolls, C.; Rebek, Jr., J. *J. Am. Chem. Soc.* **2000**, *122*, 7876–7882.
10. (a) Houk, K. N.; Nakamura, K.; Sheu, C.; Keating, A. E. *Science* **1996**, *273*, 627–629. (b) Nakamura, K.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 1853–1854. (c) Sheu, C.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 8056–8070.

11. Cram, D. J.; Jaeger, R.; Deshayes, K. *J. Am. Chem. Soc.* **1993**, *115*, 10111–10116.
12. Abyshev, A. Z.; Klimov, V. G.; Krylov, S. S.; Semenov, E. V.; Sidorova, I. P. *Khim. Farm. Zh.* **1985**, *19*, 756–760.
13. Upon further addition of toluene, the integral of this singlet reached a value equivalent to three protons. The remaining three guest multiplets are covered by multiplets assigned to **1** and could not be identified.
14. Haino, T.; Rudkevich, D. M.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1999**, *121*, 11253–11254.
15. (a) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/π interaction*; Wiley-VCH: New York, 1998. (b) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2000**, *122*, 3746–3753.