on lanthanide chemistry, and Professors R. H. Grubbs and B. M. Trost for helpful discussions.

Registry No. 1, 41718-44-9; 2, 141983-52-0; 3, 32836-50-3; 3·HCl, 141983-74-6; 4, 18094-01-4; 5, 141983-53-1; 5·HCl, 141983-77-9; 6, 141983-54-2; 7, 141983-55-3; 8, 3433-03-2; 8·HCl, 1660-17-9; 9, 42044-72-4; 9·HCl, 141983-78-0; 10, 141983-56-4; 10·HCl, 141983-79-1; 11, 141983-57-5; 12, 5824-40-8; 13, 141983-58-6; 13·HCl, 141983-80-4; 14, 141983-59-7; 14 *p*-tolylurea derivative, 141983-81-5; 15, 141983-60-0; 15 phenylurea derivative, 141983-82-6; 16, 141983-61-1; 17, 141983-62-2; 17·2HCl, 141983-91-7; 18, 141983-63-3; 18·2HCl, 141983-83-7; 19, 141983-64-4; 19·2HCl, 141983-84-8; 20, 141983-65-5; 20·HCl, 141983-85-9; 21, 141983-66-6; 21·HCl, 141983-86-0; *cis*-22, 141983-71-3; *cis*-22·HCl, 141983-72-4; *trans*-22, 141983-67-7; *trans*-22·HCl, 141983-73-5; 23, 141983-68-8; 24, 141983-69-9; 25, 141983-70-2; 25·fumarate, 141983-87-1; 27, 99868-56-1; 28, 33083-81-7; 28·HCl, 141983-88-2; 29, 22308-24-3; 29·HCl, 19274-92-1; $CeCl_3$, 7790-86-5; $BuCeCl_2$, 94616-73-6; $MeCeCl_2$, 94616-84-9; *i*-$PrCeCl_2$, 119021-56-6; *s*-$BuCeCl_2$, 141983-75-7; $PhCeCl_2$, 99354-16-2; benzonitrile, 100-47-0; acetophenone, 98-86-2; α-butyl-α-methylbenzenemethanol, 4396-98-9; 4-cyanobenzophenone, 1503-49-7; dodecanenitrile, 2437-25-4; 2-methylpropionitrile, 78-82-0; 2,2-dimethylpropionitrile, 630-18-2; cycloheptanecarbonitrile, 32730-85-1; 1-adamantanecarbonitrile, 23074-42-2; *p*-tolylacetonitrile, 2947-61-7; 4-phenylbenzonitrile, 2920-38-9; 2-furancarbonitrile, 617-90-3; 1-naphthalenecarbonitrile, 86-53-3; 2-furanylcerium dichloride, 141983-76-8; 2-thienylcerium dichloride, 138769-83-2; 2-tridecanone, 593-08-8; 2-methyl-2-tridecene, 62060-10-0; naphthalene, 91-20-3; furan, 110-00-9; 2-bromothiophene, 1003-09-4; *p*-phenylenedicarbonitrile, 623-26-7; 4-pyridinecarbonitrile, 100-48-1; 1-phenethyl-4-piperidinecarbonitrile, 23793-56-8; (*E*)-cinnamonitrile, 1885-38-7; (*Z*)-3-cyclohexylacrylonitrile, 78978-70-8; (*E*)-3-cyclohexylacrylonitrile, 22031-57-8; 1-methyl-4-(3-pyridyl)-4-piperidinecarbonitrile, 104742-20-3; 1-methyl-4-(3-chlorophenyl)-4-piperidinecarbonitrile, 126555-97-3; (*E*)-2,2-dimethyl-3-heptanimine, 141983-89-3; valerophenone imine, 16659-09-9; benzophenone imine, 1013-88-3; (*Z*)-2,2-dimethyl-3-heptanimine, 141983-90-6.

Supplementary Material Available: ^{13}C NMR spectra of 4, 6, 7, 11, and 16 for which elemental analyses were not obtained (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Calixarenes. 27. Synthesis, Characterization, and Complexation Studies of Double-Cavity Calix[4]arenes

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Received February 24, 1992

The ease with which calix[4]arenes can be selectively substituted at the distal phenolic oxygens is employed to advantage to build a second cavity and create two classes of "double-cavity calixarenes". Through the use of 3,5-dinitrobenzoyl chloride, 3-nitro-5-carbomethoxybenzoyl chloride, 3,5-dinitrobenzyl chloride, or 3-nitro-5-carbomethoxybenzyl chloride the diesters 2 and 16, diethers 3 and 17, and ether–ester 10 have been prepared. The second cavity is built by reduction of the nitro groups to amino groups to give compounds 4, 5, 13, 18, and 19 followed by treatment with a diacyl chloride. The products obtained from 4, 5, and 13 are double-spanned double-cavity calix[4]arenes; those from 18 and 19 are single-spanned double-cavity calix[4]arenes. A study of the complexation characteristics of the double-spanned double-cavity calixarenes (6, 7, and 14) shows the diester double-cavity calix[4]arene 6 to be the most effective of the three in forming complexes with acidic compounds (i.e., phenols and carboxylic acids) as well as basic compounds (i.e., pyridines, imidazoles, aliphatic amines). The K_{assoc} values range from < 5 to 55 M^{-1} and are dependent both on the shape and the acidity or basicity of the guest. Several lines of evidence, including molecular modeling studies, indicate that complexation occurs at the side rather than the bottom of the host molecule, providing an explanation for the differences in K_{assoc} for various pairs of guests and also establishing the rationale for the synthesis of the single-spanned double-cavity calix[4]arenes (20, 21) which form quite strong complexes ($K_{assoc} > 10^3$) with certain guests such as resorcinol.

The calix[4]arenes[1] are easily synthesized cavity-containing molecules possessing hydroxyl groups on the "lower rim" and potentially free para positions on the "upper rim". Several of the methods for achieving upper rim functionalization have been developed in this laboratory,[2] our major attention in the past having been devoted to the cavity on which these introduced functions reside. The hydroxyl groups, however, also provide convenient points for attachment of various moieties, as numerous other workers have actively demonstrated.[3] The present paper deals with this latter aspect of calixarene functionalization and describes methods whereby a second cavity is introduced into the calix[4]arenes. The program had its inception in the discovery that calix[4]arenes can be converted in good yield to compounds containing a pair of 3,5-dinitrobenzoyl moieties attached in a 1,3-fashion to oxygens on the lower rim (i.e., positions 25 and 27).[4]

Synthesis of Double-Spanned Double-Cavity Calix[4]arenes

The three double-spanned double-cavity calix[4]arenes that have been synthesized for a comparison of their complexing abilities are designated as the diester double-spanned double-cavity calix[4]arene 6, the ester–ether double-spanned double-cavity calix[4]arene 14, and the diether double-spanned double-cavity calix[4]arene 7. They are prepared as described below.

(1) (a) Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; Royal Society of Chemistry: London, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic: Dordrecht, 1991.

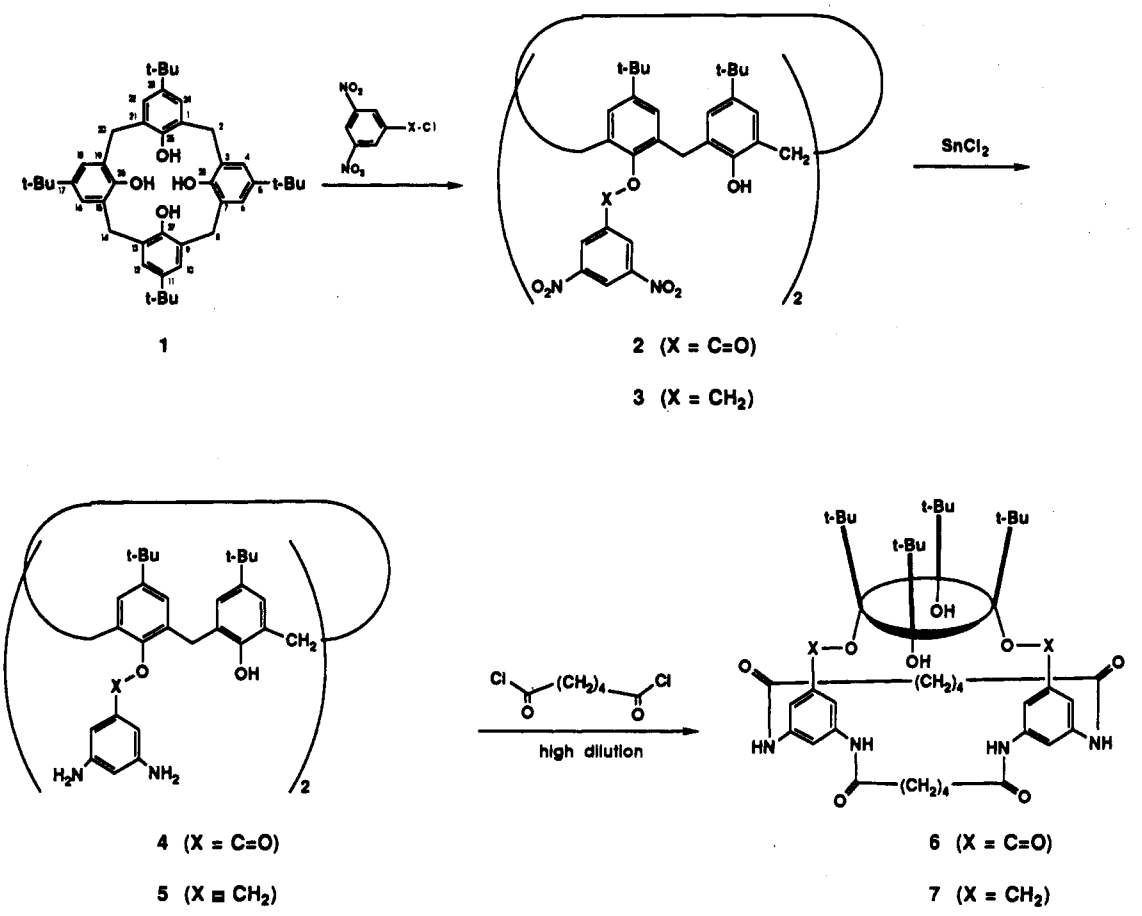
(2) Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* **1985**, *50*, 5795. Gutsche, C. D.; Levine, J. A.; Sujeeth, P. K. *J. Org. Chem.* **1985**, *50*, 5802. Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, *110*, 6153.

(3) For example, see: Collins, E. M.; McKervey, M. A.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 372. Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing-Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681.

(4) See: K. A.; Fronczek, F. R.; Watson, W. H.; Gutsche, C. D. *J. Org. Chem.* **1991**, *56*, 7256.

0022-3263/92/1957-4527$03.00/0

Scheme I



1

2 (X = C=O)

3 (X = CH_2)

4 (X = C=O)

5 (X = CH_2)

6 (X = C=O)

7 (X = CH_2)

Diester Double-Spanned Double-Cavity Calix[4]arene (6) from 1,3-Diester 2. The 1,3-diester **2**, available in almost quantitative yield[4] by the action of 3,5-dinitrobenzoyl chloride on *p-tert*-butylcalix[4]arene (**1**)[5] in the presence of pyridine, is reduced in 75% yield to the corresponding tetraamino compound **4** by the action of stannous chloride,[6] using the modification of Bellamy and Ou.[7] Treatment of **4** with adipoyl chloride in the presence of triethylamine in CH_2Cl_2 under very high dilution conditions produces the diester double-spanned double-cavity calix[4]arene **6** in 40–50% yields. Of the numerous other difunctional spanners that were tested for converting **4** to a double-spanned double-cavity calixarene only pimeloyl chloride and suberoyl chloride give isolable products.[8] Glutaryl chloride, phthaloyl chloride, terephthaloyl chloride, *p,p'*-bis(chlorocarbonyl)diphenylmethane, and *p,p'*-bis(chlorocarbonyl) diphenyl ether all failed to yield characterizable products.

Ester–Ether Double-Spanned Double-Cavity Calix[4]arene 14 from Ester–Ether 13. The synthesis of the ester–ether **13**, the precursor for the construction of an ester–ether double-spanned double-cavity calix[4]arene **14**, initially presented difficulties. 3,5-Dinitrobenzoylation of the monoether **9**, prepared by treating the vicinal diester **8** with 3,5-dinitrobenzyl chloride followed by hydrolysis of the resulting mixture of ether–diesters, yielded material from which the desired ester–ether **10** could not be isolated. The alternative pathway starting with the monoester **11** also failed in the initial attempts, yielding the diester–ether **12** and the diether **3** as the only isolable products. However, when the same reaction is carried out in acetonitrile rather than acetone using only stoichiometric amounts of base and aroylating agent, the desired ester–ether **10** is obtained in 66% yield. Reduction of the nitro groups of **10** affords the tetraamino compound **13** which is treated with adipoyl chloride to produce the ester–ether double-spanned double-cavity calix[4]arene **14**.

Diether Double-Spanned Double-Cavity Calix[4]arene 7 from 1,3-Diether 3. The transformation of a calix[4]arene to a diether, first demonstrated in this laboratory[9] and subsequently employed to advantage by others,[10] is used to produce the 1,3-diether **3**. Reduction of the nitro groups of **3** affords the tetraamino compound **5** which upon treatment with adipoyl chloride yields the double-spanned diether double-cavity calix[4]arene **7**.

Structure Proof and Spectral Properties of Double-Spanned Double-Cavity Calix[4]arenes

The structure of the double-spanned diester double-cavity calix[4]arene **6** is based on an elemental analysis,[11,12]

(5) The term "calixarene" is variously employed in different contexts. In colloquial usage (i.e., in the Discussion section), it implies the presence of hydroxyl groups as, for instance, in "*p-tert*-butylcalix[4]arene" for **1**. In the precise and complete specification of a compound (i.e., in the Experimental Section) it implies only the basic skeleton to which the substituents, including the OH groups, are attached at the positions that are designated by appropriate numbers.

(6) Xing, W. K.; Ogata, Y. *J. Org. Chem.* **1982**, *47*, 3577.

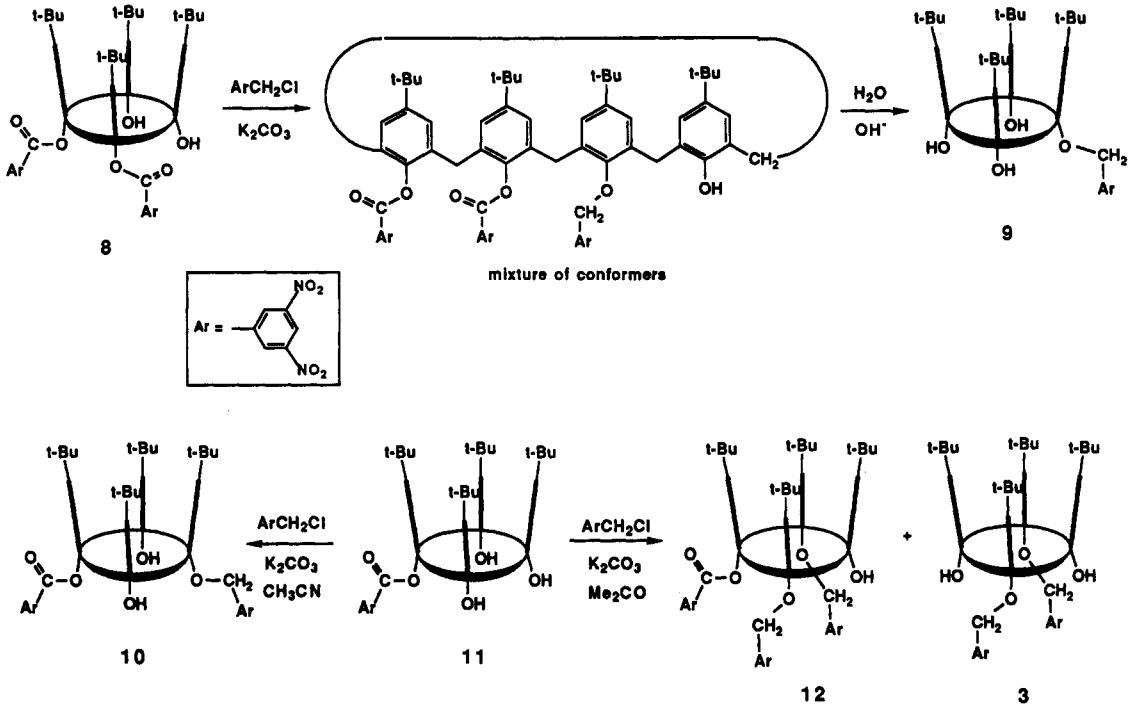
(7) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839.

(8) The elemental analytical values for these compounds are rather poor, and their unexciting complexation characteristics did not warrant attempts to improve their syntheses.

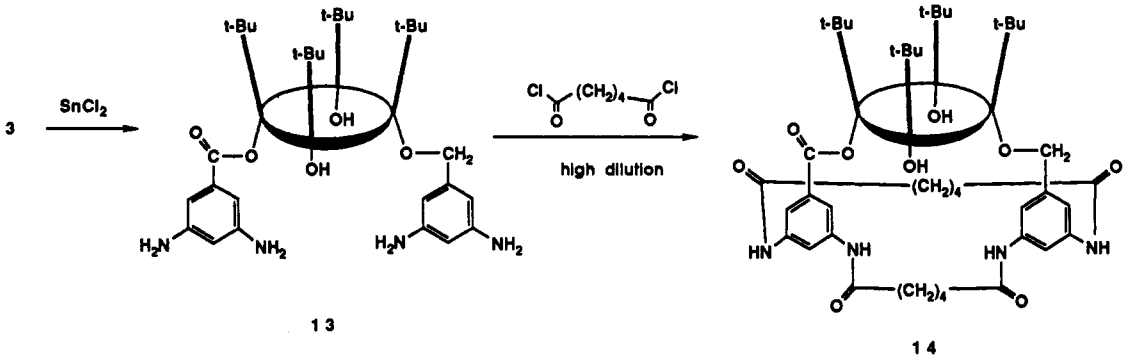
(9) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.

(10) von Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.

Scheme II



Scheme III



a mass spectrum showing a signal for the parent ion at m/e 1137; an IR spectrum with absorptions for ester and amide carbonyl groups; a ^{13}C NMR spectrum containing two resonances for NC=O, one resonance for OC=O, 11 resonances for quaternary aromatic carbons, seven resonances for ArH carbons, six resonances for $ArCH_2Ar$ and $NCO(CH_2)_4NCO$, two resonances for CMe_3, and two resonances for $C(CH_3)_3$; and a ^1H NMR spectrum in $CDCl_3$ (see Figure 1) containing two singlets from the *tert*-butyl groups, a multiplet from the tetramethylene groups of the two spanner moieties, eight lines (two sets of pairs of doublets) from two sets of equivalent methylene groups, three singlets from the aromatic and aroyl rings, a pair of doublets from the aromatic rings of the calixarene (the aryl protons assigned on the basis of peak areas and a COSY spectrum), a singlet at δ 6.23 from OH,[13] and singlets at δ 10.50 and

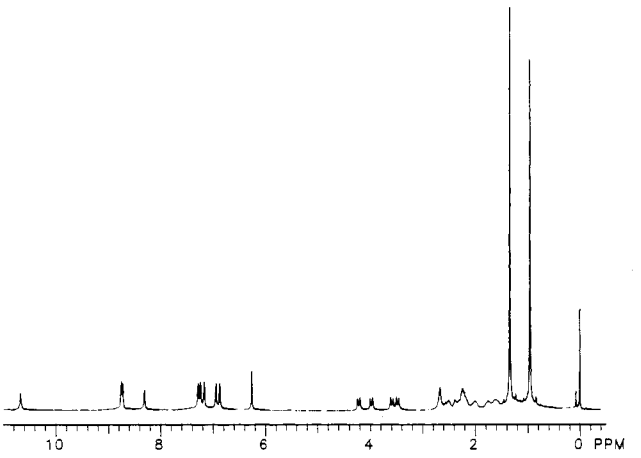


Figure 1. ^1H NMR spectrum of diester double-cavity calix[4]arene 6 in $CDCl_3$ at 25 °C (300 MHz).

(11) Carbon values for 6 as well as several other compounds in this study were invariably low, a common occurrence with cavity-containing compounds. Repeated analyses by different laboratories and on different samples (including one independently prepared by Dr. Amruta Reddy of this laboratory) dried in various ways gave identical results. One apparent solution to the problem was to assume the inclusion of $CHCl_3$, but elemental analysis showed an absence of chlorine. When a strenuously dried sample of 6 was weighed immediatly upon withdrawal from the drying pistol and then again 30 min later it was found to have gained weight, suggesting that one or more components of the atmosphere have been absorbed. If one assumes that H_2O and CO_2 are the entities absorbed, excellent agreement is obtained between the calculated and observed values for C, H, and N as well as the weight gained. The incorporation of H_2O and O_2 leads to satisfactory agreement in most of the other instances in which the elemental value for C is low, giving some credence to this hypothesis which, however, remains to be proved. Incomplete combustion has been advanced as still another possible explanation for the low C values of certain calixarene compounds.[12]

(12) Böhmer, V.; Jung, K.; Schön, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790 (ref 12).

8.21 from NH. In DMSO-d_6 the ^{1}H NMR is less complex, showing only a pair of doublets for the calixarene methylene groups, probably the result of equilibration (rapid on the NMR time scale) between two or more conformations and/or hydrogen-bonded structures. The resonances from OH and NH in the spectrum in $CDCl_3$ can be washed out by treatment with D_2O, but the rate of exchange varies considerably among these three protic moieties. Upon addition of D_2O to a $CDCl_3$ solution of **6**, only the δ 8.21 peak quickly disappears at room temperature; it is tentatively assigned to a pair of amide groups in which the NH's are oriented outward. When the $CDCl_3$–D_2O solution is warmed the peak at δ 10.50 gradually disappears over a period of a few minutes; it is tentatively assigned to the pair of amide groups in which the NH's are oriented inward, protected from access to the D_2O because of this inward orientation. After standing in contact with $CDCl_3$–D_2O overnight the peak at δ 6.23 finally disappears; it is tentatively assigned to the OH groups whose inward orientation makes them difficulty accessible to D_2O. The two sets of NH resonances, present in a ratio of 1:1, can be attributed to any of several possibilities: viz. (a) all four amide groups in a syn configuration but with opposing dipolar arrangements; (b) all four amide groups in an anti configuration but with opposing dipolar arrangements; or (c) two amide groups in a syn configuration and two in an anti configuration. The eight-line pattern in the δ 3.3–4.3 region indicates that there are two different sets of equivalent methylene groups. This can be attributed, inter alia, to the presence of phenolic OH groups intramolecularly hydrogen bonded to the adjacent oxygens of the ester moieties (and changing partners slowly on the NMR time scale at room temperature) and/or to the lack of C_{2v} symmetry in the lower ring. In the absence of an X-ray crystallographic determination[14] the conformation of **6** remains uncertain (see later Discussion). When **6** is heated the sharp lines in the δ 3.3–4.3 region broaden, coalesce, and then start again to sharpen to a simpler pattern containing a singlet and a doublet (or, possibly, a pair of doublets). This same phenomenon is noted with **7**, as discussed below, where the higher temperature spectrum is better resolved.

The structure of the ester–ether double-spanned double-cavity calix[4]arene **14** is based on an elemental analysis; a mass spectrum (signal for parent ion at m/e 1123); a ^{13}C NMR spectrum showing a NCO resonance, an OCO resonance, 32 Ar and ArH resonances, eight CH_2 and CMe_3 resonances, and three $C(CH_3)_3$ resonances; and a ^{1}H NMR spectrum showing three singlets (2:1:1 ratio) from the *tert*-butyl groups, a multiplet from the tetramethylene groups of the spanner moieties, eight lines (two sets of pairs of doublets) from two sets of equivalent methylene groups, two singlets from the aromatic protons of the aroyl rings, four singlets from the aromatic protons of the calixarene rings, a singlet at δ 7.33 for OH, and singlets at δ 9.57 and 7.88 from NH.

The structure of the diether double-spanned double-cavity calix[4]arene **7** is based on an elemental analysis and a ^{1}H NMR spectrum[15] which at −20 °C displays the same general features that the ^{1}H NMR spectrum of the diester

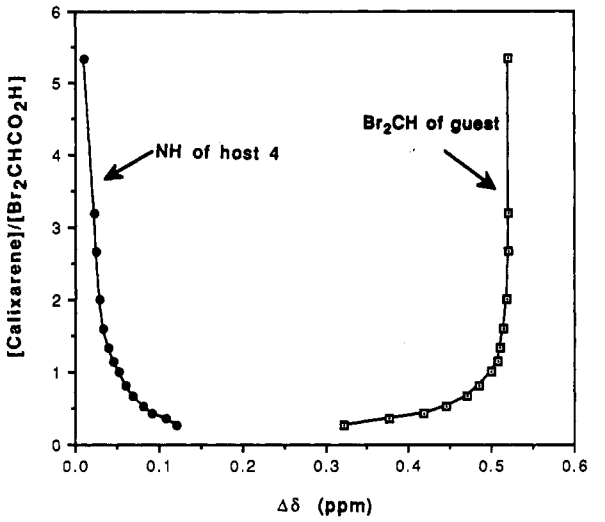


Figure 2. Plot of $\Delta\delta$/[guest] vs $\Delta\delta$ for the complex of **6** with dibromoacetic acid.

double-spanned double-cavity calixarene **6** shows at room temperature. At room temperature, however, the spectrum of **7** contains a broad, ill-resolved resonance in the δ 3–5 region arising from the methylene hydrogens of the calixarene ring and the 3,5-dinitrobenzyl moieties. As the temperature is lowered these sharpen to three resonance envelopes, each containing four lines. The pair of doublets at δ 5.65–5.9 is associated with the methylene hydrogens of the benzyl groups (absent in **6**), and the two sets of pairs of doublets centered at δ 4.45 and 3.5 arise from the methylene hydrogens of the calixarene ring. When the temperature is raised above 20 °C the envelope at δ 5.9 sharpens to a singlet and that in the δ 3.3–4.7 region sharpens to a pair of doublets, the latter resembling the methylene pattern of **6** at room temperature. The same explanations that are invoked to interpret the nonequivalence of the calixarene methylenes in **6** can again be invoked, viz. equilibrations (slow on the NMR time scale at lower temperature but rapid at higher temperatures) between hydrogen-bonded structures involving the phenolic moieties and/or between conformations of the lower ring comprising the four amide groups. In comparing **6** with **7** it is clear that their dynamic ^{1}H NMR characteristics are similar but that **7** (coalescence temperature ca. 20 °C) is somewhat more flexible than **6** (coalescence temperature ca. 50 °C).

Complexation Studies with Double-Spanned Double-Cavity Calix[4]arenes

Host–guest chemistry constitutes a major area of current study, and many examples of synthetic hosts showing high affinity for organic guests have appeared in the recent literature.[16] Complexation constants for most of the

(13) The assignment of the δ 6.23 resonance of **6** to the OH group is based on the appearance of the OH resonance of the precursor diester **2** at δ 5.20.[4]

(14) The complexity of the unit cell has not permitted adequate interpretation of the reflection data.

(15) Although a ^{1}H NMR spectrum could be obtained, **7** was insufficiently soluble in $CHCl_3$, $CHCl_3$–MeCN, $CHCl_3$–CS_2, DMSO, DMSO–CS_2, pyridine, or pyridine–CS_2 to obtain a satisfactory ^{13}C NMR spectrum.

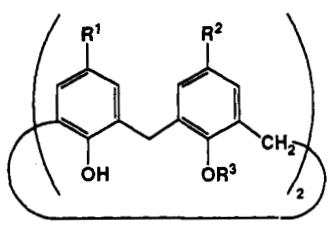
(16) The following references are recent typical examples arbitrarily selected from a large group of papers dealing with the solution complexation of organic molecules by synthetic host molecules: (a) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201. (b) Zimmerman, S. C.; Wu, W.; Zeng, Z. *J. Am. Chem. Soc.* **1991**, *113*, 196. (c) Neder, K. M.; Whitlock, H. W. Jr. *J. Am. Chem. Soc.* **1990**, *112*, 9412. (d) Garcia-Tellado, F.; Goswami, S.; Chang, S-K.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393. (e) Harmata, M.; Barnes, C. I. *J. Am. Chem. Soc.* **1990**, *112*, 5655. (f) Smithrud, D. B.; Sanford, E. M.; Chao, I.; Ferguson, S. B.; Carcanague, D. R.; Evanseck, J. D.; Houk, K. N.; Diederich, F. *Pure Appl. Chem.* **1990**, *62*, 2227. (g) Thilgen, C.; Vögtle, F. *Chem. Ber.* **1990**, *123*, 2445. (h) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055. (i) Chapman, K. T.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 3075. (j) Petti, M. A.; Shepodd, T. J.; Barrans, R. E. Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825. (k) Kelly, T. R.; Maguire, M. *J. Am. Chem. Soc.* **1987**, *109*, 6549. (l) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440.

Table I. Association Constants (K_{assoc}) of O-Disubstituted Calix[4]arenes and Imidazoles

	K_{assoc}, M^{-1}						
guest molecule	2	3	8	15a[10]	15b	15c[4]	15d
imidazole	dec	7	12	14	10	0	10
1-methylimidazole		4		5	5		
4-methylimidazole				9	6		
1-butylimidazole				0			

compounds cited in ref 14 are greater than 10^3 M^{-1} and in some instances greater than 10^4 M^{-1}. Those observed in the present study with the double-spanned double-cavity calix[4]arenes are well below these levels, falling in the 5–50 M^{-1} range. Nevertheless, the differences that are observed in the complexation constants for a given host with a series of guest provide some insight into the nature of the host–guest interactions in this system.

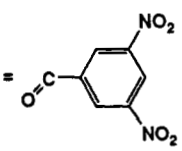
The complexation behavior of the compounds included in the present study is conveniently monitored by ^1H NMR spectroscopy wherein a known concentration of the host in $CDCl_3$ is mixed with various concentrations of the putative guest. Initially a determination is made with a 1:1 ratio of host to guest to ascertain if there is sufficient change in the chemical shift of the protons of the host and/or guest to warrant further experiments, a 0.02 ppm shift being taken as the threshold for significant complexation. Plots of [calixarene]/[guest] vs $\Delta\delta$ show breaks when [host]/[guest] = 1, indicating that 1:1 complexes are being observed. A typical example is illustrated in Figure 2. To obtain K_{assoc} values determinations are made with the ratio of guest to host 10-fold or greater, thereby allowing application of the Benesi–Hildebrand expression.[17] The data shown in Tables II–VI were obtained in this fashion for double-spanned double-cavity calix[4]arenes 6, 14, and 7 with phenols, carboxylic acids, aromatic amines, and aliphatic amines as guests. To provide points of reference, the complexation constants of several single-cavity O-disubstituted calix[4]arenes (2, 3, 8, 15a–d)



15a $R^1 = R^2 = t$-Bu, R^3 = Me

15b R^1 = H, $R^2 = t$-Bu, R^3 = Me

15c R^1 = H, $R^2 = t$-Bu, R^3 =



15d $R^1 = R^2$ = H, R^3 = Me

were also measured against pyridine, pyrazole, pyrrole, aniline, *n*-butylamine, *tert*-butylamine, and several imidazoles. Only the imidazoles give measurable values, as shown in Table I. The ability of imidazoles to form complexes with these hosts is attributed to the bifunctional character of these bases. The imidazoles probably nestle into the cleft at the lower rim of the calixarene where they

(17) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.

Table II. Association Constants (K_{assoc}) of Double-Cavity Calix[4]arenes with Phenols

	K_{assoc}, M^{-1}		
guest molecule	diester 6	ester–ether 14	diether 7
phenol	7	5	0
4-nitrophenol	55	48	40
3-nitrophenol	40		36
2-nitrophenol	0		0
2,4-dinitrophenol	0		0
4-nitro-3,5-dimethylphenol	0		0
4-cyanophenol	31		
4-(trifluoromethyl)phenol	21		
4-bromophenol	21	16	10
2-bromophenol	0		0

act both as hydrogen bond donors and acceptors. The interaction of imidazole with dimethyl ether **15a**, for example, produces a downfield shift of the OH resonance of the host (indicative of increased hydrogen bonding) and an upfield shift of the *tert*-butyl resonances, particularly those of the aryl rings carrying the OMe groups. This can be ascribed to a change from a flattened cone conformation to a more symmetrical cone conformation wherein the aryl rings carrying the OH groups swing upward to facilitate hydrogen bonding with imidazole. The introduction of a methyl group at N-1 or N-4 of imidazole reduces the complexation constant by a factor of 2–3, while introduction of an *n*-butyl group at N-1 reduces it to zero, suggesting that steric factors are operative. The failure of the 1,3-diester **15c** (1,3-alternate conformation) to form a complex with imidazole may be due to the inability of the guest to span the distance between the OH groups in **15c** which are shown by X-ray crystallography[4] to be 4.95 Å apart. The failure of the 1,2-diester 8 to form a complex with imidazole similarly is ascribed to the distance between the OH groups which are anti to one another in the 1,3-alternate conformation. The requirement of one or more phenolic groups for effective complexation is indicated by the failure of the tetrabenzyl ether of *p-tert*-butylcalix[4]arene to form a complex with imidazole. As discussed elsewhere,[4] **15a** forms a complex with Pirkle's reagent in which a doubling of the ^1H NMR resonances in the host is observed. Several other O-disubstituted calix[4]arenes in this series, possessing C_{2v} symmetry, show similar behavior.

In contrast to the single-cavity O-disubstituted calix[4]arenes, the double-spanned double-cavity calix[4]arenes display a much wider spectrum of complexation behavior, in some instances forming complexes both with acidic and basic guests, as discussed below.

Complexation of Phenols. The data in Table II show that although the diester double-spanned double-cavity calix[4]arene 6 forms only a weak complex (K_{assoc} = 7 M^{-1}) with phenol (pK_a = 10.0) it forms a fairly tight complex (K_{assoc} = 55 M^{-1}) with the more acidic 4-nitrophenol (pK_a = 7.2). 4-Bromophenol (pK_a = 9.3), 3-nitrophenol (pK_a = 8.4), and 4-cyanophenol (pK_a = 8.0) have intermediate K_{assoc} values, ranging from 21–40. That acidity alone is not the determining factor, however, is shown by the fact that 2-nitrophenol (pK_a = 7.2) and 2,4-dinitrophenol (pK_a = 4.1), both of which are more acidic than 4-nitrophenol, fail to form complexes, as also do 3,5-dimethyl-4-nitrophenol and 2-bromophenol. These data suggest that steric factors must play an important part.

The diether double-spanned double-cavity calix[4]arene 14 resembles the diester double-spanned double-cavity calix[4]arene 6 qualitatively but quantitatively is a somewhat less effective host molecule. The ester–ether double-spanned double-cavity calix[4]arene 14 falls between the diester and diether double-spanned double-

Table III. Relaxation Time (T_1) Values for 3-Nitrophenol and Carboxylic Acids in the Presence of 6 or *n*-Butylamine

guest molecule	T_1 (neat) s^{-1}	T_1 (with 6), s^{-1}	T_1 (with *n*-$BuNH_2$), s^{-1}
3-nitrophenol			
H-2	5.00	1.60	2.76
H-4	4.11	1.48	2.88
H-5	4.27	1.67	3.37
H-6	4.86	3.23	4.38
butanoic acid			
H_a	2.71	0.62	1.32
H_b	3.03	0.61	1.50
H_{CH_3}	2.78	0.80	1.80
trimethylacetic acid	2.50	1.81	1.45
nonanoic acid			
H_a	1.26	0.47	0.59
H_b	1.29	0.49	0.87
H_{CH_3}	2.42	1.23	2.00
undecanoic acid			
H_a	1.19	0.58	0.66
H_b	1.32	0.50	1.05
H_{CH_3}	2.57	1.87	2.26

Table IV. Comparison of T_1 and K_{assoc} Values for 4-Nitrophenol Complexes of Double-Cavity Calix[4]arenes 6, 14, and 7

	T_1, s^{-1}			
guest molecule	neat	with 6	with 14	with 7
4-nitrophenol, H-2	5.1 ± 0.3	0.6 ± 0.1	1.3 ● 0.1	2.2 ● 0.4
H-3	4.7 ● 0.4	0.7 ± 0.1	0.5 ± 0.1	1.4 ± 0.3
K_{assoc}, M^{-1}		55	48	40

cavity calixarenes in the strength of the complexes it forms with phenols.

The ^1H NMR spectra of the complexes of 6 with phenols show a shift in the *tert*-butyl resonances but no significant changes for the protons of the upper cavity of the calixarene. Protons associated with the lower cavity, however, undergo a downfield shift, suggesting that complexation occurs in this region of the molecule. This is substantiated by a NOESY experiment with 3-nitrophenol and 6 which reveals that H-4 of the phenol is proximate to one of the protons of the spanner. As in the case of the complex of **15a** with imidazole, the resonance arising from the OH groups of 6 moves downfield while that arising from the *tert*-butyl groups moves upfield, attributable to tighter hydrogen bonding that is facilitated by a conformational change of the calixarene.

To gain further insight into the nature of the complexes several relaxation time (T_1) measurements were made, the results of which are shown in Table III. With 3-nitrophenol the T_1 values for all four of its hydrogens are lowered upon addition of 6, but H-2, H-3, and H-5 are lowered to a considerably greater extent than H-6 (the hydrogen furthest from the NO_2 group). To a lesser extent a mixture of 3-nitrophenol and *n*-butylamine also shows lowered T_1 values, even though butylamine is a far stronger base than 6. Although this suggests that proton transfer per se is not involved in the complexation of phenols with the double spanned double-cavity calix[4]arenes, partial transfer of the phenolic proton of the guest is indicated by the hypsochromic shift from 325 to 333 nm that occurs in the UV spectrum upon the addition of 6 to 4-nitrophenol. The T_1 values parallel the complexation constants fairly closely, although the data in Table IV indicate that the tracking is not perfect. For example, the T_1 for the complex of the ester–ether double-cavity calix[4]arene 14 is lower than that of the diester compound 6, whereas the latter has the higher K_{assoc} value.

Complexation of Carboxylic Acids. Since 6 forms effective complexes with strongly acidic phenols it was anticipated that the same would hold true for carboxylic acids. α-Haloacetic acids do, indeed, show large chemical shifts of the α-H upon addition of 6. However, when tested in the manner described above, the K_{assoc} values proved to be less than 10, as shown in Table V. Stronger complexation is observed with butyric acid and with 2-bromopropionic acid, indicating that acidity per se is not the sole determining factor. As in the case of the phenols, an increase in the steric bulk in the guest curtails complexation with 6, as indicated by the zero value for trimethylacetic acid. In this context it is interesting to note the difference between 4-*n*-butylbenzoic acid (K_{assoc} = 13 M^{-1}) and 4-*tert*-butylbenzoic acid (K_{assoc} = 0). The importance of the carboxyl group for complexation is shown by the failure of *n*-butylbenzene to form a complex, and the effect of the size of the para substituent suggests that the entire molecule resides in a cavity of the host. The ester–ether double-spanned double-cavity calix[4]arene 14 behaves slightly differently, forming complexes with dibromoacetic acid, 2-bromopropionic acid, and 4-*n*-butylbenzoic acid but not with butyric acid itself.

Table V. Association Constants (K_{assoc}) of Double-Spanned Double-Cavity Calix[4]arenes with Carboxylic Acids

	K_{assoc}, M^{-1}		
guest molecule	diester 6	ester–ether 14	diether 7
iodoacetic acid	9		
dichloroacetic acid	6		
3-chloropropionic acid	5		
bromoacetic acid	5		
dibromoacetic acid	5	19	15
butyric acid	18	0	0
isobutyric acid	7		
2-bromopropionic acid	15	13	10
trimethylacetic acid	0		
4-*n*-butylbenzoic acid	13		12
4-*tert*-butylbenzoic acid	0		

Table VI. Association Constants (K_{assoc}) of Diester Double-Spanned Double-Cavity Calixarene 6 with Amines

aniline	0	isobutylamine	13
pyridine	33	*n*-butylamine	12
3-methylpyridine	6	isopropylamine	13
3-cyanopyridine	0	*sec*-butylamine	0
2,5-dimethylpyridine	0	*tert*-butylamine	0
2,4,6-trimethylpyridine	0	neopentylamine	0
imidazole	16	diethylamine	0
4-methoxybenzylamine	19	2-aminopropanol	20
(4-methoxyphenyl)ethylamine	16	3-aminopropanol	15
(4-methoxyphenyl)propylamine	19	2-hydroxypropylamine	11

The T_1 values for several carboxylic acids in the presence of 6 or butylamine are shown in Table II. In the case of butyric acid, all of the hydrogens of the alkyl group show reductions in T_1 that are considerably larger than those noted with butylamine, indicative of tight binding that is not solely the result of proton transfer. Trimethylacetic acid with 6 shows only a slight reduction in T_1, less than with butylamine and commensurate with its failure to form a complex with a measurable K_{assoc} value. With nonanoic and undecanoic acids the reduction in the T_1 values for hydrogens at the ω position is less than for those at the α and β positions, although they still exceed those induced by butylamine. This indicates that complexation restricts the motion even of the hydrocarbon termini of these acids, furnishing additional evidence that a considerable portion of the guest is in contact with the host.

Complexation with Aniline, Pyridines, and Imidazole. *p-tert*-Butylcalix[4]arene (1) forms complexes with alkylamines,[18] and it was anticipated that 4 might do

(18) Gutsche, C. D.; Iqbal, M.; Alam, I. *J. Am. Chem. Soc.* **1987**, *109*, 4314.

likewise as a consequence of its two phenolic functions. That this proves to be the case is shown by the data in Table VI. However, the fact that pyridine forms a complex with 6 but not with 1 suggests that the reasons for complexation are different in the two cases. For 1 it has been postulated that complex formation with amines is the result of complete proton transfer to produce a calixarene oxyanion and an amine cation which then associate with one another. But, pyridine is not a strong enough base to effect proton transfer with 1 and, as a consequence, does not form a complex with 1. Since 6 is an even weaker acid than 1, its ability to form a complex with pyridine must be due to factors other than complete proton transfer. The attraction between host and guest in this case is ascribed to hydrogen bonding (the phenolic groups of the host acting as the donor and the guest as the acceptor) and to $\pi-\pi$ interaction between the pyridine ring and an aromatic ring of the host (see later discussion). 3-Cyanopyridine, a weaker base than pyridine and, consequently, a weaker hydrogen bond donor, fails to form a complex with 6, and 2,5-dimethylpyridine and 2,4,6-trimethylpyridine also fail, although they are stronger bases than pyridine. Thus, basicity is seen to be necessary but not sufficient attribute, steric factors also playing a role. The failure of the diether double-cavity calix[4]arene 7 to form a complex with pyridine ($K_{assoc} = 0$) is ascribed to stronger intramolecular hydrogen bonding in 7 than in 6, the oxygen attached to the phenolic rings at positions 26 and 28 being more basic in the diether than in the diester. For 6 and 7 to act as intermolecular hydrogen bond donors in complex formation their intramolecular hydrogen bonds must be broken, intramolecular and intermolecular hydrogen bonding thus competing with one another. The ester–ether double-spanned double-cavity compound 14 might still be expected to form a complex with pyridine since it retains a phenolic OH that could possess the same hydrogen bonding capacity as those in 6. Its failure to do so ($K_{assoc} = 0$) may indicate that *two* phenolic OH groups are required for effective interaction of the double-cavity calix[4]arenes with amines. That other structural features are also required is indicated by the failure of unspanned compounds such as the 1,3-diester 2 and 1,3-diether 15a to form complexes with pyridine.

Imidazole as the guest presents still another picture, for 6, 14, and 7 all form complexes of essentially equal strength (K_{assoc} = 16–17). Since the unspanned diethers 3, 15a, 15b, and 15d and the diester 8 also form complexes with imidazole it appears that (a) while the lower cavity in the double-spanned double-cavity calixarenes probably plays a part in the complexation of pyridine, the spanners are not necessary for the complexation of imidazole and (b) complexation arises from the bifunctional character of imidazole and requires only a phenolic group in the host to act as hydrogen donor along with an OH, OR, or OCOR group to act as a hydrogen bond acceptor.

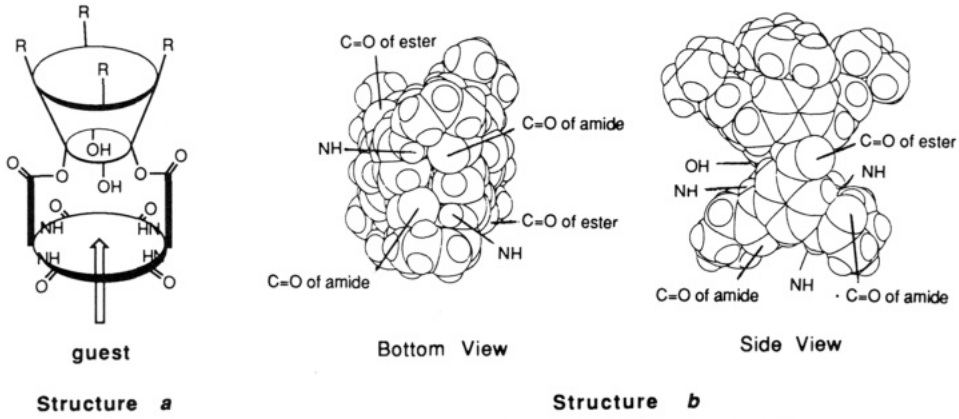
Complexation with Aliphatic Amines. Table VI shows the K_{assoc} values of 6 with a variety of aliphatic amines. Although earlier studies in this laboratory[19] seemed to show significant differences in the strength of the complexes of 6 with 4-methoxybenzylamine, (4-methoxyphenyl)ethylamine, and (4-methoxyphenyl)propylamine (based on the magnitude of the ^{1}H NMR shifts), a careful analysis using the methods described above shows that all three compounds have approximately the same K_{assoc} values. Butylamine, isobutylamine, and isopropylamine form moderately strong complexes, while *sec*-butylamine, *tert*-butylamine, neopentylamine, and diethylamine give zero values, showing again that the shape of the guest molecule plays a critical role. The presence of an OH group on a propylamine framework does not interfere with complex formation and, in fact, may slightly enhance it, as in the case of 2-aminopropanol. With optically active 2-aminopropanol the resonances arising from the OH and NH groups of 6 are doubled, suggesting that a pair of diastereosiomeric complexes are formed from chiral 6. This conclusion must be viewed with caution, however, for the achiral compound 15a behaves in a similar fashion.[4] It is surprising that neither the ester–ether double-spanned double-cavity calix[4]arene 14 nor the diether double-spanned double-cavity calix[4]arene 7 forms measurable complexes with the aliphatic amines. This is ascribed to the same factors that are discussed above for the failure of these compounds to form complexes with pyridine.

Discussion of Complexation Results with Double-Spanned Double-Cavity Calix[4]arenes

The patterns of the data in Tables II–VI indicate that hydrogen bonding plays a major role in determining the strength of the complexes with the double-spanned double-cavity calix[4]arenes. Thus, guests without protic moieties, such as benzene, toluene, *p*-nitroanisole, phenylacetylene, and *n*-butylbenzene all fail to form complexes. And, for complexation to be observed it is necessary to use solvents that do not compete with the host for hydrogen bond formation, no complexation occurring with the systems under study in DMSO-d_6 or in $CDCl_3$ to which a drop of MeOD has been added. In addition to hydrogen bonding, the space-filling characteristics of the guest play a part, steric bulk in certain cases curtailing complex formation in compounds that otherwise possess sufficient hydrogen bonding capacity. At the outset of this investigation it was assumed that the interaction between host and guest would involve the entry of the latter through the annulus of the lower ring of the former, as illustrated by structure a in Figure 3. However, the presence of two NH resonances in the ^{1}H NMR spectrum and two NCO resonances in the ^{13}C NMR spectrum of 6 in $CDCl_3$ solution belies the symmetry that would be required to give the lower cavity a large enough annulus (without conformational reorganization) to allow this mode of complexation to occur. In the absence of an X-ray crystallographic structure for the complex 6 with 4-nitrophenol,[14] recourse was made to molecular modeling[20] to gain insight into the structures of 6 and its complexes. The uncertainty in this approach, of course, is whether a particular structure represents a global minimum or simply a local minimum. Of the numerous conformations of 6 that were tested, the one of lowest energy has all four of the amide groups in the anti configuration with two of them oriented with the NH hydrogens upward and two downward to give structure b in Figure 3 (in accord with two NH resonances in the ^{1}H NMR spectrum and two NCO resonances in the ^{13}C NMR spectrum). The presence of three intramolecular hydrogen bonds in 6 is indicated in the energy-minimized structure, two of them between the phenolic OH's and the oxygens of the adjacent ester groups and a third between an NH and a phenolic oxygen. The distance between another of the NH groups and a proximate phenolic loxygen is just slightly greater than the arbitrarily chosen hydrogen bond cut-off distance, leading to an almost symmetrical structure. As shown in Figure

(19) Gutsche, C. D.; Iqbal, M.; Nam, K. C.; See, K-A.; Alam, I. *Pure Appl. Chem.* **1988**, *60*, 483.

(20) Silicon Graphics IRIS-4D/210VGX using the QUANTA and CHARMm programs.



Structure a Structure b

Figure 3. Schematic and molecular modeling representations of diester double-cavity calix[4]arene **6**.

3, the result is a closing of the lower annulus, leaving the cavity or cleft at the side of the lower rim as the most likely site for complexation.

Although quantitative comparisons of various host–guest combinations using the CHARMm program do not agree with experimental values in all cases,[21-24] qualitative comparisons between pairs of complexes using the graphic displays shown in Figure 4 are informative. In all three cases the complex with a measurable K_{assoc} (left-hand structures) has the aromatic ring of its guest closer to the aromatic ring of the host than the complex that gives a K_{assoc} of 0 (right-hand structures). For example, the aromatic ring of 4-bromophenol is almost parallel with an aromatic ring of the host, the smallest and largest distances of separation being 3.490 and 4.764 Å, respectively, whereas that of 2-bromophenol is canted outward, with the comparable distances being 3.756 and 5.610 Å. The importance of $\pi-\pi$ interactions suggested by these displays may ex-

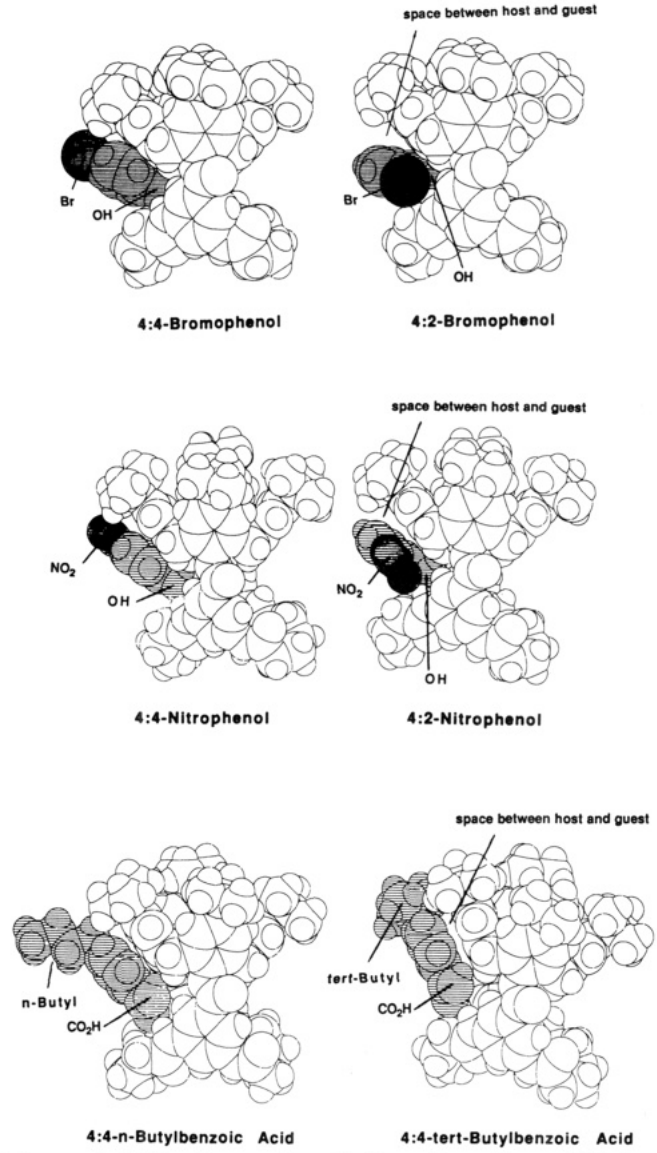


Figure 4. Molecular graphics displays of complexes of diester double-cavity calixarene **6** with 2- and 4-bromophenol, 2- and 4-nitrophenol, 4-*n*-butylbenzoic acid, and 4-*tert*-butylbenzoic acid. The complexes in the left-hand column have measurable K_{assoc} values (>5 M^{-1}); those in the right-hand column do not.

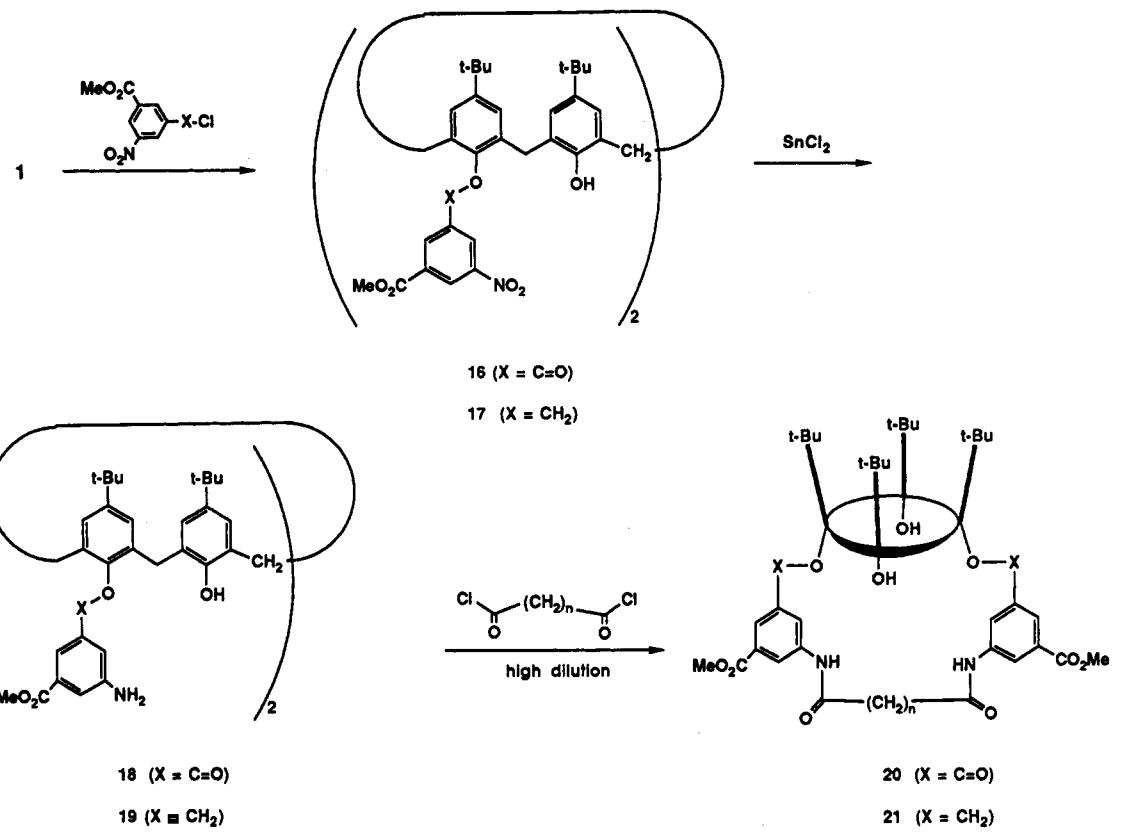
(21) The differences in the energies of the complexes (see supplementary material for table of values) are instructive. For example, the difference of 1.63 kcal/mol for the complexes of **4** with *n*-butylamine and *tert*-butylamine, corrected for the 0.78 kcal/mol energy difference between the guest molecules, gives a 2.40 kcal/mol advantage to the **4**–*n*-butylamine complex, in qualitative agreement with the data in Table VI. The difference of 2.06 kcal/mol for the complexes of **4** with 4-bromo- and 2-bromophenol, corrected for the 1.57 kcal/mol energy difference between the guest molecules, gives a 3.63 kcal/mol advantage to the **4**:4-bromophenol complex, in qualitative agreement with the data in Table II. Particularly striking is the difference of 8.48 kcal/mol for the complexes of **4** with 4-*n*-butyl and 4-*tert*-butylbenzoic acid which, corrected for the 2.28 kcal/mol differences in energy between the guest molecules, gives an advantage of 6.20 kcal/mol to the **4**:4-*n*-butylbenzoic acid complex, in qualitative agreement with the data in Table V. That such calculations must be viewed cautiously, however, is seen in the difference of 4.91 kcal/mol for the complexes of **4** with 4-nitro- and 2-nitrophenol, which when corrected for the 6.15 kcal/mol difference between the guest molecules gives an advantage of 1.50 kcal/mol to the **4**:2-nitrophenol complex, in disagreement with the data in Table II. In comparing the individual energy contributions to the various complexes of **4** it is noted that most, though not all, of the differences between the pairs chosen for comparison appear in the Lennard–Jones and electrostatic terms, presumably reflecting differences in nonbonded interactions and hydrogen bonding, respectively. A particularly large difference occurs in the electrostatic terms of the nitrophenols and their complexes with **4**; the **4**:4-nitrophenol complex is 6.40 kcal/mol lower in electrostatic energy than the **4**:2-nitrophenol complex. However, this advantage is offset to a considerable extent by the 4.45 kcal/mol difference between the free guests 4-nitro- and 2-nitrophenol. The molecular modeling display indicates that the intramolecular hydrogen bond that exists in 2-nitrophenol changes upon complexation to intermolecular hydrogen bonds between (a) the nitro group and an amide NH of the host, (b) the OH of the guest (donor) and an OH of the host (acceptor), and (c) the OH and ester C=O groups of the host. It also shows the guest to be slightly twisted from the completely planar structure that it possesses in its uncomplexed state. The failure of the program to produce energy differences in agreement with experiment in this case may be the result of difficulties in its handling of the nitro group.[22-24]

(22) The 6.415 kcal/mol difference in energy between 4-nitro- and 2-nitrophenol generated by the CHARMm program falls midway between the 0.9 kcal/mol and 12.2 kcal/mole values calculated by the PCMODEL and AMPAC programs, respectively.[23] The experimental value[24] for the difference is 2.39 kcal/mol which, if used with the CHARMm-generated values for the **4**:4-nitrophenol and **4**:2-nitrophenol complexes, gives a corrected difference of 2.52 kcal/mol in favor of the **4**:4-nitrophenol complex, in qualitative agreement with the data in Table II.

(23) We are indebted to Professor William B. Smith for the calculations using the PCMODEL and AMPAC programs.

(24) Finch, A.; Gardner, P. J.; Wu, D. *Thermochim. Acta.* **1983**, *66*, 333.

Scheme IV



plain why 6 forms a complex with pyridine but not with aniline. Since aniline should be as effective a hydrogen bonding guest as pyridine its failure to form a measurable complex can be ascribed to weaker π–π interaction arising from the enhanced electron density of the aromatic ring produced by electron donation from the amino group. In contrast, the pyridine ring is electron poor as the result of electron attraction by the nitrogen. The influence of similar donor–acceptor interactions has been nicely illustrated by Diederich[25] with a series of naphthalene guest that form complexes with a host containing electron-rich aromatic rings.

The reasons why the diester double-spanned double-cavity compound 6 forms generally stronger complexes than the ester–ether or diether double-spanned double-cavity compounds 14 and 7 are not immediately evident from molecular modeling studies. One possibility already mentioned is that the intramolecular hydrogen bond between the phenolic groups and adjacent oxygen moieties in the host is stronger for ethers than for esters, thus diminishing the ease with which intermolecular hydrogen bond formation occurs between 14 or 7 and guest molecules. Another factor that is not taken into account in the calculations cited above is the role of the solvent. Chloroform, the solvent of choice, is known to form a solid-state complex with *p-tert*-butylcalix[4]arene[26] in which the $CHCl_3$ is inside the calix (corresponding to the upper cavity in 6, 14, and 7). In addition to its probable presence at this site, $CHCl_3$ must also be associated with other portions of the hosts and must be displaced by the guest. The CHARMm program does, in fact, show a 3.2 kcal/mol lower energy for a 7:$CHCl_3$ complex than for a 6:$CHCl_3$ complex; however, a 14:$CHCl_3$ complex fails to fall in-between.

Synthesis and Complexation of Single-Spanned Double-Cavity Calix[4]arenes

Although no single datum proves that the site of complexation of the double-spanned double-cavity calixarenes is at the side of the molecule, the weight of the evidence discussed above clearly supports such a conclusion. This being the case, it can be postulated that the presence of two spanner groups in the lower cavity perhaps is unnecessary and might even be a deterrent to strong complex formation. Single-spanned double-cavity calix[4]arenes would have deeper side-of-the-molecule clefts than their double-spanned double-cavity counterparts and, as a consequence, might form tighter complexes. To conclude this paper preliminary data in support of this premise are presented, along with blueprints for future work.

Reaction of 3-nitro-5-carbomethoxybenzoyl chloride or 3-nitro-5-carbomethoxybenzyl chloride with *p-tert*-butylcalix[4]arene (1) under appropriate conditions yields the 1,3-diester 16 and the 1,3-diether 17, respectively, which undergo reduction with $SnCl_2$ to the corresponding diamino compounds 18 and 19. Treatment of 18 or 19 with diacyl chlorides introduces a spanner between the amino groups of the pendant arylmethyl moieties to give the single-spanned double-cavity calix[4]arenes 20 and 21. Each of the members of the 1,3-diether series (21, n = 1–8) forms a measurable complex with 4-nitrophenol, although the K_{assoc} values are not significantly larger than those observed with the double-spanned double-cavity compounds. An interesting variation in values is observed among these compounds; those hosts having even values of n form tighter complexes than those with odd values, and the zigzag plot of these K_{assoc} values shows an upward slope as n increases. Molecular graphics displays of the complexes of 21 (n = 1–8) with 4-nitrophenol indicate that

(25) Ferguson, S. B.; Diederich, F. *Angew. Chem., Intl. Ed. Engl.* **1986**, *25*, 1127.
(26) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005.

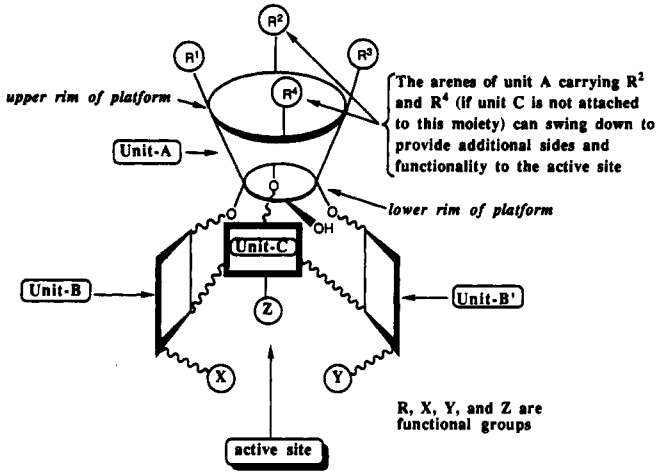


Figure 5. Schematic representation of functionalized single-spanned double-cavity calix[4]arene as putative molecular receptors for catalysis.

the ability of the lower cavity of **21** to envelop the guest increases as n increases, in accord with the upward slope of the K_{assoc} plot, but they provide no obvious explanation for its zigzag character. More interesting as guests are the polyhydroxybenzenes, resorcinol forming a strong complex with **21** (n = 7) with $K_{assoc} > 10^3$ M^{-1} but catechol, hydroquinone, and 2-resorcinol forming complexes with very much lower K_{assoc} values.

A more extensive presentation of the complexation characteristics of **20** and **21** will be reported at a later date. The preliminary information on the single-spanned double-cavity calix[4]arenes is included in the present paper as a protocol for continuing work. Calix[4]arenes, for which excellent procedures are now in hand for selectively functionalizing both the upper and lower rims, provide ideal frameworks (unit A in Figure 5) for the attachment of additional cavities, as the present work has demonstrated. By taking advantage of the rich chemistry of aromatic systems a wide variety of cavity sides (units B in Figure 5) can be introduced at the lower rim of the calixarene. A spanner moiety (unit C in Figure 5), for which a wide variety of structural possibilities exists, joints to the B units and establishes the back face of the active site region and, if properly constituted, can be joined to the A unit as well. The conformational flexibility of the calix[4]arene system permits the phenolic residues to be in an "up" or "down" orientation, thus adding to the functional group diversity at the active site.

Experimental Section[27,28]

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(3,5-diaminobenzoyl)oxy]-26,28-dihydroxycalix[4]arene (4). A solution of 3.2 g (2.9 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(3,5-dinitrobenzoyl)oxy]-26,28-dihydroxycalix[4]arene (**2**)[4] and 12.0 g (53 mmol) of $SnCl_2 \cdot 2H_2O$ in 150 mL of EtOH was refluxed 4 h. The solution was cooled, poured onto ice, neutralized (pH 7–8) by the addition of NaOH, and extracted two times with CH_2Cl_2. The organic phase was separated, washed with brine, dried (Na_2SO_4), and evaporated to leave a brownish solid. This was triturated with 75 mL of MeOH, and the insoluble material was crystallized from *i*-PrOH to yield 2.0 g (75%) of **4** as light brown, flaky crystals: mp > 350 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.13 (d, 4, J = 2.1 Hz, NH_2ArH), 7.09 (s, 4, ArH), 6.78 (s, 4, ArH), 6.23 (t, 2, J = 2.1 Hz, NH_2ArH), 5.38 (s, 2, OH), 4.00 (d, 4, J = 13.8 Hz, $ArCH_2Ar$), 3.75 (br s, 8, NH_2), 3.38 (d, 4, J = 13.8 Hz, $ArCH_2Ar$), 1.29 (s, 18, $C(CH_3)_3$), 0.92 (s, 18, $C(CH_3)_3$). Anal. Calcd for $C_{58}H_{68}N_4O_6$: C, 75.95; H, 7.47; N, 6.10. Found: C, 75.51; H, 7.44; N, 6.11.

Diester Double-Spanned Double-Cavity Calix[4]arene 6 from 5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(3,5-diaminobenzoyl)oxy]-26,28-dihydroxycalix[4]arene (4). A solution of 0.23 mL (1.7 mmol) of adipoyl chloride in 250 mL of CH_2Cl_2 was placed in an addition funnel. A mixture of 0.20 g (0.22 mmol) of **3** and 0.53 mL (3.8 mmol) of triethylamine in 500 mL of CH_2Cl_2 was placed in a second addition funnel. Both funnels were fitted to an oven-dried, N_2-flushed 3-L three-neck flask containing 1 L of CH_2Cl_2. The contents of the two addition funnels were simultaneously added dropwise over a period of 60 h, and the reaction mixture was then quenched with 800 mL of 5% NaOH. The product was worked up in conventional fashion to give an oil which upon the addition of 10 mL of MeOH and 3 mL of Me_2CO yielded 0.11 g (45%) of **6** as a white powder. An analytical sample was obtained by crystallization from $CHCl_3$–MeOH and obtained as colorless rhombs: mp >390 °C dec; IR (KBr), 3530 (OH stretch), 1750 (ester C=O stretch), 1680 (amide C=O stretch) cm^{-1}; MS (FAB) m/e 1137 (M^+); ^{1}H NMR ($CDCl_3$) δ 10.50 (s, 2, NH), 8.83 (s, 2, NCOArH), 8.75 (s, 2, NCOArH), 8.21 (s, 2, NH), 7.29 (s, 2, NCOArH), 7.24 (s, 2, ArH), 7.17 (s, 2, ArH), 6.94 (s, 2, ArH), 6.87 (s, 2, ArH), 6.23 (s, 2, OH), 4.21 (d, 2, $ArCH_2Ar$), 3.98 (d, 2, $ArCH_2Ar$), 3.59 (d, 2, $ArCH_2Ar$), 3.44 (d, 2, $ArCH_2Ar$), 2.7–1.5 (m, 16, $(CH_2)_4$), 1.36 (s, 18, $(CH_3)_3$), 0.96 (s, 18, $(CH_3)_3$); ^{1}H NMR (DMSO-d_6) δ 9.61 (br s, 4, NH), 8.32 (s, ca. $^1/_2$, $CHCl_3$), 8.30 (br s, 2, CONHArH), 7.84 (br s, 4, COArH), 7.28 (s, 4, ArH), 7.21 (s, 4, ArH), 6.77 (br s, 2, OH), 4.04 (d, 5, $ArCH_2Ar$), 3.56 (d, 4, $ArCH_2Ar$), 2.41 (br s, 4, adipoyl CH_2), 2.20 (br s, 4, adipoyl CH_2), 2.01 (br s, 4, adipoyl CH_2), 1.65 (br s, 4, adipoyl CH_2), 1.23 (s, 18, $C(CH_3)_3$, 1.14 (s, 18, $C(CH_3)_3$; ^{13}C NMR ($CDCl_3$) δ [174.5, 173.1] (NC=O), 165.6 (OC=O), [149.2, 148.9, 144.2, 141.1, 140.0, 132.4, 131.6, 130.7, 128.7, 126.4] (Ar), [125.8, 125.7, 125.6, 125.5, 116.9, 116.2, 116.1, 113.4] (ArH), 125.4 (CO_2?), [38.2, 34.6] ($NCOCH_2$), 34.1 ($ArCH_2Ar$), [31.9, 29.7] ($C(CH_3)_3$), [31.6, 30.8] ($C(CH_3)_3$), [24.1, 24.0, 22.3] ($NCOCH_2CH_2$). Anal. Calcd for $C_{70}H_{80}N_4O_{10} \cdot H_2O \cdot CO_2$: C, 71.10; H, 6.89; N, 4.67. Found: C, 71.16; H, 7.01, N, 4.64.

5,11,17,23-Tetra-*tert*-butyl-25-[(3,5-dinitrobenzyl)oxy]-26,27,28-trihydroxycalix[4]arene (9). A 2.60-g (2.5 mmol) sample of the 25,26-diester **8**,[4] 0.57 g (2.6 mmol) of 3,5-dinitrobenzyl chloride, 0.3 g (2.0 mmol) of NaI, and 0.37 g (2.8 mmol) of anhydrous K_2CO_3 were mixed in 60 mL of dry CH_3CN. The orange suspension was stirred at rt for 16 h under N_2 and worked up to give 2.9 g (95%) of a mixture of ether–diesters. A 1.8-g (1.44 mmol) sample of this mixture was refluxed 90 min with 0.36 g (5.76 mmol) of KOH in 50 mL of EtOH, cooled, and filtered and the filtrate treated with 15 mL of 2 N HCl. The precipitate was removed by filtration to give 0.96 g (80%) of solid which was recrystallized from $CHCl_3$–MeOH to afford **9** as small feathery yellow needles: mp 153–155 °C; ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1, OH), 9.67 (s, 2, OH), 9.27 (br s, 1, O_2NArH), 9.23 (br s, 2, O_2NArH), 7.15 (s, 2, ArH), 7.07 (d, 2, J = 2.4 Hz, ArH), 7.04 (s, 2, ArH), 7.00 (d, 2, J = 2.4 Hz, ArH), 5.29 (s, 2, $ArCH_2O$), 4.26 (d, 2, J = 13.8 Hz, $ArCH_2Ar$), 4.21 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 3.50 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 3.44 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 1.20 (s, 36, $C(CH_3)_3$). Anal. Calcd for $C_{51}H_{60}N_2O_8$: C, 73.89; H, 7.29; N, 3.38. Found: C, 73.88; H, 7.09; N, 3.42.

5,11,17,23-Tetra-*tert*-butyl-25-[(3,5-dinitrobenzyl)oxy]-27-[(3,5-dinitrobenzoyl)oxy]-26,28-dihydroxycalix[4]arene (10). A solution of 1.27 g (1.5 mmol) of the monoester **11**[4] in 100 mL of CH_3CN was treated with 0.11 g (0.8 mmol) of K_2CO_3, 0.36 g (1.6 mmol) of 3,5-dinitrobenzyl chloride, and 0.15 g (1.0 mmol) of NaI under N_2. The orange suspension was stirred overnight

(27) Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. THF was always freshly distilled from Na–benzophenone. The melting points of all compounds melting above 250 °C were taken in sealed and evacuated capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) with use of a 500 °C thermometer calibrated against a thermocouple. HPLC analyses employed an Analtech reversed-phase C-18 column. ^{1}H NMR spectra were recorded at 300 MHz. TLC analyses were carried out on Analtech silica gel plates (absorbant thickness 250 μm) containing a fluorescent indicator. Flash chromatography[28] was carried out with J. T. Baker silica gel No. JT7042-2 (40-μm particles) on columns 50 mm in diameter filled to a height of ca. 7 in. Elution rates were 2 in./min; fractions of 50 mL were collected. Analytical samples were dried at least 36 h at 100–140 °C and 1–2 mm of pressure. Agreement between the calculated and found values was obtained in a number of instances by the addition of H_2O or H_2O and CO_2 to the molecular formula (see ref 11).

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

at rt and worked up to yield a yellow solid showing three spots on TLC. Flash chromatography using 3:2 CH_2Cl_2/petroleum ether (bp 36–60 °C) as eluant yielded a 1.0 g (66%) of **10** (R_f 0.49) as a yellow powder. An analytical sample was obtained as yellow feathery crystals by recrystallization from $CHCl_3$–MeOH: mp 184–186 °C; ^1H NMR ($CDCl_3$) δ 9.63 (d, 2, J = 2.1 Hz, O_2NArH), 9.24 (t, 1, J = 2.1 Hz, O_2NArH), 8.98 (t, 1, J = 2.1 Hz, O_2NArH), 8.88 (d, 2, J = 2.1 Hz, O_2NArH), 7.12 (s, 4, ArH), 6.89 (s, 2, ArH), 6.84 (s, 2, ArH), 5.97 (s, 2, OH), 5.41 (s, 2, $ArCH_2O$), 4.02 (d, 2, J = 13.8 Hz, $ArCH_2Ar$), 3.97 (d, 2, J = 13.8 Hz, $ArCH_2Ar$), 3.42 (d, 2, J = 13.8 Hz, $ArCH_2Ar$), 3.40 (d, 2, J = 13.8 Hz, $ArCH_2Ar$), 1.30 (s, 18, $C(CH_3)_3$), 1.00 (s, 18, $C(CH_3)_3$), 0.94 (s, 18, $C(CH_3)_3$). Anal. Calcd for $C_{58}H_{62}N_4O_{13}$: C, 68.09; 6.11; N, 5.48. Found: C, 67.81; H, 5.94; N, 5.47.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(3,5-dinitrobenzyl)oxy]-26-[(3,5-dinitrobenzoyl)oxy]-28-hydroxycalix[4]arene (12). A solution of 0.84 g (1.0 mmol) of monoester **11**[4] in 80 mL of dry Me_2CO was treated with 0.63 g (3.0 mmol) of 3,5-dinitrobenzyl chloride, 0.3 g (20 mmol) of NaI, and 0.6 g (4.2 mmol) of anhydrous K_2CO_3. The dark blue suspension was stirred at room temperature for 20 h and worked up to produce a yellowish powder that was crystallized from $CHCl_3$–MeOH to give 0.6 g (50%) of **12** as tiny yellow crystals: mp 276–279 °C; ^1H NMR ($CDCl_3$) δ 9.87 (d, 2, J = 2.1 Hz, $O_2NArHCH_2O$), 9.11 (t, 1, J = 2.1 Hz, O_2NArH), 8.91 (d, 2, J = 2.1 Hz, O_2NArH), 8.05 (d, 2, J = 2.1 Hz, $O_2NArHCH_2O$), 7.28 (s, 2, ArH), 7.09 (s, 2, ArH), 6.68 (d, 2, J = 2.4 Hz, ArH), 6.62 (d, 2, J = 2.0 Hz, ArH), 5.54 (s, 1, OH), 4.82 (d, 2, J = 6.0 Hz, $ArCH_2O$), 4.73 (d, 2, J = 12.0 Hz, $ArCH_2O$), 4.17 (d, 2, J = 13.5 Hz, $ArCH_2Ar$), 3.83 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 3.21 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 3.16 (d, 2, J = 13.5 Hz, $ArCH_2Ar$), 1.38 (s, 9, $C(CH_3)_3$), 1.33 (s, 9, $C(CH_3)_3$), 0.85 (s, 18, $C(CH_3)_3$). Anal. Calcd for $C_{65}H_{66}N_6O_{17}$: C, 64.88; H, 5.53; N, 6.98. Found: C, 64.80; H, 5.38; N, 6.73.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(3,5-dinitrobenzyl)oxy]-26,28-dihydroxycalix[4]arene (3). A 2.0-g (3.0 mmol) sample of *p*-*tert*-butylcalix[4]arene (**1**),[29] 1.27 g (6.0 mmol) of 3,5-dinitrobenzyl chloride, 0.9 g (6.0 mmol) of NaI, and 8.0 g of anhydrous K_2CO_3 were suspended in 150 mL of anhydrous Me_2CO, stirred at rt under N_2 for 6 h, and worked up to give 3.0 g of crude material. Purification by flash chromatography using 10:3 CH_2Cl_2/hexane as eluant yielded 2.0 g (60%) of **3** (R_f 0.67) as a yellow powder: mp 224–226 °C; ^1H NMR ($CDCl_3$) δ 9.10 (d, 4, J = 2.1 Hz, O_2NArH), 8.88 (t, 2, J = 2.1 Hz, O_2NArH), 7.45 (s, 2, OH), 7.10 (s, 4, ArH), 6.89 (s, 4, ArH), 5.33 (s, 4, $ArCH_2O$), 4.20 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.38 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 1.29 (s, 18, $C(CH_3)_3$), 0.99 (s, 18, $C(CH_3)_3$). Anal. Calcd for $C_{58}H_{64}N_4O_{12}$: C, 69.03; H, 6.39; N, 5.35. Found: C, 69.10; H, 6.25; N, 5.33.

5,11,17,23-Tetra-*tert*-butyl-25-[(3,5-diaminobenzyl)oxy]-27-[(3,5-diaminobenzoyl)oxy]-26,28-dihydroxycalix[4]arene (13). A 0.46-g sample of **10** (see above) was reduced with $SnCl_2{\cdot}2H_2O$ as described above for the preparation of **4** to yield 0.46 g (88%) of **13** as a brownish solid: mp >280 °C dec; ^1H NMR ($CDCl_3$) δ 7.15 (d, 2, J = 2.1 Hz, H_2NArH), 7.09 (s, 4, ArH), 6.81 (s, 2, ArH), 6.65 (s, 2, ArH), 6.38 (d, 2, J = 2.1 Hz, H_2NArH), 6.27 (s, 2, OH), 6.21 (t, 2, J = 2.1 Hz, H_2NArH), 5.95 (t, 2, J = 2.1 Hz, H_2NArH), 4.87 (s, 2, $ArCH_2O$), 4.22 (d, 2, J = 13.4 Hz, $ArCH_2Ar$), 4.07 (d, 2, J = 13.4 Hz, $ArCH_2Ar$), 4.07 (d, 2, J = 13.4 Hz, $ArCH_2Ar$), 3.68 (br s, 8, NH_2), 3.40 (d, 2, J = 13.4 Hz, $ArCH_2Ar$), 3.29 (d, 2, J = 13.4 Hz, $ArCH_2Ar$), 1.31 (s, 18, $C(CH_3)_3$), 0.96 (s, 9, $C(CH_3)_3$), 0.82 (s, 9, $C(CH_3)_3$). Anal. Calcd for $C_{58}H_{70}N_4O_5{\cdot}^1/_2H_2O{\cdot}^1/_2CO_2$: C, 75.21; H, 7.66; N, 6.00. Found: C, 75.48; H, 7.57; N, 6.17.

Ester–Ether Double-Spanned Double-Cavity Calix[4]arene 14. In the fashion described above for the preparation of **6**, a 0.25-g sample of **13** was converted to 0.10 g (32%) of **14** as a white powder. An analytical sample was prepared by crystallization from $CHCl_3$–MeOH and obtained as colorless rhombs: mp >290 °C dec; MS (FAB) m/e 1123 (M^+); ^1H NMR (DMSO-d_6) δ 9.57 (s, 2, OCNArH), 9.53 (s, 2, OCNArH), 8.23 (s, 1, OCNArH), 8.02 (s, 1, OCNArH), 7.88 (s, 2, NH), 7.45 (s, 2, NH), 7.33 (s, 2, OH), 7.29 (s, 2, ArH), 7.24 (s, 2, ArH), 7.23 (s, 2, ArH), 7.12 (s, 2, ArH), 4.71 (s, 2, $ArCH_2O$), 4.19 (d, 2, J = 13.5 Hz, $ArCH_2Ar$), 4.14 (d, 2, J = 15.3 Hz, $ArCH_2Ar$), 3.72 (d, 2, J = 12.6 Hz, $ArCH_2Ar$), 3.40 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 2.4-1.6 (m, 14, $(CH_2)_4$), 1.22 (s, 18, $C(CH_3)_3$), 1.18 (s, 9, $C(CH_3)_3$, 1.13 (s, 9, $C(CH_3)_3$, 1.00 (br s, CCH_2); ^{13}C NMR (C_5D_5N) δ 179.4 (NC=O), 167.4 (OC=O), [150.8, 150.6. 149.3, 149.2, 149.15, 148.8, 148.2, 147.3, 143.2, 142.2, 141.2, 141.0, 136.2, 135.0, 134.92, 134.88, 134.83, 133.3, 129.2](Ar), [126.8, 125.9, 125.4, 124.2, 124.1, 122.9, 122.8, 122.7, 122.6, 114.7, 114.64, 114.58, 114.52] (ArH), [81.2, 79.8] ($ArOCH_2Ar$?), [34.2, 33.9, 33.7, 32.5, 30.5, 30.0] ($ArCH_2Ar$, $C(CH_3)_3$ and $NCOCH_2CH_2$), [32.1, 30.8, 30.6] ($C(CH_3)_3$). Anal. Calcd for $C_{70}H_{82}N_4O_9{\cdot}H_2O{\cdot}CO_2$: C, 71.94; H, 7.14 N, 4.73. Found: C, 72.18; H, 7.07; N, 4.62.

5,11,17,23-Tetra-*tert*-butyl-25,26,27-tris[(3,5-dinitrobenzyl)oxy]-28-hydroxycalix[4]arene was isolated in 17% yield by flash chromatography of a mixture prepared as described above and obtained as a pale yellow powder: mp >250 °C; ^1H NMR ($CDCl_3$) δ 8.96 (d, 2, J = 2.1 Hz, O_2NArH), 8.95 (t, 1, J = 2.1 Hz, O_2NArH), 8.80 (t, 2, J = 2.1 Hz, O_2NArH), 8.46 (d, 4, J = 2.1 Hz, O_2NArH), 7.16 (s, 2, ArH), 7.07 (s, 2, ArH), 6.57 (d, 2, J = 2.1 Hz, ArH), 6.53 (d, 2, J = 2.1 Hz, ArH), 5.18 (s, 2, $ArCH_2O$), 5.02 (d, 2, J = 12.6 Hz, $ArCH_2O$), 5.01 (s, 1, OH), 4.93 (d, 2, J = 12.6 Hz, $ArCH_2O$), 4.13 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 4.00 (d, 2, J = 12.6 Hz, $ArCH_2Ar$), 3.21 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 3.00 (d, 2, J = 12.6 Hz, $ArCH_2Ar$), 1.45 (s, 9, $C(CH_3)_3$), 1.31 (s, 9, $C(CH_3)_3$), 0.82 (s, 18, $C(CH_3)_3$). Anal. Calcd for $C_{65}H_{68}N_6O_{16}$: C, 65.65; H, 5.76; N, 7.07. Found: C, 65.55; H, 5.76; N, 6.94.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(3,5-diaminobenzyl)oxy]-26,28-dihydroxycalix[4]arene (5). A 1.5-g sample of **3** (see above) was reduced with $SnCl_2{\cdot}2H_2O$ as described above for the preparation of **4** to yield 0.96 g (72%) of **5** as pale brown, feathery crystals after crystallization from $CHCl_3$–*i*-PrOH: mp >270 °C dec; ^1H NMR ($CDCl_3$) δ 7.30 (s, 2, OH), 7.05 (s, 4, ArH), 6.76 (s, 4, ArH), 6.45 (s, 4, H_2NArH), 5.97 (s, 2, H_2NArH), 4.85 (s, 4, $ArCH_2O$), 4.32 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.28 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.1–2.2 (br s, 8, NH_2), 1.29 (s, 18, $C(CH_3)_3$), 0.93 (s, 18, $C(CH_3)_3$). Anal. Calcd for $C_{58}H_{72}N_4O_4{\cdot}^1/_2H_2O{\cdot}^1/_2CO_2$: C, 76.35; H, 8.00 N, 6.09. Found: C, 76.36; H, 8.16; N, 6.18.

Diether Double-Spanned Double-Cavity Calix[4]arene 7. In the fashion described above for the preparation of **6**, a sample of **5** was converted in 39% yield to **7** which was obtained as a white powder by column chromatography using 25:1 $CHCl_3$/MeOH as eluant: mp >260 °C; MS (FAB) m/e 1109 (M^+); ^1H NMR (DMSO-d_6) δ 9.53 (s, 4, NCOArH), 8.10 (s, 2, OH), 7.98 (s, 2, NCOArH), 7.42 (s, 4, NCOArH), 7.17 (s, 4, ArH), 7.14 (s, 4, ArH), 4.48 (s, 4, $ArCH_2O$), 4.30 (d, 4, J = 12.7 Hz, $ArCH_2Ar$), 3.49 (d, 4, J = 12.7 Hz, $ArCH_2Ar$), 2.37 (br s, 8, $(CH_2)_4$), 1.80 (br s, 8, $(CH_2)_4$), 1.20 (s, 18, $(CH_3)_3$), 1.13 (s, 18, $C(CH_3)_3$). Anal. Calcd for $C_{70}H_{84}N_4O_8{\cdot}2\ H_2O{\cdot}CO_2$: C, 71.69; H, 7.46; N, 4.71. Found: C, 71.98; H, 7.38; N, 4.75.

5,17-Di-*tert*-butyl-25,27-dimethoxy-26,28-dihydroxycalix[4]arene (15b). To a suspension of 3.0 g (22.5 mmol) of anhydrous $AlCl_3$ in 100 mL of CH_2Cl_2 cooled to 0 °C was added 1.0 g (1.5 mmol) of **15a**. The mixture was stirred 45 min at 0 °C and treated with 100 mL of cold H_2O with vigorous stirring. The organic layer was separated, dried over Na_2SO_4, the solvent removed under vacuum, and the residue triturated with MeOH to yield 1.0 g of a white powder. Recrystallization from Me_2CO gave 0.6 g (55%) of **15b** as fluffy white crystals: mp >282 °C; ^1H NMR ($CDCl_3$) δ 7.445 (s, 2, OH), 7.07 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.95 (s, 6, OCH_3), 3.37 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 0.97 (s, 18, $C(CH_3)_3$). Anal. Calcd for $C_{38}H_{44}O_4{\cdot}H_2O$: C, 78.32; H, 7.96. Found: C, 78.54; H, 7.48.

25,27-Dimethoxy-26,28-dihydroxycalix[4]arene (15d). A solution 4.0 g (10.4 mmol) of *p*-H-calix[4]arene in 200 mL of Me_2CO was mixed with 4.9 g (35.5 mmol) of K_2CO_3 and 5.7 g (31.2 mmol) of methyl tosylate, refluxed 24 h, and worked up to give 3.5 g of a white powder which was recrystallized from $CHCl_3$–MeOH to yield 3.2 g (71%) of **15d** as small colorless crystals: mp 318–320 °C; ^1H NMR ($CDCl_3$) δ 7.76 (s, 2, OH), 7.08 (d, 4, J = 7.5 Hz, ArH), 6.88 (d, 4, J = 7.5 Hz, ArH), 6.72 (t, 2, J = 7.5 Hz, ArH), 6.69 (t, 2, J = 7.5 Hz, ArH), 4.31 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.98 (s, 6, OCH_3), 3.41 (d, 4, J = 13.2 Hz, $ArCH_2Ar$). Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.59; H, 5.98.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(3-carbomethoxy-5-nitrobenzoyl)oxy]-26,28-dihydroxycalix[4]arene (16). A

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stirred slurry of 0.75 mL (5 mmol) of dichlorophenylphosphate and 0.60 mL (7.8 mmol) of DMF at 0 °C was mixed with 0.85 g (4 mmol) of 3-carbomethoxy-5-nitrobenzoic acid and 40 mL of CH_2Cl_2, and 1.00 g (1.5 mmol) of **1** was added followed by 1.20 mL (15 mmol) of pyridine. The reaction mixture was stirred at rt for 12 h, treated with 1 N HCl, and worked up as described above to yield 1.20 g (75%) of **16** as yellow needles after recrystallization from $CHCl_3$–MeOH: mp 158–160 °C; ^1H NMR ($CDCl_3$) δ 9.60 (t, 2, J = 2.1 Hz, O_2NArH), 9.39 (t, 2, J = 1.5 Hz, O_2NArH), 9.03 (t, 2, J = 2.1 Hz, O_2NArH), 7.17 (s, 4, ArH), 6.83 (s, 4, ArH), 5.44 (s, 2, OH), 4.02 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.85 (s, 6, $COCH_3$), 3.48 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 1.33 (s, 18, $ArC(CH_3)_3$), 0.94 (s, 18, $ArC(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ [163.8, 162.9] (C=O), [149.9, 149.4, 148.5, 143.3, 142.3, 136.8, 132.7, 131.7, 131.1, 129.1, 128.7, 128.0, 125.9, 125.5] (Ar), 52.8 (OCH_3), 34.00, 33.96 (CMe_3), 31.8 (CH_2), 31.6, 30.8 (CH_3). Anal. Calcd for $C_{62}H_{66}N_2O_{14}$: C, 70.04; H, 6.26; N, 2.63. Found: C, 70.08; H, 6.12; N, 2.57.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(3-carbomethoxy-5-nitrobenzyl)oxy]-26,28-dihydroxycalix[4]arene (17). A suspension of 3.3 g (5 mmol) of **1**, 2.0 g (12 mmol) of 3-carbomethoxy-5-nitrobenzyl chloride, 10.0 g (100 mmol) of $KHCO_3$, and 0.5 g (3 mmol) of NaI in 75 mL of DMF was stirred at rt under N_2 for 20 h. The cooled reaction mixture was treated with 100 mL of cold 1 N HCl, forming a precipitate that was removed by filtration and washed with cold MeOH to give 3.7 g (81%) of **17**. An analytical sample was obtained by recrystallization from $CHCl_3$–MeOH: mp 194–196 °C; ^1H NMR ($CDCl_3$) δ 9.09 (t, 2, J = 1.8 Hz, O_2NArH), 8.72 (t, 2, J = 1.8 Hz, O_2NArH), 8.56 (br s, 2, O_2NArH), 7.46 (s, 2, OH), 7.06 (s, 4, ArH), 6.88 (s, 4, ArH), 5.26 (s, 4, $ArCH_2O$), 4.21 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.91 (s, 6, $COCH_3$), 3.32 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 1.28 (s, 18, $ArC(CH_3)_3$), 1.00 (s, 18, $ArC(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 164.8 (C=O), 150.5, 149.2, 148.6, 147.9, 142.0, 140.0, 133.4 132.4, 131.6, 127.2, 126.4, 125.9, 123.8 (Ar), 76.0 ($ArCH_2O$), 52.7 (OCH_3), 34.0, 33.8 ($ArCMe_3$), 31.8 ($ArCH_2Ar$), 31.6, 31.0 (CH_3). Anal. Calcd for $C_{62}H_{70}N_2O_{12}$: C, 71.93; H, 6.92; N, 2.71. Found: C, 72.07; H, 6.75; N, 2.67.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(3-carbomethoxy-5-aminobenzoyl)oxy]-26,28-dihydroxycalix[4]arene (18). A solution of 3.2 g (2.9 mmol) of **16** and 12.0 g (53.2 mmol) of $SnCl_2 \cdot 2H_2O$ in 150 mL of EtOH was refluxed 4 h, cooled, and poured onto ice. The solution was made basic (pH 7.8) with NaOH, extracted twice with CH_2Cl_2, and the organic phase separated, washed with brine, and evaporated to give a brownish residue. This was triturated with 75 mL of MeOH to leave 2.0 g (75%) of **18**, an analytical sample of which was obtained by recrystallization from $CHCl_3$–MeOH: mp 302–304 °C; ^1H NMR ($CDCl_3$) δ 7.53 (t, 2, J = 1.8 Hz, H_2NArH), 7.43 (br s, 2, H_2NArH), 7.28 (t, 2, J = 1.8 Hz, H_2NArH), 7.21 (s, 2, OH), 7.07 (s, 4, ArH), 6.79 (s, 4, ArH), 4.99 (s, 4, $ArCH_2O$), 4.28 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.84 (s, 6, $COCH_3$), 3.69 (s, 4, NH), 3.30 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 1.30 (s, 18, $ArC(CH_3)_3$), 0.94 (s, 18, $ArC(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 166.1, 164.7 (C=O), 150.1, 148.8, 147.1, 143.0, 142.5, 132.1, 131.4, 130.6, 128.2, 125.7, 125.5, 121.5, 120.6, 119.9 (Ar), 52.1 (OCH_3), 33.94, 33.90 ($ArCMe_3$), 32.1 ($ArCH_2Ar$), 31.6, 30.9 (CH_3). Anal. Calcd for $C_{62}H_{70}N_2O_{10} \cdot H_2O \cdot CO_2$: C, 71.03; H, 6.81; N, 2.63. Found: C, 70.39; H, 6.57; N, 2.75.

Diester Single-Spanned Double-Cavity Calix[4]arenes (20). A General Procedure. A solution of 0.25 g (0.25 mmol) of the diamino diester **18** in 350 mL of CH_2Cl_2 was treated with 0.12 mL (1.5 mmol) of pyridine. A solution of 0.40 mmol of the diacyl chloride in 150 mL of CH_2Cl_2 was added dropwise over a 12-h period. The reaction was continued for an additional hour, solvent was removed, and the product was purified by chromatography on silica gel (70–230 mesh, 60 Å).

Diester Single-Spanned Double-Cavity Calix[4]arene 20 (n = 8). Following the general procedure described above, using sebacoyl chloride, the crude product was chromatographed, and the fractions collected that eluted with $CHCl_3$–EtOAc (90:10) were recrystallized from $CHCl_3$–MeOH to give 180 mg (62%) of **20** (n = 8): mp 320–322 °C; ^1H NMR ($CDCl_3$) δ 8.93 (br s, 2, OCNArH and NH), 8.92 (br s, 2, OCNArH), 8.47 (br s, 2, OCNArH), 8.10 (br s, 2, OCNArH), 7.16 (s, 4, ArH), 6.78 (s, 4, ArH), 5.74 (s, 2, OH), 4.26 (d, 2, J = 12.9 Hz, $ArCH_2Ar$), 3.71 (s, 6, OCH_3), 3.32 (d, 4, J = 12.9 Hz, $ArCH_2Ar$), 2.22 (t, 4, $COCH_2CH_2$), 1.85 (m, 4, $COCH_2CH_2$), 1.40 (m, 8, CH_2CH_2), 1.31 (s, 18, $ArC(CH_3)_3$), 0.94 (s, 18, $ArC(CH_3)_3$). Anal. Calcd for $C_{72}H_{84}N_2O_{12} \cdot {}^1/_2H_2O$: C, 73.38; H, 7.27, N, 2.38. Found: C, 73.31; H, 7.44; N, 2.26.

Diester Single-Spanned Double-Cavity Calix[4]arene 20 (n = 6). Following the general procedure described above using azeloyl chloride, the crude product was chromatographed, and the fractions collected that eluted with $CHCl_3$–EtOAc (90:10) were recrystallized from $CHCl_3$–MeOH to give 180 mg (65%) of **20** (n = 6): mp 240–242 °C; ^1H NMR ($CDCl_3$) δ 8.74 (br s, 4, OCNArH and NH), 8.47 (br s, 2, OCNArH), 8.32 (br s, 2, OCNArH), 7.14 (s, 4, ArH), 6.77 (s, 4, ArH), 5.21 (br s, 2, OH), 4.05 (d, 2, J = 14.1 Hz, $ArCH_2Ar$), 3.78 (br s, 6, OCH_3), 3.46 (d, 4, J = 14.1 Hz, $ArCH_2Ar$), 2.27 (br s, 4, $COCH_2CH_2$), 1.79 (br s, 4, $COCH_2CH_2$), 1.53 (br s, 2, CH_2CH_2), 1.32 (s, 18, $ArC(CH_3)_3$), 0.93 (s, 18, $ArC(CH_3)_3$). Anal. Calcd for $C_{69}H_{78}N_2O_{12} \cdot H_2O \cdot CO_2$: C, 70.69; H, 6.78, N, 2.36. Found: C, 70.73; H, 6.87; N, 2.32.

Diester Single-Spanned Double-Cavity Calix[4]arene 20 (n = 4). Following the general procedure described above, using adipoyl chloride, the crude product was chromatographed, and the fractions collected that eluted with $CHCl_3$–EtOAc (90:10) were recrystallized from $CHCl_3$–MeOH to give 170 mg (60%) of **20** (n = 4): mp 321–2 °C; ^1H NMR ($CDCl_3$) δ 8.68 (br s, 2, OCNArH or NH), 8.63 (br s, 2, OCNArH or NH), 8.58 (br s, 2, OCNArH), 8.52 (br s, 2, OCNArH), 7.11 (s, 4, ArH), 6.76 (s, 4, ArH), 4.80 (br s, 2, OH), 4.26 (d, 2, J = 13.8 Hz, $ArCH_2Ar$), 3.90 (br s, 6, OCH_3), 3.32 (d, 4, J = 13.8 Hz, $ArCH_2Ar$), 2.42 (br s, 4, $COCH_2CH_2$), 1.85 (br s, 4, $COCH_2CH_2$), 1.27 (s, 18, $ArC(CH_3)_3$), 0.95 (s, 18, $ArC(CH_3)_3$. Anal. Calcd for $C_{68}H_{76}N_2O_{12} \cdot H_2O$: C, 72.19; H, 6.95, N, 2.48. Found: C, 72.51; H, 7.11; N, 2.33.

Diether Single-Spanned Double-Cavity Calix[4]arenes (21). A solution of 3.1 g (3.0 mmol) of **17** and 12.0 g (53.2 mmol) of $SnCl_2 \cdot 2H_2O$ in 150 mL of EtOH was refluxed 4 h and worked up as described above for **18** to give 1.5 g (86%) of **5,11,17,23-tetra-*tert*-butyl-25,27-bis[(3-carbomethoxy-5-aminobenzyl)oxy]-26,28-dihydroxycalix[4]arene (19)** as flaky light brown crystals after recrystallization from *i*-PrOH: ^1H NMR ($CDCl_3$) δ 7.53 (t, 2, J = 1.8 Hz, H_2NArH), 7.43 (br s, 2, H_2NArH), 7.28 (t, 2, J = 1.8 Hz, H_2NArH), 7.21 (s, 2, OH), 7.07 (s, 4, ArH), 6.79 (s, 4, ArH), 4.99 (s, 4, $ArCH_2O$), 4.28 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 3.84 (s, 6, $COCH_3$), 3.69 (s, 4, NH), 3.30 (d, 4, J = 13.2 Hz, $ArCH_2Ar$), 1.30 (s, 19, $C(CH_3)_3$), 0.94 (s, 18, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 167.1 (C=O), 150.5, 149.7, 147.4, 147.1, 141.6, 138.6, 132.3, 131.1, 127.8, 125.5, 125.0, 118.3, 117.9, 115.2 (Ar), 77.5 ($ArCH_2O$), 52.0 (OCH_3), 33.86, 33.79 ($ArCMe_3$), 31.55 ($ArCH_2Ar$), 31.65, 30.92 (CH_3). **A General Procedure.** A suspension of 0.25 g (0.25 mmol) of the diamino diether **19** in 350 mL of CH_2Cl_2 was treated with 0.12 g (1.50 mmol) of pyridine and stirred until a clear solution formed. A solution of 0.40 mmol of the diacyl chloride in 150 mL of CH_2Cl_2 was added dropwise over a 12-h period. The reaction was continued for an additional hour, solvent was removed, and the product was purified by chromatography on silica gel (70–230 mesh, 60 Å).

Diether Single-Spanned Double-Cavity Calix[4]arene 21 (n = 8). Following the general procedure described above using sebacoyl chloride, the crude product was chromatographed, and the fractions that eluted with $CHCl_3$–EtOAc (90:10) were collected and recrystallized from $CHCl_3$–MeOH to give 138 mg (55%) of **21** (n = 8): mp 307–309 °C; ^1H NMR ($CDCl_3$) δ 8.19 (br s, 4, OCNArH and NH), 7.95 (br s, 2, OCNArH), 7.83 (br s, 2, OCNArH), 7.10 (s, 2, OH), 7.09 (s, 4, ArH), 6.78 (s, 4, ArH), 5.02 (br s, 4, CH_2), 4.26 (d, 2, J = 12.9 Hz, $ArCH_2Ar$), 3.71 (s, 6, OCH_3), 3.32 (d, 4, J = 12.9 Hz, $ArCH_2Ar$), 2.22 (t, 4, $COCH_2CH_2$), 1.85 (m, 4, $COCH_2CH_2$), 1.40 (m, 8, CH_2CH_2), 1.31 (s, 18, $ArC(CH_3)_3$), 0.94 (s, 18, $ArC(CH_3)_3$). Anal. Calcd for $C_{72}H_{88}N_2O_{10}$: C, 75.76; H, 7.77, N, 2.45. Found: C, 75.30; H, 7.68; N, 2.30.

Diether Single-Spanned Double-Cavity Calix[4]arene 21 (n = 4). Following the general procedure described above, using adipoyl chloride, the crude product was chromatographed, and the fractions that eluted with $CHCl_3$–EtOAc (90:10) were collected and recrystallized from $CHCl_3$–MeOH to give 138 mg (55%) of **21** (n = 4): mp 312–314 °C; ^1H NMR ($CDCl_3$) δ 8.69 (br s, 2, NH), 8.36 (br s, 2, OCNArH), 8.22 (br s, 2, OCNArH), 7.73 (br s, 2, OCNArH), 7.09 (s, 4, ArH), 6.74 (s, 4, ArH), 6.57 (s, 2, OH), 4.94 (s, 4, $ArCH_2$), 4.27 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 3.88 (s, 6, OCH_3), 3.35 (d, 4, J = 12.9 Hz, $ArCH_2Ar$), 2.48 (t, 4, $COCH_2CH_2$), 1.93 (m, 4, $COCH_2CH_2$), 1.31 (s, 18, $ArC(CH_3)_3$), 0.94 (s, 18, $ArC(CH_3)_3$).

Anal. Calcd for $C_{68}H_{80}N_2O_{10}$: C, 75.25; H, 7.43, N, 2.58. Found: C, 74.97; H, 7.66; N, 2.39.

Diether Single-Spanned Double-Cavity Calix[4]arene 21 (n = 3). Following the general procedure described above, using glutaroyl chloride, the crude product was chromatographed, and the fractions that eluted with $CHCl_3$–EtOAc (90:10) were collected and recrystallized from $CHCl_3$–MeOH to give 138 mg (55%) of **21** (n = 3): mp 318–319 °C; ^{1}H NMR ($CDCl_3$) δ 8.87 (br s, 2, NH), 8.41 (br s, 2, OCNArH), 8.25 (br s, 2, OCNArH), 7.65 (br s, 2, OCNArH), 7.08 (s, 4, ArH), 6.70 (s, 4, ArH), 6.33 (s, 2, OH), 4.96 (s, 4, $ArCH_2O$), 4.23 (d, 2, J = 13.2 Hz, $ArCH_2Ar$), 3.86 (s, 6, OCH_3), 3.22 (d, 4, J = 12.9 Hz, $ArCH_2Ar$), 2.60 (t, 4, $COCH_2CH_2$), 2.19 (m, 2, $COCH_2CH_2$), 1.31 (s, 18, $ArC(CH_3)_3$), 0.90 (s, 18, $ArC(CH_3)_3$). Anal. Calcd for $C_{67}H_{78}N_2O_{10}$: C, 75.11; H, 7.34, N, 2.61. Found: C, 74.89; H, 7.11; N, 2.53.

Determination of K_{assoc} Values. Commercially available materials were used without purification as guest compounds. In a typical determination 500 μL of a 10^{-2} M solution of **4** in $CDCl_3$ was treated with incremental amounts (5–10 μL) of a 1 M solution of the guest compound in $CDCl_3$. The ^{1}H NMR spectrum was measured at 25 °C after each addition, and the chemical shift values for **4** and the guest compound were recorded for the various stoichiometries. A typical example is shown by the data in Figure 2. A plot of $\Delta\delta$ vs $\Delta\delta/[\text{guest}]_0$ at high guest concentrations gives a straight line, the slope of which allows the determination of the K_{assoc} value by the application of the Benesi–Hildebrand expression.[14]

Determination of Spin-Lattice Relaxation Times (T_1). Using the inversion recovery method,[30] a series of spectra, each consisting of 8–20 scans, was obtained by using 180–τ–90 pulse sequences. The equilibrium time (D_1) was chosen to be three to four times the longest T_1 of interest (20–24 s). For data acquisition for various recovery times (D_2) an array of D_2 values was created to cover a range of 0.1–3 times T_1, 8–12 values of D_2 being selected to ensure accurate results. All of the T_1 determinations were repeated three times, providing values accurate to ±5%.

Molecular Modeling Studies. Molecular mechanics calculations were carried out with the programs QUANTA/CHARMm (version 3.0, released June 1990 by Polygen Corp, Waltham, MA). A 2D representation of a double-cavity calixarene (e.g., **4**) was first drawn in CHEMNOTE, then transferred to QUANTA, the charges smoothed only on carbon atoms, and the structure minimized by Steepest Descents to improve the initial conformation, Adopted Basis Newton-Raphson for refinement, and Powell Conjugate Gradient for convergence to a root mean square value of 0.000 01 or less. Conformational searches were carried out in the quest of a global minimum. The more successful of these with **4** started with the ester carbonyl groups anti and involved 256 unique conformations, each of which were partially minimized. The lower energy conformers (ca. 20), covering a spread of 20 kcal/mol, were then fully minimized, leading to the structure shown in Figure 4. Calculations on complexes were carried out by first generating Connoly surfaces[31] which allows the docking of the two molecules to be carried out in a way that maximizes attractive dispersion forces, avoids steric repulsions, and optimizes electrostatic complementarity. With the use of this technique it became quickly apparent that productive complexation with **4** occurs only at the side of the lower cavity.

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Supplementary Material Available: Temperature-dependent ^{1}H NMR spectrum of the diether double-cavity double-bridged calix[4]arene and the energies of guests and host–guest complexes generated by the CHARMm molecular mechanics program (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Notes

Cycloadditions of Electron-Deficient 8,8-Disubstituted Heptafulvenes to Electron-Rich 6,6-Disubstituted Fulvenes

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Introduction

Interest in the discovery of cycloadditions involving more than 6π electrons has continued for the 20 years since the discovery of the Woodward–Hoffmann selection rules for concerted cycloadditions.[1]

The competition among [4 + 2], [6 + 4], [8 + 2], and [8 + 6] cycloadditions, all symmetry allowed thermal processes, has prompted much investigation. Houk reported the periselective formation of 1:1 [6 + 4] adduct **3a**, in the reaction of tropone (**1a**) with 6,6-dimethylfulvene (**2a**), which immediately underwent a 1,5-sigmatropic hydrogen shift to yield the thermodynamically more stable cyclopentadiene **4a**, which subsequently underwent a second [6 + 4] cycloaddition with tropone to form 2:1 [6 + 4] adduct **5**. A trace of 1:1 [4 + 2] adduct **6a** was also observed (Scheme I).[2] In the reaction of 2-chlorotropone (**1b**) with **2a**, **4b** can be isolated as a major product because further reaction is kinetically slowed.[3] However, no cycloaddition was observed with 2,7-dichlorotropone (**1c**).[3] By contrast, Sasaki reported that 6,6-diphenylfulvene (**2b**) reacted with tropone to afford only 1:1 [4 + 2] adduct **6b** instead of the expected [6 + 4] adduct.[4] The differing

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