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Molecular Engineering. Container Hosts Having Eight Undecyl Substituents Have High Solubility in Chlorinated Solvents

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Nine new solubility-increased container hosts having eight undecyl substituents were synthesized and characterized. ^{1}H NMR spectral data showed integral inclusion state of carceplexes and their stability. ^{1}H NMR chemical shifts of guest DMA were correlated to the host's cavity dimensions shrinked by constrictive binding. Carceplex and hemicarcerand showed their distinctive FD mass spectra.

Introduction

Container hosts, carcerand and hemicarcerand, are constructed on cavitands derived from octols which are obtained by cyclotetramerization of resorcinol and aldehydes.[1] Carcerands are hosts having spherical cavity for the inclusion of guest molecules, but once the guest is captured inside it cannot escape the cavity even at high temperature unless some chemical bonds of host shell are broken.[2] Usually the guests are captured during the formation of carcerands so it exists as carceplex from the beginning. Hemicarcerands are similar to carcerands except that the guests can enter or exit the hosts interior through the shell's portals.[3] The binding energy of hemicarcerands is called a constrictive binding energy which is defined as the steric repulsions that must be overcome for dissociation of a hemicarceplex. The steric constraints are imposed by the size and shape of the guest, and those of the portal and attractions of the inner phase. Many interesting properties of hemicarcerands are reported such as shell's role as chemical reactor,[4] control of guest's in-and-out kinetics,[5] molecular container,[6] etc., which implies the tremendous applicabilities of container hosts in various fields from material sciences to medicinal chemistry.

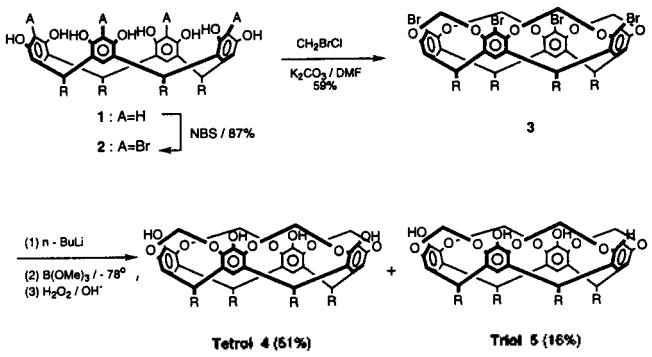
The physicochemical properties of hemicarcerands have been controlled by variation of portal size using different functionality, number, or length of bridging units between two polar caps (hemispheres), which varies the circumstance of its core sphere.

Also the solubility of container host has been controlled mainly by using various substituents (legs) such as methyl,[2a] pentyl,[2b] or 2-phenylethyl.[2c] But still the solubility is not enough for the easy manipulation of intermediates or hosts. By incorporating dodecanal in octol, highly soluble cavitand intermediates and nine new container hosts were synthesized and characterized.

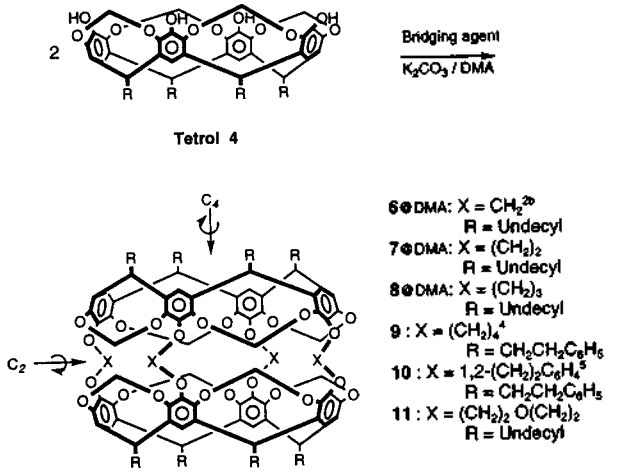
Results and Discussion

Synthesis of Highly Soluble Intermediates. Octol **1** was obtained in 83% yield from the acidic cyclotetramerization of resorcinol and dodecanal. Octol **1** itself was used as a host which binds multihydroxy guests using hydrogen bonding as well as CH-π interaction.[7] It was easily brominated to compound **2** in 87% yield with NBS in MEK at room temperature. Adjacent hydroxyl groups of compound **2** were linked using CH_2BrCl to give a rigidified tetrabromide **3** in 59% yield. Tetrabromide **3** was transformed to tetrol **4** and triol **5** using normal reaction conditions[2c] in 51% and 16% yield, respectively. The semifinal intermediates, tetrol **4** and triol **5**, were easily separated in large scale by column chromatography due to their high solubility in chlorinated solvents. Their analogues having pentyl or 2-phenylethyl substituents were much less soluble and accordingly difficult to purify, especially in large quantity.

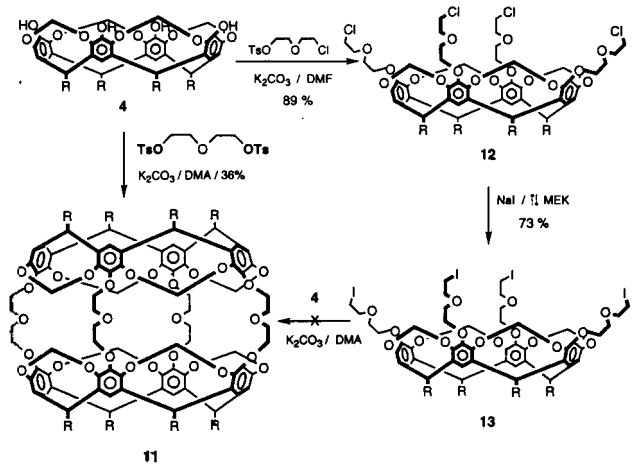
Synthsis of Container Hosts Having Four Portals. Container hosts **6**, **7**, and **8** having four portals and un-



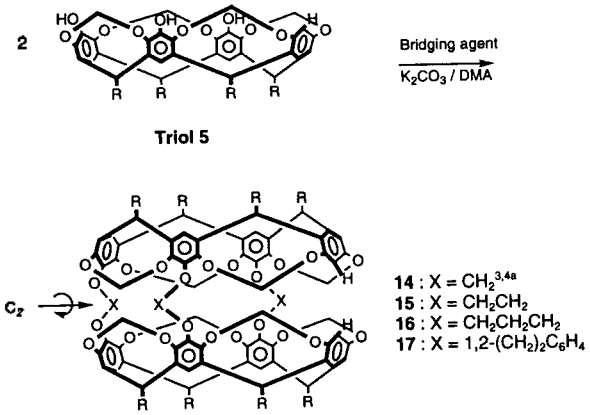
Scheme 1. Synthesis of Solubility-Increased Tetrol **4** and Triol **5** ($R=(CH_2)_{10}CH_3$).



Scheme 2. Synthesis of Container Hosts Having Four Portals.



Scheme 3. Synthetic Route of Hemicarcerand **11** ($R=(CH_2)_{10}CH_3$).



Scheme 4. Synthesis of Container Hosts Having Three Portals.

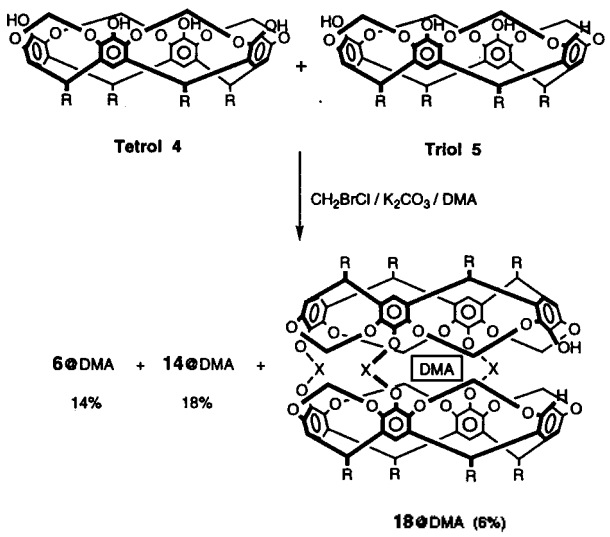
decyl legs were obtained by shell-forming reaction of two tetrols **4** with CH_2BrCl, $TsOCH_2CH_2OTs$, or $TsOCH_2CH_2CH_2OTs$ as bridging agent (Scheme 2). The DMA templated shell-forming reactions gave 7@DMA and 8@DMA in 20% and 26% yield, respectively. 6@DMA was obtained from one-pot procedure described later. 6@DMA, 7@DMA and 8@DMA are carceplexes and the chemical shifts of host's core and incarcerated DMA were similar to them of their analogues, which implies the alkyl legs increase host's solubility and do not influence its core significantly as expected. Hosts **9** (R=pentyl or 2-phenylethyl)[4a] and **10** (R=2-phenylethyl)[5a] were reported as hemicarcerands and showed strong constrictive binding properties.

Step-wise trial to obtain host **11** (R=undecyl) *via* compound **12** and **13** was unsuccessful (Scheme 3), but direct shell-forming reaction with diethylene glycol ditosylate gave host **11** in 36% yield.[6b] It is presumable that phenoxide of tetrol **4** can attack tosylated carbon much better than iodocarbon of **13**, which could be explained by the so-called hard and soft acid and base concept. The high yield also implies the versatility of solvent-templated shell-forming reaction.[8]

Synthsis of Container Hosts Having Three Portals. Three methylene-portal host **14** (R=2-phenylethyl) was reported as molecular reactor and its sanctuary.[3,4a] Triol **5** (R=undecyl) was subjected to shell-forming reaction using ethylene ditosylate, propylene ditosylate, or α,α'-dibromo-o-xylene as bridging agents to give hosts **15**, **16**, or **17** in 25%, 26%, and 10% yield, respectively. All these hosts were obtained as free hosts, which means the embeded DMA escaped easily during work-up through the large portal formed by longer bridges.

One-Pot Synthesis of Three Kinds of Container Hosts. The extraordinary high yields of final shell-forming reactions due to the solvent-templation[8] made it possible to design one-pot trial as shown in Scheme 5.[9]

A carceplex 6@DMA, a hemicarceplex **14**@DMA, and a gate-hydroxylated carceplex **18**@DMA were obtained in 14%, 18%, and 6% yield, respectively, by an efficient one-pot synthesis using tetrol **4** and triol **5**. Their distinct R_f values on SiO_2 in a 2 : 1 mixture of hexane and CH_2Cl_2 are 0.4, 0.5, and 0.2 respectively, which made the chromatographic separation easy. The first two homo-coupled hosts are spectroscopically similar to those[2b,3] reported except they have the longer legs which give higher solubilities in various organic solvents. The hetero-coupled last one has a hydroxy group on its largest portal. IR spectrum of hydroxycarceplex **18**@DMA (KBr) shows the stretching band of hydroxy group at 3,447 cm^{-1} and that of DMA's carbonyl group at 1,643 cm^{-1}. Hydroxy group could be a modulator for guest in-and-out procedure. It could also be used to tie-up (hemi)carcerands together or graft to polymer backbone, which might result in unprecedented supramolecular



Scheme 5. One-Pot Synthesis of Three Container Hosts **6**, **14**, and **18** Having DMA (R=$(CH_2)_{10}CH_3$).

properties such as intratransport of guest, intra-redox switching molecule, multi-cellar polymer, etc.

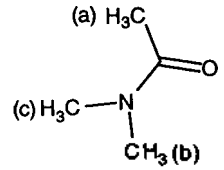
^{1}H NMR Spectral Characteristics of Container Hosts and Their Guest. ^{1}H NMR spectral data of new carceplexes **6**@DMA, **7**@DMA, **8**@DMA, and **18**@DMA are exactly those anticipated. Hosts **6**, **7**, and **8** having D_{4h} symmetry gave rather simple ^{1}H NMR spectra, which means guest DMA rotate rapidly through C_4 as well as C_2 axes on NMR time scale. Due to its low C_s symmetry of **18**@DMA its ^{1}H NMR spectrum (300 MHz) is very complex. But three singlets of DMA in **18** implies the up-down rotation of DMA at ambient temperature along the long axis through the two polar caps is rapid on 300 MHz NMR time scale, which might be hindered at low temperature.[10] Hemicarcerands **14**, **15**, **16**, and **17** also gave complex ^{1}H NMR spectra due to their low C_{2v} symmetry.

Table 1 summaries the chemical shifts and upfield-shifted values ($\Delta\delta$ in ppm) of DMA protons H(a), H(b), and H(c) in container hosts having different length of bridges. Guest peaks in these container hosts are very distinctive due to the large shielding effect from each polar caps composed of four benzene units. As expected the alkyl substituents (legs) do not affect the core's shielding effect significantly (**7** and **8**). The shorter bridges make more dense inner phase and accordingly its guest is more magnetically shielded (methylene (**6**) vs. propylene (**8**)). When the bridge is methylene, three portal hosts have virtually the same shielding effect as that of four portal host (**6** *vs.* **14** or **18**).

The largest $\Delta\delta$ values for each H are 4.48 ppm for H(a) in **6** or **18**, 4.52 ppm for H(b) in **18**, and 2.05 ppm for H(c) in **14**. Except host **10**, the longer bridges result in less $\Delta\delta$. Even though host **10** has 6 atom bridges (1,2-$(OCH_2)_2C_6H_4$), it has denser core than that of **7** (4 atom bridges) or **8** (5 atom bridges), which is presumably due to the more efficient constrictive binding of **10**.

Their $\Delta\delta$ values are compared in Figure 1. Average $\Delta\delta$ difference between H(a) or H(b) and H(c) is 2.0-2.4 ppm, which tells that the spacial arrangement of these two species are quite different. As expected by CPK molecular

Table 1. Comparison of ^{1}H NMR Spectral Data of Free and Incarcerated DMA (N,N-Dimethylacetamide) in $CDCl_3$ ($\Delta\delta=\delta_{Free}-\delta_{Incarcerated}$)



Host	δ (Δδ) in ppm H(a)	H(b)	H(c)
Free DMA	2.08	3.02	2.94
6 (R=$CH_2CH_2C_6H_5$)[a]	−2.40 (4.48)	−1.46 (4.48)	1.04 (1.90)
7 (R=$CH_2CH_2C_6H_5$)[b]	−1.98 (4.06)	−0.99 (4.01)	1.39 (1.55)
7 (R=$(CH_2)_{10}CH_3$)[c]	−1.84 (3.92)	−0.83 (3.85)	1.39 (1.55)[g]
8 (R=$CH_2CH_2C_6H_5$)[b]	−1.62 (3.70)	−0.50 (3.52)	1.43 (1.51)
8 (R=$(CH_2)_{10}CH_3$)[c]	−1.62 (3.70)	−0.48 (3.50)	1.43 (1.51)[g]
9 (R=$CH_2CH_2C_6H_5$[d]	−1.64 (3.72)	−0.42 (3.44)	1.61 (1.33)
10 (R=$CH_2CH_2C_6H_5$[e]	−2.19 (4.29)	−1.15 (4.20)	1.20 (1.75)
14 (R=$CH_2CH_2C_6H_5$[f]	−2.24 (4.33)	−1.43 (4.37)	0.97 (2.05)
18 (R=$(CH_2)_{10}CH_3$)[c]	−2.40 (4.48)	−1.50 (4.52)	0.94 (2.00)[g]

[a]ref. 2c. [b]ref. 8a. [c]this work. [d]ref. 4b. [e]ref. 5a. [f]ref. 3. [g]estimatd value from Figure 1.

study, due to the steric complementarity between host and guest, H(a) and H(b) are directing to the polar caps (through the longer C_4 axis) and accordingly upfield-shifted much more than H(c) which is directing to the tropic (through the shorter C_2 axis). The relative linear fitting shows that H(b) is the most sensitive to the core dimension and H(c) is the least sensitive to those. The better sensitibity of H(b) than that of H(a) also means the larger crowdedness of H(b) than that of H(a). Figure 1 or the similar comparisons could be used to estimate the guest's chemical shifts which were buried under other larger peaks. Also the role of unprecedented bridges could be deduced in terms of the efficiency of constrictive binding. From Figure 1, the chemical shift of H(c) in **18**@DMA was estimated to be 0.94 ppm which is buried under that of undecyl group.

Mass Spectral Characteristics of Container Hosts. Incarceration can be also detected by mass spectrum. Field desorption mass spectra of carceplex **7**@DMA and hemicarcerand **15** were compared in Figure 2. **7**@DMA gave two major peaks in 1 : 1 intensity for **7**@DMA (2625; 100%, $(M+DMA)^+$) and **7** (2538; 98%, M^+), whereas **15** gave a dominant single peak for its shell (2481; 100%, M^+).

In conclusion, 9 new container hosts (4 carceplexes and 5 hemicarcerands) were efficiently synthesized and characterized using ^{1}H NMR, IR, and mass spectrometry. These new hosts have 8 undecyl legs which solubilize them almostly freely in chlorinated solvents. The comparison of chemical shifts of incarcerated DMA in various hosts illustrates the relative host's core dimensions and guest's orientation. The physicochemical properties as well as multifunctionalization of these container hosts are under investigation.

Experimental Section

General. All chemicals were reagent grade (Aldrich)

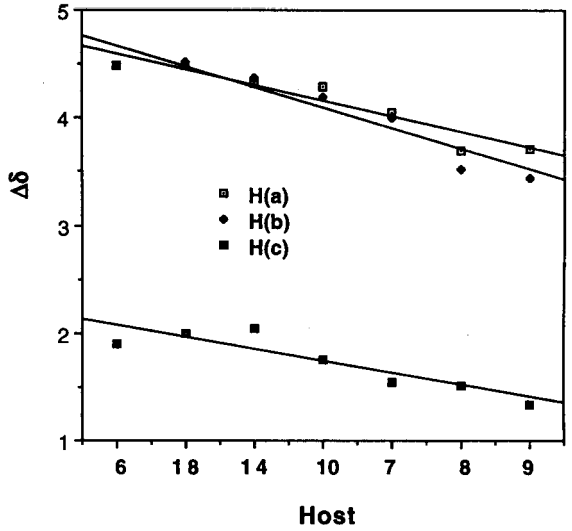


Figure 1. Comparison of Δδ Values (ppm) of Incarcerated DMA in Various Container Hosts.

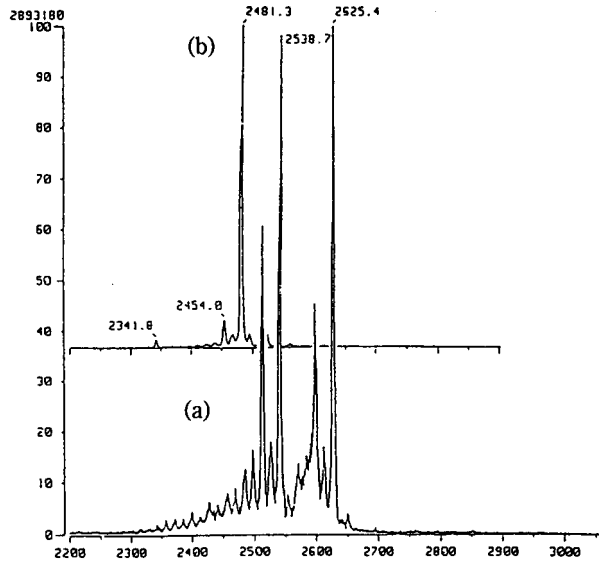


Figure 2. Field Desorption Mass Spectra of (a) Carceplex **7**@ DMA and (b) Hemicarceplex **15**.

and used directly unless otherwise specified. THF was stored under calcium hydride over a week and was freshly distilled under N_2 from sodium benzophenone ketyl just prior to use. All anhydrous reactions were conducted under argon or nitrogen atmosphere. Melting points were measured on a electrothermal 9100 apparatus and uncorrected. The ^{1}H NMR spectra were run on a Bruker Aw-80 (80 MHz) or Gemini-300 (300 MHz) spectrometer and referenced to TMS (80 MHz, 0.0 ppm) or deuterated solvents (300 MHz). Mass spectra were run on a VG70-VSEQ (for FAB$^+$ MASS) or JMS-AX 505H (for FD MASS). Infrared spectra were taken with Mattson 3000 FT-IR spectrometer. Gravity column chromatography was performed on E. Merck silica gel 60 (70-230 mesh ASTM). Thin-layer chromatography was done on plastic sheets silica gel 60 F_{254} (E. Merck, 0.2 mm).

5,11,17,23-Tetrabromo-2,8,14,20-tetraundecyl-pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1,(25),3,5,7,(28),9,11,13,(27),15,17,19,(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol, Stereoisomer (2). To 200 mL of MEK were added 20 g (18 mmol) of octol **1** and 19 g (108 mmol) of N-bromosuccinimide. After the mixture was stirred for 3 d at room temperature, the precipitate was filtered, washed with water, and then with cold MEK. The precipitate was recrystallized from EtOAc to afford 22 g (87%) of product: mp >265-275 °C (dec); ^{1}H NMR (DMSO-d_6, 80 MHz) δ 0.95 (t, 12H, C*H*$_3$), 1.35 (br s, 72H, (C*H*$_2$)$_9$CH$_3$), 2.35 (br s, 8H, CHC*H*$_2$), 4.51 (t, 4H, C*H*CH$_2$), 7.58 (s, 4H, Ar*H*), 8.30 (br s, 8H, O*H*).

7,11,15,18-Tetrabromo-1,21,23,25-tetraundecyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5',4'-*i*']benzo[1,2-*d*:5,4-*d*']bis[1,3]benzodioxocin, Stereoisomer (3). To 120 mL of DMF were added 30 g (21 mmol) of octol **2** and 18 g (127 mmol) of K_2CO_3 and 8.3 mL (127 mmol) of CH_2BrCl. The mixture was stirred at 60 °C for 2 d. Additional 3.4 mL of CH_2BrCl and 7.3 g of K_2CO_3 were added, and then the mixture was further stirred for 1 d at 60 °C. The reaction mixture was allowed to cool, and the solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2, washed with water, brine, and then dried over $MgSO_4$. The crude product was chromatographed on silica gel gravity column using 3 : 1 mixture of hexane and CH_2Cl_2 to give 18 g (59%) of product: mp 80-83 °C; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.95 (t, 12H, C*H*$_3$), 1.35 (br s, 72H, (C*H*$_2$)$_9$CH$_3$), 2.18 (s, 8H, CHC*H*$_2$), 4.35 (d, 4H, H-C-*H*$_{in}$, *J*=7.8 Hz), 4.85 (t, 4H, C*H*CH$_2$), 5.95 (d, 4H, H-C-*H*$_{out}$, *J*=7.8 Hz), 7.05 (s, 4H, Ar*H*).

1,21,23,25-Tetraundecyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5',4'-*i*']benzo[1,2-*d*:5,4-*d*']bis[1,3]benzodioxocin-7,11,15,28-tetrol, Stereoisomer (4) and 1,21,23,25-Tetraundecyl-2, 20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5',4'-*i*']benzo[1,2-*d*:5,4-*d*']bis[1,3]benzodioxocin-7,11,15-triol, Stereoisomer (5). A solution of 3.0 g (2.0 mmol) of tetrabromide **3** in THF (200 mL) was cooled to −78 °C, and 13 mL (20 mmol) of n-butyllithium (1.6 N solution in hexane) was slowly added. The mixture was stirred for 10 min, and then 2.3 mL of $B(OMe)_3$ was added. This mixture was allowed to room temperature for 1 h, and then cooled to −78 °C. After the addition of 40 mL of a 1 : 1 mixture of 28% aqueous H_2O_2 and 3 N NaOH solution, the mixture was allowed to room temperature for 2 h. After careful addition of 16 g of $Na_2S_2O_5$, the mixture was stirred for 1 h and then acidified with 6 N HCl. The organic layer was washed with brine and dried over $MgSO_4$. The products were separated by silica gel gravity column using 1 : 2 mixture of EtOAc and hexane, which gave 1.3 g (51%) of tetrol **4** and 0.39 g (16%) of triol **5** as off-white solids: tetrol **4**: mp 190-192 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 12H, C*H*$_3$), 1.35 (br s, 72H, (C*H*$_2$)$_9$CH$_3$), 2.17 (br s, 8H, CHC*H*$_2$), 4.42 (d, 4H, H-C-*H*$_{in}$), 4.71 (t, 4H, C*H*CH$_2$), 5.97 (d, 4H, H-C-*H*$_{out}$), 6.63 (s, 4H, Ar*H*), 7.25 (s, 4H, ArO*H*): triol **5**: mp 135-137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 12H, C*H*$_3$), 1.30 (br s, 72H, (C*H*$_2$)$_9$CH$_3$), 2.20 (s, 8H, CHC*H*$_2$), 4.44 (two d, 4H, H-C-*H*$_{in}$, *J*=6.0 Hz), 4.70 (m, 4H, C*H*CH$_2$), 5.35 (s, 3H, ArO*H*), 5.86 (d, 2H, H-C-*H*$_{out}$, *J*=6.9 Hz), 5.96 (d, 2H, H-C-

H_{out}, J=6.9 Hz), 6.52 (s, 1H, Ar*H*), 6.64 (s, 3H, Ar*H*), 7.09 (s, 1H, Ar*H*).

32,43-(Epoxyethanoxy)-18,22:53,57-dimetheno-2,48:15,27-dimetheno-3,47,14,28-(methynoxyethanoxymethyno)-1*H*,16*H*,24*H*,26*H*,49*H*,51*H*-bis[1,3]benzodioxocino[9,8-*d*:9',8'-*d*']bis[1,3]benzodioxocino[9',10':15,16;10",9":21,22][1,3,6,9,12,14,17,20]octaoxacyclodocosino[4,5-*j*:11,10-*j*']bis[1,3]benzodioxocin,8,9,37,38-tetrahydro-1,16,24,26,49,51,59,72-octaundecyl @ N,N-Dimethylacetamide Stereoisomer (7@DMA). A solution of 0.20 g (0.16 mmol) of tetrol **4** and 0.12 g (0.33 mmol) of ethylene glycol di-*p*-tosylate in 40 mL of dry DMA was added over 12 h through dropping funnel to a mixture of 0.45 g (3.3 mmol) of K_2CO_3 and 60 mL of dry DMA at 70 °C. An additional 61 mg of ethylene glycol di-*p*-tosylate was added, and the solution was stirred for 24 h at 70 °C. After a final 61 mg of ethylene glycol di-*p*-tosylate was added, the temperature was raised to 80 °C. The mixture was stirred for 24 h more, and then allowed to room temperature. The solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2, washed with water, brine, and then dried over $MgSO_4$. The product was purified by silica gel gravity column using $CHCl_3$ and then recrystallized from CH_2Cl_2/acetone to afford 83 mg (20%) of product: mp >282 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) −1.84 (s, 3H, C*H*$_3$C=O), −0.83 (s, 3H, N-C*H*$_3$), 0.87 (t, 24H, C*H*$_3$), 1.23-1.80 (m, 147H, N-C*H*$_3$+(C*H*$_2$)$_9$CH$_3$), 2.13 (br s, 16H, CHC*H*$_2$), 4.34 (d, 8H, H-C-*H*$_{in}$, J=6.8 Hz), 4.52 (s, 16H, OC*H*$_2$C*H*$_2$O), 4.71 (t, 8H, C*H*CH$_2$), 5.82 (d, 8H, H-C-*H*$_{out}$, J=6.8 Hz), 6.74 (s, 8H, Ar*H*); FD MS m/z 2538 (M^+, 98%), 2625 ((M+ DMA)$^+$, 100%).

33,45-(Epoxypropanoxy)-19,23:55,59-dimetheno-2,50:16,28-dimetheno-3,49,15,29-(methynoxypropanoxymethyno)-1*H*,8*H*,17*H*,25*H*,27*H*,38*H*,51*H*,53*H*-bis[1,3]benzodioxocino[9,8-*d*:9',8'-*d*']bis[1,3]benzodioxocino[9',10':16,17;10",9":23,24][1,3,6,10,13,15,18,22]octaoxacyclotetracosino[4,5-*j*:12,11-*j*"]bis[1,3]benzodioxocin,9,10,39,40-tetrahydro-1,17,25,27,51,53,61,76-octaundecyl @ N,N-Dimethylacetamide Stereoisomer (8@DMA). A solution of 0.44 g (0.33 mmol) of tetrol **4** and 0.25 g (0.66 mmol) of propanediol di-*p*-tosylate in 50 mL dry DMA was added over 24 h to a mixture 0.91 g (6.6 mmol) of K_2CO_3 and 150 mL of dry DMA at 70 °C. An additional 0.25 g of propanediol di-*p*-tosylate was added, and the temperature was raised to 80 °C. The solution was stirred for 24 h more, and then allowed to room temperature. The solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2, washed with water, brine, and then dried over $MgSO_4$. The product was purified by silica gel gravity column using CH_2Cl_2 and then recrystallized from CH_2Cl_2/acetone to give 114 mg (26%) of product: mp >286 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ −1.62 (s, 3H, C*H*$_3$C=O), −0.48 (s, 3H, N-C*H*$_3$), 0.89 (t, 24H, C*H*$_3$), 1.27-1.58 (m, 147H, N-C*H*$_3$+(C*H*$_2$)$_9$CH$_3$), 2.16 (m, 24H, OCH$_2$C*H*$_2$CH$_2$O+CHC*H*$_2$), 4.14 (t, 16H, OC*H*$_2$CH$_2$C*H*$_2$O), 4.29 (d, 8H, H-C-*H*$_{in}$, J=7.3 Hz), 4.71 (t, 8H, C*H*CH$_2$), 5.77 (d, 8H, H-C-*H*$_{out}$, J=7.3 Hz), 6.78 (s, 8H, Ar*H*); FD MS m/z 2683 (M^+, 100%).

Diethylene Glycol Bridged Hemicarcerand (11). A solution of 0.20 g (0.16 mmol) of tetrol **4** and 0.34 g (0.82 mmol) of diethylene glycol di-*p*-tosylate in 40 mL of dry DMA was added over 9 h to a mixture 0.23 g (1.6 mmol) of K_2CO_3 and 80 mL of dry DMA at 60 °C. The solution was further stirred for 12 h at 60 °C, and then allowed to room temperature. The solvent was removed *in vacuo*. The mixture was partitioned between CH_2Cl_2 and 600 mL of 3 N HCl. The organic phase was washed with water, brine, and then dried over $MgSO_4$. The product was purified by silica gel gravity column using CH_2Cl_2 and then recrystallized from CH_2Cl_2/acetone to afford 80 mg (36%) of product: mp >230 °C (dec); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.95 (t, 24H, C*H*$_3$), 1.10-1.60 (m, 144H, (C*H*$_2$)$_9$CH$_3$), 2.10 (br s, 16H, CHC*H*$_2$), 3.80-4.00 (m, 32H, OC*H*$_2$C*H*$_2$O), 4.52 (d, 8H, H-C-*H*$_{in}$, J=6.8 Hz), 4.71 (t, 8H, C*H*CH$_2$), 5.78 (d, 8H, H-C-*H*$_{out}$, J=6.8 Hz), 6.78 (s, 8H, Ar*H*); FAB$^+$ MS m/z 2714 (M^+, 9%).

7,11,15,28-Tetrakis-[2-(2-chloroethoxy)ethoxy]-1,21,23,25-tetraundecyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5',4'-*i*']benzo[1,2-*d*:5,4-*d*']bis[1,3]benzodioxocin Stereoisomer (12). To 7.0 mL of dry DMF were added 0.50 g (0.40 mmol) of tetrol **4**, 0.60 g (2.2 mmol) of 2-(2-chloroethoxy)ethane tosylate and 0.60 g (4.3 mmol) of K_2CO_3. The mixture was stirred for 20 h at 70 °C. The mixture was allowed to room temperature, and the solvent was removed *in vacuo*. The mixture was partitioned between CH_2Cl_2 and 3 N HCl. The organic phase was washed with water, brine, and then dried over $MgSO_4$. The mixture was recrystallized from MeOH/acetone to give 0.61 g (89%) of product: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.86 (t, 12H, C*H*$_3$), 1.10-1.50 (m, 72H, (C*H*$_2$)$_9$CH$_3$), 2.10 (m, 16H, CHC*H*$_2$), 3.58-3.79 (m, 24H, C*H*$_2$OC*H*$_2$C*H*$_2$Cl), 4.12 (t, 8H, OC*H*$_2$CH$_2$O), 4.38 (d, 4H, H-C-*H*$_{in}$, J=7.0 Hz), 4.69 (t, 4H, C*H*CH$_2$), 5.80 (d, 4H, H-C-*H*$_{out}$, J=7.0 Hz), 6.78 (s, 4H, Ar*H*).

7,11,15,28-Tetrakis-[2-(2-iodo)ethoxy)ethoxy]-1,21,23,25-tetraundecyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5',4'-*i*']benzo[1,2-*d*:5,4-*d*']bis[1,3]benzodioxocin, Stereoisomer (13). A solution of 0.20 g (1.3 mmol) of NaI in 8 mL of MEK was refluxed for 1 h. 0.20 g (0.12 mmol) of tetrachloride **12** was added to this solution and then the mixture was refluxed for 48 h more. The mixture was allowed to room temperature, and the solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2, washed with water, brine, and then dried over $MgSO_4$. The product was purified by silica gel gravity column using 4:1 mixture of hexane and EtOAc, which gave 0.18 g (73%) of product as an oilic solid: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.86 (t, 24H, C*H*$_3$), 1.13 (m, 72H, (C*H*$_2$)$_9$CH$_3$), 2.15 (br s, 16H, CHC*H*$_2$), 3.22 (t, 8H, C*H*$_2$I), 3.76 (t, 16H, OC*H*$_2$), 4.17 (t, 8H, OC*H*$_2$CH$_2$O), 4.42 (d, 4H, H-C-*H*$_{in}$, J=7.4 Hz), 4.73 (t, 4H, C*H*CH$_2$), 5.84 (d, 4H, H-C-*H*$_{out}$, J=7.4 Hz), 6.79 (s, 4H, Ar*H*).

Ethylene Bridged Hemicarcerand (15). A solution of 0.40 g (0.33 mmol) of triol **5** and 0.19 g (0.55 mmol) of ehtylene glycol di-*p*-tosylate in 50 mL of dry DMA was added over 12 h to a mixture of 0.92 g (6.7 mmol) of K_2CO_3 and 150 mL of dry DMA at 70 °C. The solution was further stirred for 24 h. An additional 0.19 g of ethylene glycol di-*p*-tosylate was added, and the stirring was con-

tinued for 24 h. After a final 92 mg of ethylene glycol di-*p*-tosylate was added, and the temperature was raised to 80 °C. The solution was stirred for 24 h more, and then allowed to room temperature. The solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2, washed with water, brine, and then dried over $MgSO_4$. The product was purified by silica gel gravity column using CH_2Cl_2 and then recrystallized from CH_2Cl_2/acetone to give 0.21 g (25%) of product: mp >245 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 24H, C*H*$_3$), 1.22-1.55 (m, 144H, (C*H*$_2$)$_9$CH$_3$), 2.18 (br s, 16H, CHC*H*$_2$), 4.16 (br s, 16H, OC*H*$_2$C*H*$_2$O), 4.25 (d, 8H, H-C-*H*$_{in}$, *J*=7.0 Hz), 4.71 (t, 8H, C*H*CH$_2$), 5.80 (d, 4H, H-C-*H*$_{out}$, *J*=7.0 Hz), 5.86 (d, 4H, H-C-*H*$_{out}$, *J*=7.0 Hz), 6.38 (s, 2H, Ar*H*), 6.77 (s, 6H, Ar*H*), 7.03 (s, 2H, Ar*H*); FD MS m/z 2481 (M$^+$, 100%).

Propylene Bridged Hemicarcerand (16). A solution of 0.40 g (0.33 mmol) of triol **5** and 0.26 g (0.66 mmol) of propanediol di-*p*-tosylate in 50 mL of dry DMA was added over 12 h to a mixture of 0.92 g (6.7 mmol) of K_2CO_3 and 150 mL of dry DMA at 70 °C. The solution was further stirred for 24 h. An additional 0.13 g of propanediol di-p-tosylate was added, and the stirring was continued for 24 h. After a final 0.13 g of propanediol di-*p*-tosylate was added, and the temperature was raised to 80 °C. The solution was stirred for 24 h more, and then allowed to room temperature. The solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2, washed with water, brine and then dried over $MgSO_4$. The product was purified by silica gel gravity column using CH_2Cl_2 and then recrystallized from CH_2Cl_2/acetone to give 0.11 g (26%) of product: mp 217 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 24H, C*H*$_3$), 1.28-1.53 (m, 144H, (C*H*$_2$)$_9$CH$_3$), 1.60 (s, 6H, OCH$_2$C*H*$_2$CH$_2$O), 2.20 (m, 16H, CHC*H*$_2$), 4.24 (d, 4H, H-C-*H*$_{in}$, *J*=6.1 Hz), 4.33 (d, 4H, H-C-*H*$_{in}$, *J*=6.1 Hz), 4.60 (s, 12H, OC*H*$_2$CH$_2$C*H*$_2$O), 4.70 (br s, 8H, C*H*CH$_2$), 5.78 (d, 4H, H-C-*H*$_{out}$, *J*=6.1 Hz), 5.88 (d, 4H, H-C-*H*$_{out}$, *J*=6.1 Hz), 6.32 (s, 2H, Ar*H*), 6.75 (s, 4H, Ar*H*), 7.05 (s, 2H, Ar*H*); FD MS m/z 2523 (M$^+$, 100%).

α-α'-Dibromo-*o*-xylene Bridged Hemicarcerand (17). A solution of 0.40 g (0.33 mmol) of triol **5**, 0.18 g (0.66 mmol) of α-α'-dibromo-*o*-xylene, and 50 mL of dry DMA was added over 12 h to the mixture of 0.92 g (6.7 mmol) of K_2CO_3 and 150 mL of dry DMA at 70 °C. An additional 0.18 g (0.66 mmol) of α-α'-dibromo-*o*-xylene was added, and the temperature was raised to 70 °C. The solution was stirred for 24 h more, and then a final 92 mg of α-α'-dibromo-*o*-xylene was added. After stirring for 24 h, the solution was allowed to room temperature. The solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2, washed with water, brine, and then dried over $MgSO_4$. The product was purified by silica gel gravity column using 3 : 1 mixture of hexane and CH_2Cl_2 and then recrystallized from CH_2Cl_2/acetone to give 44 mg (10%) of product: mp 193 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 24H, C*H*$_3$), 1.25-1.60 (m, 144H, (C*H*$_2$)$_9$CH$_3$), 2.19 (m, 16H, CHC*H*$_2$), 4.07 (d, 4H, H-C-*H*$_{in}$, *J*=7.1 Hz), 4.13 (d, 4H, H-C-*H*$_{in}$, *J*=7.1 Hz), 4.58 (t, 8H, C*H*CH$_2$), 5.02 (br s, 12H, OC*H*$_2$ArC*H*$_2$O), 5.42 (d, 4H, H-C-*H*$_{out}$, *J*=7.1 Hz), 5.62 (d, 4H, H-C-*H*$_{out}$, *J*= 7.1 Hz), 6.28 (s, 2H, Ar*H*), 6.80 (s, 4H, Ar*H*), 7.01 (s, 2H, Ar*H*), 7.21-7.32 (m, 12H, Ar*H*).

Carceplex (6@DMA), Hemicarceplex (14@DMA), and Carceplex (18@DMA). A solution of 0.20 g (0.16 mmol) of tetrol **4**, 0.20 g (0.17 mmol) of triol **5**, and 0.04 mL (0.67 mmol) of CH_2BrCl in 50 mL of dry DMA was added over 12 h to a mixture of 0.68 g (4.9 mmol) of K_2CO_3 and 150 mL of dry DMA at 60 °C. The solution was further stirred for 30 h at 60 °C, and then allowed to room temperature. The solvent was removed *in vacuo*. The mixture was partitioned between CH_2Cl_2 and 3 N HCl. The organic phase was washed with water, brine, and then dried over $MgSO_4$. The solvent was evaporated *in vacuo*. The crude mixture was chromatographed on silica gel with 2 : 1 mixture of hexane and CH_2Cl_2. The best fractions corresponding to each carceplex or hemicarceplex were collected and concentrated. The products were recrystallized from CH_2Cl_2/acetone to afford 28 mg (14%) of carceplex **6**@DMA, 37 mg (18%) of hemicarceplex **14**@DMA and 12 mg (6%) of carceplex **18**@DMA: **6@DMA**: mp >250 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ −2.38 (s, 3H, C*H*$_3$C=O), −1.42 (s, 3H, N-C*H*$_3$), 0.87 (t, 24H, C*H*$_3$), 1.02 (s, 3H, N-C*H*$_3$), 1.19-1.65 (m, 144H, (C*H*$_2$)$_9$CH$_3$), 2.17 (m, 16H, CHC*H*$_2$), 4.42 (d, 8H, H-C-*H*$_{in}$, *J*=7.1 Hz), 4.76 (t, 8H, C*H*CH$_2$), 5.85 (d, 8H, H-C-*H*$_{out}$, *J*=7.1 Hz), 6.45 (s, 8H, OC*H*$_2$O), 6.76 (s, 8H, Ar*H*): **14@DMA**: mp >248 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ −2.25 (s, 3H, C*H*$_3$C=O), −1.44 (s, 3H, N-C*H*$_3$), 0.88 (t, 24H, C*H*$_3$), 0.97 (s, 3H, N-C*H*$_3$), 1.22-1.58 (m, 144H, (C*H*$_2$)$_9$CH$_3$), 2.20 (br s, 16H, CHC*H*$_2$), 4.33 (d, 4H, H-C-*H*$_{in}$, *J*=7.3 Hz), 4.40 (d, 4H, H-C-*H*$_{in}$, *J*=7.3 Hz), 4.75 (t, 8H, C*H*CH$_2$), 5.76 (d, 4H, H-C-*H*$_{out}$, *J*=7.3 Hz), 5.84 (d, 4H, H-C-*H*$_{out}$, *J*=7.3 Hz), 6.18 (s, 6H, OC*H*$_2$O), 6.42 (s, 2H, Ar*H*), 6.81 (s, 6H, Ar*H*), 7.04 (s, 2H, Ar*H*): **18@DMA**: FT-IR (KBr) 3477 (OH), 1643 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −2.40 (s, 3H, C*H*$_3$C=O), −1.50 (s, 3H, N-C*H*$_3$), 0.90 (t, 27H, N-C*H*$_3$+C*H*$_3$), 1.22-1.68 (m, 144H, (C*H*$_2$)$_9$CH$_3$), 2.18 (br s, 16H, CHC*H*$_2$), 4.18-4.28 (m, 8H, H-C-*H*$_{in}$), 4.70-4.80 (two t, 8H, C*H*CH$_2$), 5.94-6.02 (m, 8H, H-C-*H*$_{out}$), 6.21-6.41 (two s, 6H, OC*H*$_2$O), 6.52-6.75 (m, 9H, Ar*H*).

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Conformational and Complexational Properties of Distal Dialkyl Ester Derivatives of *p-tert*-Butylcalix[4]arene

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Complexation of primary alkylammonium ions by 1,3-distal calix[4]arene diesters was studied by NMR spectroscopy. The guest alkylammonium ions are found to bind mainly to the two ester moieties and are oriented outward with respect to the cone cavity of the host, forming *exo*-type complexes unlike the case of alkylammonium-calix[6]arene systems. Measurement of T_1 also revealed that the primary binding site is the two ester moities and phenolic OH groups. The temperature dependence of the chemical shifts of phenolic OH protons in these diesters correlates with the basicity of the solvent moderately well and the temperature coefficients of their chemical shifts are found to significantly decrease upon complexation with propylammonium ion.

Introduction

Calix[4]arenes are popular and well-known building blocks in supramolecular chemistry.[1] When selectively functionalized either at the phenolic OH group in the lower rim and/or at the para position of the aromatic ring in the upper rim, they can provide versatile platforms, such as calixcrowns, calixquinones, calixspherands, etc., appropriate for complexation with various guests.[2-4]

Four conformational isomers are possible for calix[4] arenes: cone, partial cone, 1,2-alternate, and 1,3-alternate. Unmodified calix[4]arenes are known to adopt a cone conformation due to the stabilization by intramolecular hydrogen bonding interactions between phenolic OH groups but their structures are fluxional in the sense that they can undergo rapid inversional interconversion between two equivalent cone conformations. However, the rate of such interconversion can be made exceedingly slow by suitable derivatization at the phenolic OH groups so that the resulting derivative assumes a virtually rigid structure. Introduction of ester, keto, and amide groups into the lower rim of calix[4]arenes produces a series of new lipophilic cation receptors arranged to form a rigid cone conformation with remarkable complexing abilities toward small alkali metal cations, notably Na^+ ion. Thus, preorganization of binding sites prior to complexation seems to play a very important role in determining the complexing abilities of calixarenes.[1]

In this paper the conformational properties of 1,3-distal functionalized calix[4]arene, which is one of the most attractive framework for the development of functional ionophores, were studied from two perspectives. First, conformational behaviors of the diesters as well as their complexational properties toward several primary alkylammonium ions were investigated *via* measurement of chemical shifts and spin-lattice relaxation times (T_1) in solution state. Then, the effect of hydrogen bonding of OH groups on conformational stability was probed for the 1,3-distal modified calix[4]arenes **1-3** by means of ^1H NMR spectroscopic measurements in various solvents.

Results and Discussion

Conformational Stability. X-ray crystallography studies[5] show that several 1,3-distal modified calix[4]arenes adopt a flat cone conformation. In this conformation the planes of two confronting benzene rings bearing alkylated OR groups become more parallel with the cone axis while the remaining two phenolic rings are tilted away from the same cone axis so that the two oxygen atoms in the OR groups get farther away from each other than in the normal cone conformation and, at the same time, the two OH