

Calixarenes. 23. The Complexation and Catalytic Properties of Water Soluble Calixarenes

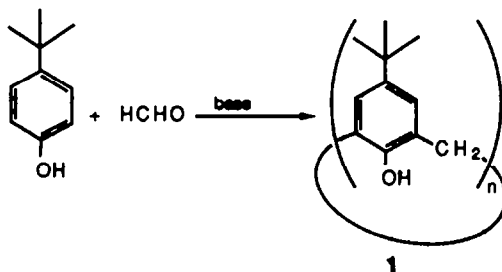
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Abstract: A series of water-soluble calixarenes containing dialkylamino groups and carboxyl groups have been prepared by the *p*-quinonemethide route of functionalization. The formation of host-guest complexes between these calixarenes and nine aromatic hydrocarbons ranging in size from durene to decacyclene has been investigated, and a correlation between the dimensions of the hydrocarbons and the "lower rim" of the calixarene, containing the array of OH groups, has been made. A study of the effect on the acid-catalyzed hydration of *N*-benzyl-1,4-dihydronicotinamide by *p*-(carboxyethyl)calix[*n*]arenes (*n* = 4,5,6,7,8) has shown that the calix[6]arene is more effective than either its larger or smaller analogs.

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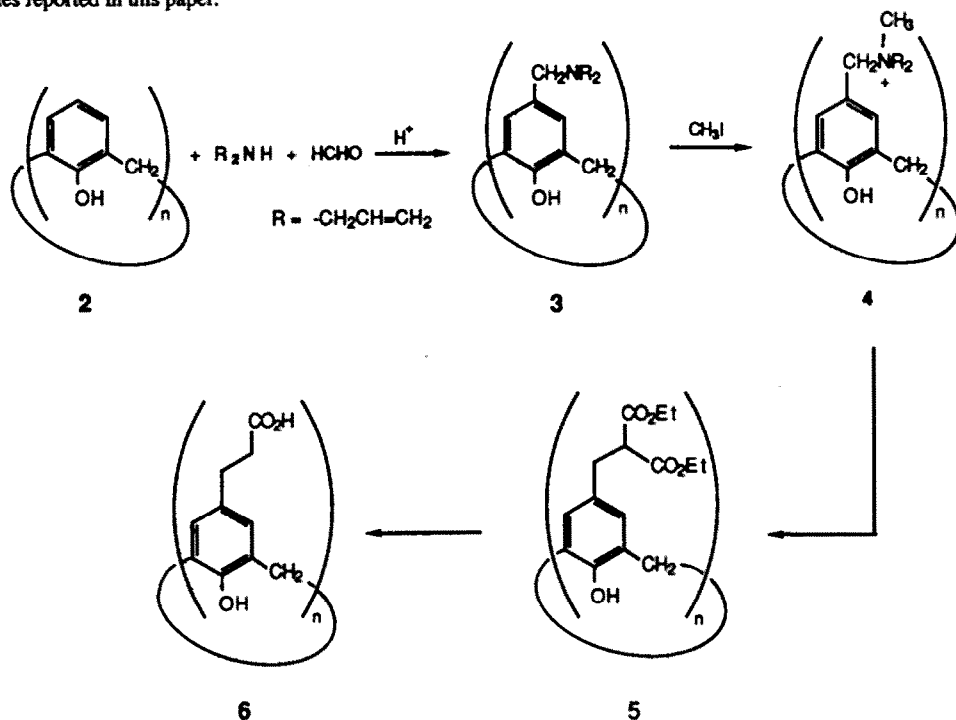
Calixarenes, which belong to the class of [1_{*n*}] cyclophanes that are of interest for their putative ability to form complexes, have been made accessible through the base-induced condensation of *p*-*tert*-butylphenol and formaldehyde¹. By the proper choice of reaction conditions the cyclic tetramer (1[4]), cyclic hexamer (1[6]), and cyclic octamer (1[8]) can be obtained² in good yield and the cyclic heptamer (1[7]) in modest yield. The cyclic pentamer (1[5]) remains a rare commodity, isolable in yields of only a few percent by fractional crystallization of mixtures containing the other cyclic oligomers in larger amounts. All of the *p*-*tert*-butyl calixarenes are very high melting compounds that possess limited



solubility in organic solvents and virtually no solubility in water. It has been shown that these compounds effectively transport certain metal ions, particularly Cs⁺, through nonaqueous phases³ and that they interact with certain amines to form proton-exchanged ionic complexes⁴. The first water soluble calixarene was prepared by Ungaro and co-workers⁵ by affixing carboxymethyl groups onto the phenolic oxygens at the "lower rim" of the calixarene; more recently, Shinkai and co-workers⁶ have obtained water soluble calixarenes by introducing sulfonic acid groups in the *p*-positions at the "upper rim". The present work adds to this list of water-soluble calixarenes and provides a series of compounds carrying amino functions and carboxyl functions, respectively, on the "upper rim".

A number of general procedures for synthesizing calixarenes functionalized on the "upper rim" have been reported, including the electrophilic substitution route as represented by the preparation of *p*-sulfonatocalixarenes⁶, the *p*-Claisen rearrangement route as represented by the preparation of *p*-allylcalix[4]arene⁷, and the recently introduced Mannich base/*p*-quinonemethide route⁸ which involves the acid-catalyzed treatment of calix[4]arene(2[4]) with formaldehyde and a secondary amine to yield a Mannich base (3[4]), quaternization to give 4[4], and treatment with two equivalents of a nucleophile to effect replacement of the trialkylamino moiety by the nucleophile. For example, diethyl sodiomalonate leads to the octa-ester 5[4] which, after hydrolysis and decarboxylation affords *p*-(carboxyethyl)calix[4]arene (6[4]) in good overall yield. That this method has general application is shown in the present work wherein the Mannich bases and the resultant *p*-(carboxyethyl)calixarenes are prepared for the entire series from cyclic tetramer to cyclic octamer. The Mannich bases of choice for the larger cyclic oligomers are those prepared from diallylamine, because these are somewhat more

soluble than the corresponding Mannich bases from dimethylamine and lead, as a result to more facile functionalization of the *p*-positions of all of the rings. It is the Mannich bases from diallylamine (3[4] - 3[8]) and the *p*-(carboxyethyl)calixarenes (6[4] - 6[8]) derived therefrom that provide the compounds for the complexation and catalysis studies reported in this paper.



Complexation Studies

Numerous studies of the complexation behavior of water soluble cyclophanes have been reported by Tabushi⁹, Murakami¹⁰, Koga¹¹, Whitlock¹², Diederich¹³, and others, and the field has been critically reviewed by Diederich¹³. Of the several methods that have been used to measure the extent of complexation the one that proved most appropriate for the calixarene Mannich bases and carboxylic acids was the solid-liquid extraction procedure that has been well described by Diederich¹⁴. In this procedure a finely ground sample of the guest molecule is added to a dilute (ca 10^{-4} M) aqueous solution of the calixarene; the mixture is vigorously stirred for an extended period of time and then centrifuged and filtered to remove all solid material; the aqueous phase is extracted with an organic solvent, and the amount of hydrocarbon present is determined by uv-vis spectrometry. To provide the necessary reference datum, viz the water solubility of the guest molecule, the same determination is carried out with a system not containing the calixarene. The quantities for evaluating the association constant, K_A , for the reaction $H_2O + G \rightleftharpoons HG_{H_2O}$ are determined in the following way: the value of G is assumed to be equal to the solubility of the guest in water; the value of HG_{H_2O} is equal to the total amount of guest molecule as determined by spectrophotometric assay less the value of G ; the value of H_2O is equal to the amount of host molecule added to the system less the value of HG_{H_2O} .

Nine aromatic hydrocarbons, the structures of which are shown in Fig 1, were tested as guests. These ranged in size from durene and naphthalene at one end to coronene and decacyclene at the other. The five *p*-(2-diallylamino-methyl)calixarenes 3[4] to 3[8] and the five *p*-(2-carboxyethyl)calixarenes 6[4] to 6[8] were tested for their ability to form complexes with these hydrocarbons, with the results shown in Table 1

Inspection of Table 1 shows that for those cases in which the magnitude of the complexation constant is above the threshold value of ca 10^2 , the K_A values go from a low of 6×10^2 to a high of 1.5×10^4 , representing only a 25-fold range. It also reveals that the values for a given guest are approximately the same for the aminomethylcalixarenes and the carboxyethylcalixarenes, suggesting that the site of complexation is *not* proximate to the water-solubilizing groups of the calixarene but is at the hydroxyl array at the "lower rim". The working premise for the following arguments, therefore, is that complexation occurs by insertion of a portion of the aromatic hydrocarbon into the "lower rim" of the calixarene.

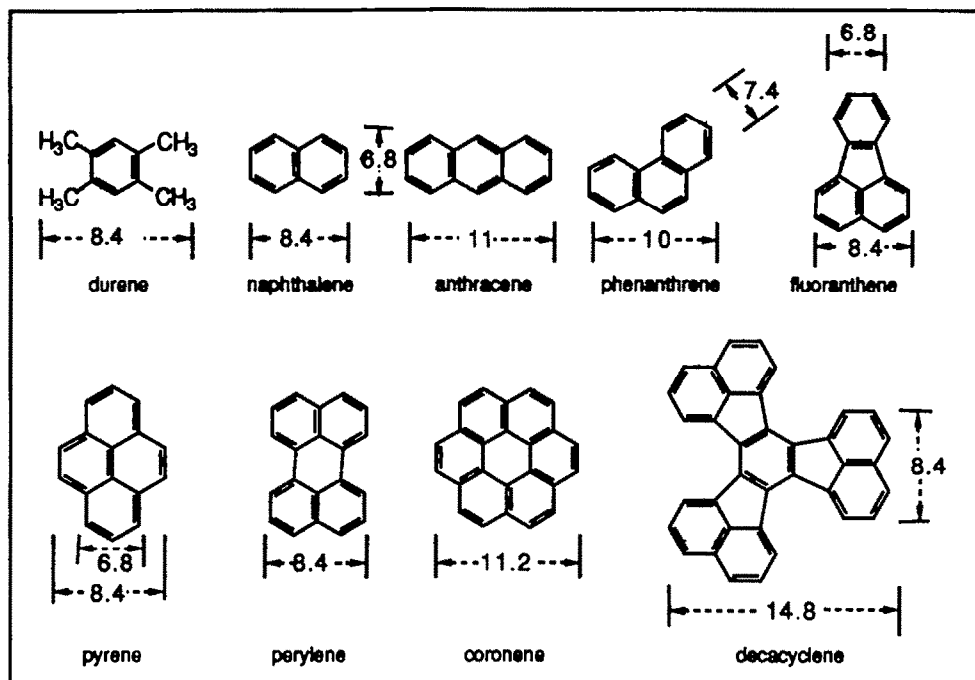


Fig 1. Structures and dimensions (in Å) of the aromatic hydrocarbons used in the complexation studies with *p*-(diallylaminomethyl)calixarenes (3) and *p*-2-carboxyethylcalixarenes (6), measured from CPK space filling models. The thickness in all cases is ca 3 Å, except for durene for which it is ca 3.6 Å

Guest:	Durene	Naphthalene	Anthracene	Phenanthrene	Fluoranthene	Pyrene	Perylene	Coronene	Decacyclene
Host									
3[4]	0	0	0	0	0	0	0	0	0
6[4]	0	0	0	0	0	0	0	0	0
3[5]	0	3.3×10^3	9.0×10^3	0	2.0×10^3	$< 10^2$	$< 10^2$	0	0
6[5]	0	3.7×10^3	9.1×10^3	0	4.0×10^3	$< 10^2$	$< 10^2$	0	0
3[6]	0	4.5×10^3	1.6×10^3	1.9×10^3	4.0×10^3	$< 10^2$	$< 10^2$	0	0
6[6]	0	3.7×10^3	1.3×10^4	3.0×10^3	3.4×10^3	$< 10^2$	$< 10^2$	0	0
3[7]	3.9×10^3	3.0×10^3	8.3×10^3	8.9×10^3	3.0×10^3	9.0×10^3	1.0×10^4	0	0
6[7]	3.9×10^3	3.9×10^3	1.1×10^4	8.9×10^3	3.6×10^3	1.1×10^4	9.0×10^3	0	0
3[8]	2.8×10^3	1.1×10^3	7.5×10^3	4.1×10^3	1.5×10^4	3.6×10^4	1.0×10^4	0	0
6[8]	2.8×10^3	6.1×10^2	9.4×10^3	4.1×10^3	1.4×10^4	4.4×10^4	8.4×10^3	0	0

Table 1. Association constants, K_a , for *p*-(diallylaminomethyl)calixarenes (3) in 0.01 M HCl and *p*-(carboxyethyl)calixarenes (6) in 0.01 M K_2CO_3 with aromatic hydrocarbons, in aqueous solution, determined by solid-liquid extraction.

Measurements made with space filling CPK molecular models give the following approximate dimensions for the elliptical "lower rim" annuli:

calix[4]arene: ca. 2Å diameter
 calix[5]arene: $3 \times 6.2\text{Å}$
 calix[6]arene: $3 \times 7.6\text{Å}$

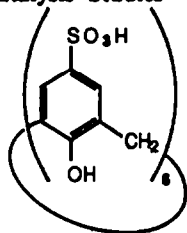
calix[7]arene: $3 \times 8.6\text{Å}$
 calix[8]arene: $3 \times 11.7\text{Å}$

Thus, the calix[4]arenes are too small to accept naphthalene or durene, and the calix[8]arenes apparently are too small to accept coronene and decacyclene. Although the calix[5]arene appears to be slightly too small to readily accept naphthalene, anthracene, and fluoranthene whose minimum dimensions are 6.8Å , complexes with all three of these hydrocarbons are observed, suggesting that the models underestimate the size of the cavity. This circumstance was made evident in earlier studies of the calix[4]arenes where it was found that although the CPK models of a calix[4]arene tetramethyl ether indicate that it should be conformationally inflexible, the actual compound undergoes conformational inversion almost as readily as

does the parent calix[4]arene¹⁵. The failure of durene to form a complex with the calix[5]arenes perhaps can be ascribed to the slightly greater thickness of the guest molecule; if the elliptical opening of the "lower rim" of a calix[5]arene is given a minor axis of 3.6 Å the major axis is reduced to *ca* 5.6 Å. However, the same argument cannot be made for the calix[6]arenes where, although the cavity *can* be contoured to accept durene, a complex is not observed. A difference between the calix[5]arene and calix[6]arene is noted with respect to phenanthrene, only the calix[6]arene forming a complex. As the size of the calixarene increases to seven and eight aromatic moieties the ability to form complexes with the larger hydrocarbons increases. Thus, both the calix[7]arene and calix[8]arene interact with pyrene and perylene. Somewhat surprisingly, however, neither of these larger calixarenes interacts with coronene or decacyclene, although CPK models indicate that their "lower rim" annuli can be distorted to accommodate these large molecules.

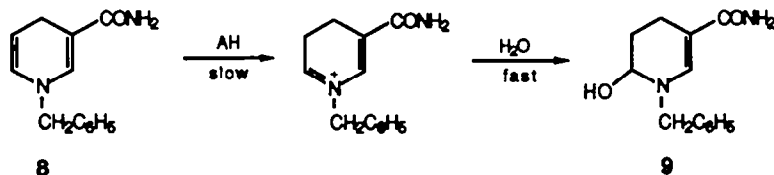
In summary, the water soluble aminomethylcalixarenes and carboxyethylcalixarenes form moderately strong complexes with a variety of aromatic hydrocarbons. It is evident that there is some size complementarity between the guest molecule and the "lower rim" of the calixarenes, but clearly much remains to be learned about the nature of these interactions.

Catalysis Studies



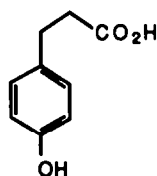
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Shinkai and coworkers⁶ have reported an elegant study of the influence of *p*-sulfonatocalix[6]arene (7) on the acid-catalyzed hydration of *N*-benzyl-1,4-dihydronicotinamide (8 → 9), a reaction reported some years ago in the biochemical literature¹⁶. With the carboxyethylcalixarenes now available it is of interest to compare the cyclic hexamer of this series with its sulfonic acid analog and also to compare the various cyclic oligomers with respect to their effect on this reaction.



8

9



10

The protocol established by Shinkai for studying this process was used in the present case, and the course of the reaction was followed by observing the change in absorptivity at 350 nm as 8 is consumed. Plots of the specific reaction rate constant as a function of calixarene concentration are shown in Fig 2, and values for k_1 , k_c , and K_a , obtained in the fashion described¹⁶ are shown in Table 2. To provide a reference point the same measurements were

Catalyst	$k_1, 10^{-4} \text{ s}^{-1}$	$k_c, 10^{-4} \text{ s}^{-1}$	$K_a, \text{ M}^{-1}$
6[5]	11	13	3800
6[6]	17	31.9	880
6[7]	4.4	6.9	5000
6[8]	4.6	6.6	3700
10	0.2	-	-
7 (see ref 6)	46.2	131	564

Table 2. Kinetic parameters for the conversion of 8 to 9.

made with *p*-hydroxyphenylpropionic acid (10). Inspection of Table 2 shows that *p*-(carboxyethyl)calix[6]arene is a better catalyst than either the smaller or larger members of the series but that it is considerably inferior to its sulfonic acid analog 7. In fact, the "calixarene effect" is even greater than these data indicate if one takes the monomeric phenol as the reference

point. The ratio of k_1 values for calixarene vs monomer is 85 for 6[6] and 1215 for 7, since the rate with *p*-hydroxybenzenesulfonic acid is only $0.038 \times 10^{-4} \text{ s}^{-1}$.

Shinkai has postulated that the catalysis of the reaction $8 \rightarrow 9$ is the result of a "push-pull" action wherein a proton is added to the substrate from one site of the calixarene and the developing positive charge is stabilized by anions at a second site. In the case of the sulfonatocalixarene, in which all of the sulfonic acid groups and one of the phenolic groups exist in the anionic form, the substrate presumably orients itself so that the phenolic functions are the proton donors and the sulfonic acid groups are the anionic sites. In the carboxyethylcalixarenes, where the carboxyl groups are considerably less acidic than sulfonic acid groups and where, in fact, $\text{p}K_1$ may be that of a phenolic group rather than a carboxyl group, the proton-donating and anionic sites may be less obvious. Also, the sulfonic acid groups in 7 are more fixed in space than are the carboxyl groups in 6 which are the termini of flexible arms. Fluorescence measurements⁶ provide reasonable evidence that the catalysis is an *endo*-calix process, and plots of the reaction rate vs calixarene concentration, showing plateaus characteristic of "saturation kinetics" (see Fig 2) are commensurate with this view. It is surprising, however, that the calix[5]arene, which contains a cavity seemingly large enough to accept 8, fails to be a better catalyst. Calix[7]arenes and calix[8]arenes, of course, are far more conformationally mobile systems and may or may not exist in cavity-containing conformations. Even the calix[6]arenes, though, are rather flexible molecules, and further insight into their mode of action in this reaction system must await the construction of more rigid and conformationally-defined analogs.

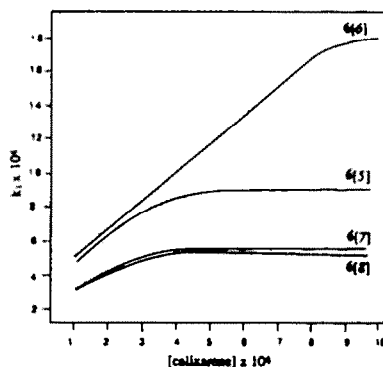


Fig 2. Plot of rate of hydration of 8 as a function of calixarene concentration

Experimental¹⁷

De-*tert*-butylation Reactions:

The removal of the *tert*-butyl groups from *p*-*tert*-butylcalixarenes (1) was carried out with AlCl_3 and phenol in toluene solution as previously described for *p*-*tert*-butylcalix[4]arene to calix[4]arene (2[4]),⁷ *p*-*tert*-butylcalix[6]arene to calix[6]arene (2[6]),¹⁸ and *p*-*tert*-butylcalix[8]arene to calix[8]arene (2[8]).¹⁹ Using this same procedure, calix[5]arene (2[5]) was prepared in 69% yield and calix[7]arene (2[7]) in 49% yield.

p-(*N,N*-Diallylaminomethyl)calixarenes (3)

p-(*N,N*-Diallylaminomethyl)calix[5]arene (3[5]). Following the procedure described by Gutsche and Nam⁸, a 0.5 g sample (0.94 mmol) of calix[5]arene was dissolved in 20 mL of DMSO, and 10 mL of HOAc was added. After 5 m of stirring, 0.92 g (11.3 mmol) of 37% HCHO and 1.4 g (14.1 mmol) of diallylamine were added, and the mixture was stirred at room temperature for 12 h. It was then poured into 100 mL of H_2O to give a clear solution. Upon the addition of a solution of K_2CO_3 a precipitate formed which was separated by filtration, dissolved in Et_2O , and filtered. Evaporation of the solvent afforded 0.8 g (79%) of a white powder: mp ca 100°C (dec); ^1H NMR (CDCl_3) δ 7.18 (s, 2, ArH), 5.86 (m, 2, CH=C), 5.18 (m, 4, C=CH₂), 4.2-3.2 (br s, 2, ArCH₂Ar), 3.41 (s, 2, ArCH₂N), 3.00 (d, 4, NCH₂C); Anal. calcd. for $\text{C}_{70}\text{H}_{85}\text{N}_5\text{O}_5$: C, 78.10; H, 7.96. Found: C, 77.52; H, 7.93

p-(*N,N*-Diallylaminomethyl)calix[6]arene (3[6]) was prepared from calix[6]arene in the manner described above to yield 57% of product as a colorless powder after recrystallization from $\text{Et}_2\text{O}/n$ -hexane: mp ca 100°C (dec); ^1H NMR (CDCl_3) δ 7.09 (s, 2, ArH), 5.88 (m, 2, CH=C), 5.17 (m, 4, C=CH₂), 4.3-3.5 (br s, 2, ArCH₂Ar), 3.44 (s, 2, ArCH₂N), 3.04 (d, 4, NCH₂C); Anal. calcd. for $\text{C}_{84}\text{H}_{102}\text{N}_6\text{O}_6$: C 78.10; H, 7.96. Found: C, 77.89; H, 7.69.

p-(*N,N*-Diallylaminomethyl)calix[7]arene (3[7]) was prepared from calix[7]arene in the manner described above to yield 50% of product as a colorless powder after recrystallization from *n*-hexane: mp ca 100°C (dec); ^1H NMR (CDCl_3) δ 7.13 (s, 2, ArH), 5.9 (m, 2, CCH=C), 5.19 (m, 4, C=CH₂), 3.91 (br s, 2, ArCH₂Ar), 3.50 (s, 2, ArCH₂N), 3.06 (d, 4, NCH₂C); Anal. calcd. for $\text{C}_{98}\text{H}_{119}\text{N}_7\text{O}_7$: C, 78.10; H, 7.96. Found: C, 77.70; H, 7.80

p-(*N,N*-Diallylaminomethyl)calix[8]arene (3[8]) was prepared from calix[8]arene in the manner described above to yield 57% of product as a colorless powder after recrystallization from $\text{CHCl}_3/\text{CH}_3\text{OH}$: mp ca 100°C (dec); ^1H NMR (CDCl_3) δ 9.50 (br s, 1, OH), 7.085 (s, 2, ArH), 5.87 (m, s, CCH=C), 5.17 (m, 4, C=CH₂), 4.34 (br d, 2, ArCH₂Ar), 3.45 (s, 2, ArCH₂N), 3.02 (d, 4, NCH₂C); Anal. calcd. for $\text{C}_{112}\text{H}_{136}\text{N}_8\text{O}_8$: 78.10; H, 7.96. Found: C, 78.26; H, 8.06.

p-(Carboxyethyl)calixarenes (6);

p-(2-Carboxyethyl)calix[5]arene (6[5]). Following the procedure described by Gutsche and Nam⁸, 0.5 g (0.46 mmol) of *p*-(*N,N*-diallylaminomethyl)calix[5]arene (3[5]) was dissolved in 30 mL of DMSO, treated with 0.53 g

(3.7 mmol) of CH_3I , and stirred at room temp for 2 h, to give a clear solution. This was treated with a slurry of diethyl sodiomalonate, prepared from 0.32 g (14 mmol) of Na in 20 mL of absolute EtOH and 2.7 g (16.2 mmol) of diethyl malonate, and stirred at room temp for 15 m. The mixture was then refluxed at 90–100°C for 16 h in an argon atmosphere, cooled to room temperature, and poured onto 200 mL of dil HCl. Extraction with CHCl_3 followed by evaporation of the solvent gave the diester 5[5] as a yellow oil that was used in the subsequent step without purification. It was dissolved in 30 mL of DMSO, 6 mL of conc HCl was added dropwise with stirring, and the reaction mixture was refluxed for 6 h at 110°C in an argon atmosphere. The reaction mixture was cooled, poured into 150 mL of H_2O , an additional 5 mL of HCl was added, and the precipitate that formed was collected by filtration to yield 0.32 g of crude product. Recrystallization from CH_3OH afforded a colorless solid: mp > 400°C: ^1H NMR (DMSO- d_6) δ 12.08 (br s, 1, CO_2H), 8.765 (br s, 1, OH), 6.99 (s, 2, ArH), 3.765 (s, 2, ArCH_2Ar), 2.65 (t, 2, CH_2CO_2), 2.45 (t, 2, ArCH_2C): Anal. calcd. for $\text{C}_{50}\text{H}_{50}\text{O}_{15}$: C, 67.41; H, 5.66. Found: C, 67.45; H, 5.69.

p-(2-Carboxyethyl)calix[6]arene (6[6]) was prepared from 3[6] and obtained in 38% overall yield as a colorless material: mp > 400°C: ^1H NMR (DMSO- d_6) δ 12.08 (br s, 1, CO_2H), 8.97 (br s, 1, OH), 6.84 (s, 2, ArH), 3.73 (s, 2, ArCH_2Ar), 2.62 (t, 2, CH_2CO_2), 2.42 (t, 2, ArCH_2C): Anal. calcd. for $\text{C}_{60}\text{H}_{60}\text{O}_{18}$: C, 67.41; H, 5.66. Found: C, 67.89; H, 5.76.

p-(2-Carboxyethyl)calix[7]arene (6[7]) was prepared from 3[7] and obtained in 55% overall yield after recrystallization from CH_3OH : mp > 400°C: ^1H NMR (DMSO- d_6) δ 12.10 (br s, 1, CO_2H), 9.06 (br s, 1, OH), 6.85 (s, 2, ArH), 3.77 (s, 2, ArCH_2Ar), 2.645 (t, 2, CH_2CO_2), 2.425 (t, 2, ArCH_2C): Anal. calcd. for $\text{C}_{70}\text{H}_{70}\text{O}_{21}$: C, 67.41; H, 5.66. Found: C, 66.96; H, 5.72.

p-(2-Carboxyethyl)calix[8]arene (6[8]) was prepared from 3[8] and obtained in 66% overall yield after recrystallization from CH_3OH as a colorless material: mp > 400°C: ^1H NMR (DMSO- d_6) δ 12.21 (br s, 1, CO_2H), 8.99 (br s, 1, OH), 6.79 (s, 2, ArH), 3.775 (s, 2, ArCH_2Ar), 2.61 (t, 2, CH_2CO_2), 2.39 (t, 2, ArCH_2C): Anal. calcd. for $\text{C}_{80}\text{H}_{80}\text{O}_{24}$: C, 67.41; H, 5.66. Found: C, 67.37; H, 6.20

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- (17) The melting points of all compounds melting above 250° were taken in sealed and evacuated capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge MA) using a 500° thermometer calibrated against a thermocouple. Proton nuclear magnetic resonance spectra (^1H NMR spectra) were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Infrared spectra were determined on a Perkin-Elmer 283B spectrometer. UV-Vis spectra were determined on a Bausch and Lomb Spectronic 1001 spectrometer. Microanalyses were carried out by Desert Laboratories, Tucson, AZ. Analytical samples were dried at least 36 h at room temp -140° C and 1-2 mm pressure. In a number of instances solvent of crystallization was retained, considerably affecting the elemental analysis. In such cases best fits between the analytical values and the appropriate fractional increment of solvent were sought, leading in some instances to seemingly adventitious amounts of solvents.
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