2-Phenyl-4-(ethoxycarbonyl)-5-(N-benzylamino)thiazole (7f): yield 85%; mp 97–98 °C; ^{1}H NMR (CDCl$_3$) δ 7.95 (b, 1 H), 7.80 (m, 2 H), 7.35 (m, 8 H), 4.55 (d, J = 5.8 Hz, 2 H), 4.40 (q, J = 7.0 Hz, 2 H), 1.45 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (CDCl$_3$) δ 165.2, 162.5, 159.4, 148.4, 136.4, 129.1, 128.9, 128.6, 128.0, 127.4, 125.9, 61.8, 60.5, 53.0, 14.5.

2-Phenyl-4-(ethoxycarbonyl)-5-(1-piperidino)thiazole (7g): yield 85%; mp 76–78 °C; ^{1}H NMR (CDCl$_3$) δ 7.75 (m, 2 H), 7.30 (m, 3 H), 4.35 (q, J = 7.1 Hz, 2 H), 3.10 (t, J = 5.3 Hz, 4 H), 1.70 (m, 4 H), 1.50 (m, 2 H), 1.35 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (CDCl$_3$) δ 164.0, 162.0, 153.8, 133.5, 129.3, 128.6, 125.9, 111.5, 60.5, 55.7, 26.7, 25.4, 24.1, 23.5, 14.4.

2-Phenyl-4-(ethoxycarbonyl)-5-(1-morpholino)thiazole (7h): yield 92%; mp 83–85 °C. ^{1}H NMR (CDCl$_3$) δ 7.88 (m, 2 H), 7.42 (m, 3 H), 4.43 (q, J = 7.2 Hz, 2 H), 3.90 (m, 4 H), 3.28 (m, 4 H), 1.43 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (CDCl$_3$) δ 162.6, 161.9, 155.2, 133.5, 130.2, 129.7, 128.7, 126.2, 66.4, 60.7, 54.2, 14.4.

Supplementary Material Available: Tables containing the crystal structure, MNDO, and MINDO/3 geometries for 4-(ethoxycarbonyl)-5-aminothiazole, MINDO/3 geometries and charge densities for oxazole **5a**, nitrile ylide **6a**, thiazole **7a**, oxazolo[5,4-d]pyrimidine-7-thione **8**, nitrile ylide **9**, and thiazolo[5,4-d]pyrimidin-7-one **10**, MINDO/3 charge densities and frontier MO energies and coefficients for nitrile ylide **6a**, and IR, mass spectral, and elemental analysis data (13 pages). Ordering information is given on any current masthead page.


Calixarenes. 24. Complexation by Water-Soluble Calixarenes

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Calixarenes (**1**), which are [1$_n$] metacyclophanes comprising para-substituted phenolic units and methylene groups, are most readily obtained from the base-induced condensation of *p-tert*-butylphenol and formaldehyde.[1]


1
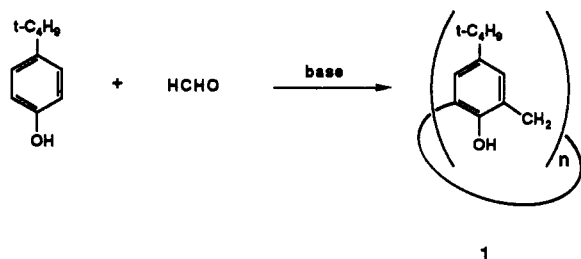
Because they have been made easily accessible, the calixarenes have become popular substrates for complexation studies, especially for the sequestration of inorganic ions.[2] That they also have the capacity for forming complexes with organic molecules has been demonstrated by Shinkai and co-workers[3] as well as by the results reported in the

previous paper in this series[4] involving the interaction of various aromatic hydrocarbons with *p*-(dialkylamino)calixarenes (**2**, n = 4–8) and *p*-(2-carboxyethyl)calixarenes (**3**, n = 4–8). The present paper is a continuation of these earlier studies and extends the list of host molecules to include various relatives of **3**.

2   **3a** (n = 6)
                      3b (n = 8)
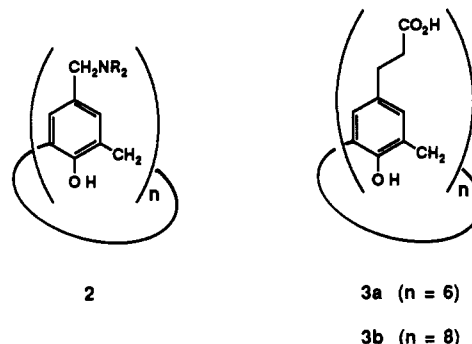
Synthesis of Host Molecules

Calixarenes **3a** and **3b** were synthesized by the *p*-quinonemethide procedure described in the previous paper involving treatment of the quaternary salt of **2** with 2 equiv of sodio diethyl malonate followed by hydrolysis and decarboxylation of the resulting polyester.[4] Calixarenes **4a**, **4b**, and **4c** were prepared by alkylation of **3a** following the general procedures that Shinkai et al.[3] used with the *p*-sulfonatocalixarenes. To our surprise, however, the elemental analyses for the *n*-hexyl ether (**4b**) and carboxymethyl ether (**4c**) agreed more closely with trisubstituted than with hexasubstituted compounds, and an inspection of the ratio of the areas for the ^{1}H NMR resonances of the aromatic protons vs the protons in the ether substituents provided reasonable support for this conclusion. Similar observations have been reported by Aoyama et al.[5] Calixarenes **5a**, **5b**, **6a**, and **6b** were prepared by carboxymethylation of calix[6]arene, *p-tert*-butylcalix[6]arene, calix[8]arene, and *p-tert*-butylcalix[8]arene, respectively, by the procedure described by Chang and Cho.[6]
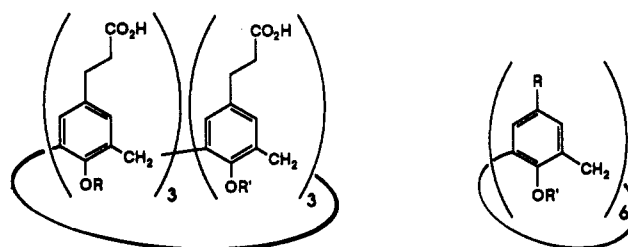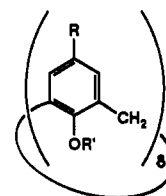

4a (R = CH$_3$, R' = CH$_3$)   **5a** (R = H, R' = CH$_2$CO$_2$H)

4b (R = n-C$_6$H$_{13}$, R' = H)   **5b** (R = t-C$_4$H$_9$, R' = CH$_2$CO$_2$H)

4c (R = CH$_2$CO$_2$H, R' = H)

6a (R = H, R' = CH$_2$CO$_2$H)

6b (R = t-C$_4$H$_9$, R' = CH$_2$CO$_2$H)

(1) For summaries of calixarene chemistry, cf.: (a) Gutsche, C. D. *Monographs in Supramolecular Chemistry: Calixarenes*; Stoddart, J. F., Ed.; Royal Society of Chemistry: London, 1989. (b) Gutsche, C. D. Calixarenes and the Art of Molecular Basketmaking. In *Synthesis of Macrocycles: The Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; John Wiley & Sons: New York, 1987; p 93. (c) Gutsche, C. D. The Calixarenes. In *Host Guest Complex Chemistry*; Vögtle, F., Weber, E. Eds.; Springer-Verlag: New York, 1985; p 375.

(2) For a compilation of pertinent references, cf.; Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E. B.; Ruhl, B. L.; Schwing-Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681.

(3) Shinkai, S.; Mori, S.; Koreishi, H.; Subaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409.

(4) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.

(5) Aoyama, Y.; Nonaka, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 1025.

Table I. Association Constants, K_a, for Calixarene–Aromatic Hydrocarbon Complexes in Aqueous Base, Determined by Solid–Liquid Extraction

guest	naphthalene	anthracene	phenanthrene	fluoranthene	pyrene	perylene
3a	3.7×10^3	1.3×10^4	3.0×10^4	3.4×10^3	$<10^2$	$<10^2$
4a	2.4×10^3	9.5×10^3		$<10^2$	$<10^2$	$<10^2$
4b	0	0	0	0	0	0
4c	0	0	0	0	0	0
5a	2.0×10^3	2.0×10^3	4.7×10^3	6.7×10^3	1.4×10^4	3.3×10^3
5b	0	0	0	0	0	0
3b	6.1×10^2	1.4×10^4	4.1×10^3	1.4×10^4	4.4×10^4	8.4×10^3
6a	3.0×10^3	2.9×10^4	2.0×10^4	1.6×10^4	7.3×10^4	4.0×10^4
6b	–	–	–	–	–	

Complexation Studies

Included among the numerous complexation studies of water-soluble cyclophanes are those reported by Tabushi,[7] Murakami,[8] Koga,[9] Whitlock,[10] and Diederich,[11] the last author having critically reviewed the field.[12] Of the several methods that have been used to obtain complexation constants the one most useful in the present study is the solid–liquid extraction procedure, well described by Diederich.[13] 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, centrifuged, and filtered to remove solids; the aqueous phase is extracted with an organic solvent, and the amount of hydrocarbon present is spectrophotometrically determined. This value is compared with that obtained in a similar fashion but in the absence of the calixarene. For the equilibrium $H_{H_2O} + G \rightleftharpoons HG_{H_2O}$ the value of G is taken as the solubility of the guest in water, the value of HG_{H_2O} as the total amount of spectrophotometrically determined guest molecule minus the value of G, and the value of H_{H_2O} as the amount of host molecule added to the system minus the value of HG_{H_2O}. As guest molecules the aromatic hydrocarbons naphthalene, anthracene, phenanthrene, fluoranthene, pyrene, and perylene were used. The K_a values for the complexation of these hydrocarbons with the various calixarenes are shown in Table I.

The similarity noted in the previous study[4] of the K_a values for p-((dialkylamino)methyl)calixarenes (2) and p-(2-carboxyethyl)calixarenes (3) of a given ring size was interpreted as indicating that the complexation takes place on the face opposite to the water-solubilizing groups, i.e. at the hydroxyl-containing annulus. Although the complexation constants are only modest in size, ranging from a threshold value of ca. 6×10^2 M^{-1} to a maximum of 1.5×10^4 M^{-1}, some complementarity between the size of the hydrocarbon and the size of the calixarene annulus was observed. To further probe the relation between K_a and annulus size the hexamethyl ether of p-(carboxyethyl)calix[6]arene (4a) and the tri-n-hexyl ether of p-(carboxyethyl)calix[6]arene (4b) are now compared with p-(2-carboxyethyl)calix[6]arene (3a). Whereas the addition of methyl groups has relatively little effect on the complexation, only modestly reducing the magnitude of K_a, the addition of n-hexyl groups reduces the complexation below the threshold value of 10^2 M^{-1}. The failure of 4b to form complexes can be ascribed to (a) "self complexation", (b)

the use of a larger amount of base to solubilize 4b, and/or (c) the formation of micelles. The flexibility of the n-hexyloxy moieties allows one or more of the hexyl groups to bend back into the annulus of the calixarene, providing the possibility of intramolecular complexation to the exclusion of intermolecular complexation. To prepare a 10^{-4} M solution of 4b it is necessary to use 4 times as high a concentration of K_2CO_3 as for 4a, and 4a in turn requires twice as high a concentration of base as 3a. That an increased amount of base lowers the K_a is shown by the comparison of the values for the 4a–anthracene complex in the presence of 1.5×10^{-3} M K_2CO_3 ($K_a = 9.5 \times 10^3$ M^{-1}) and 6×10^{-3} M K_2CO_3 ($K_a = 3.5 \times 10^3$ M^{-1}). The possibility of micelle formation cannot be discounted, although no assessments of cmc values were made in this study. Shinkai et al.[3] have measured the cmc of the hexa-n-hexyl ether of p-sulfonatocalix[6]arene as 5×10^{-4}, and it is probable that the cmc for 4b is comparable, if not lower.

The tris(carboxymethyl) ether of p-(carboxyethyl)calix[6]arene (4c) was prepared and shown to have no measurable complexing ability with any of the six aromatic hydrocarbons. Since it is unlikely that the cmc of 4c is lower than the concentrations used in these measurements and since the flexibility of the carboxymethoxy group is not great enough to allow effective "self complexation", it is likely that the failure to form complexes is due simply to the absence of a hydrophobic face; both ends of the calix in this instance are lined with hydrophilic carboxyl groups.

In compounds 5a, 5b, 6a, and 6b the structures are complementary to those of compounds 2–4 in that the water-solubilizing moieties are on the "lower rim" rather than the "upper rim" of the calixarene. In 5a and 6a, where the substituents on the "upper rim" are hydrogens, this change results in most cases in an increase in the value of K_a (comparing 5a with 3a and 6a with 3b). Thus, 6a forms stronger complexes than 3b with all of the hydrocarbons except naphthalene, while 5a forms stronger complexes than 3a with fluoranthene, pyrene, and perylene, the differences in the cases of pyrene and perylene being particularly large. However, when the substituents on the "upper rim" are *tert*-butyl groups complexation is completely curtailed in the case of the calix[6]arene compound 5b, and the calix[8]arene compound 6b is too insoluble in aqueous base to allow an assessment of its complexing abilities. The failure of 5b to form complexes is surprising, and it may partly be due to the necessity of using a more concentrated K_2CO_3 solution (i.e. 3 times as concentrated as for 5a to prepare a 10^{-4} M solution of the calixarene). However, the data cited in a previous paragraph suggest that this would not be expected to completely curtail complexation, so it seems more likely that the *tert*-butyl groups are mainly responsible for preventing the entry of the guest molecules in this case.

On the basis of the K_a values measured in this and the previous study, it can be concluded that calixarenes containing water-solubilizing carboxyl groups form moderately strong complexes with aromatic hydrocarbons and that

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(10) Miller, S. P.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 1492.
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(12) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362.
(13) Diederich, F.; Dick, K. *J. Am. Chem. Soc.* **1984**, *106*, 8024.

some size–shape complementarity can be discerned. However, it is less than that desired for effective host–guest selectivity, and further elaboration of the calixarene structure will be required to achieve the goal of enzymelike encounters.

Experimental Section[14]

5,11,17,23,29,35-Hexakis(2′-carboxyethyl)-37,38,39,40, 41,42-hexamethoxycalix[6]arene (4a). A 1.00-g (9.4 × 10^{-4} mol) sample of *p*-(2-carboxyethyl)calix[6]arene (**3a**) and 1.68 g (4.2 × 10^{-2} mol) of NaOH were dissolved in 5–7 mL of water, and a solution of 3.33 g (2.3 × 10^{-2} mol) of CH_3I in 30 mL of DMSO was added. The mixture was heated at 50 °C for 24 h, cooled to room temperature, poured into 150 mL of ice-cold water, and acidified. The precipitate was removed by filtration and washed several times with water and then with diethyl ether to leave 0.86 g (79%) of product as a colorless solid: mp 188–190 °C; ^{1}H NMR (DMSO-d_6) δ 12.10 (bs s, CO_2H) 6.757 (s, 2, ArH), 3.814 (s, 2, ArCH_2Ar), 3.50 (br s, H_2O), 3.138 (s, 3, OCH_3), 2.576 (t, 2, CH_2CO_2H), 2.352 (t, 2, ArCH$_2$C). Anal. Calcd for $C_{66}H_{72}O_{18} \cdot H_2O$: C, 67.68; H, 6.37. Found: C, 67.51; H, 5.93.

5,11,17,23,29,35-Hexakis(2′-carboxyethyl)-37(?),39(?), 41(?)-tris(*n*-hexyloxy)calix[6]arene (4b). By use of a procedure similar to that described for the preparation of **4a** but substituting *n*-hexyl bromide for methyl iodide and carrying out the reaction at 100 °C, 0.84 g (54%) of a colorless product was obtained from 1.00 g of **3a**: ^{1}H NMR (DMSO-d_6) δ 12.2 (br s, CO_2H), 6.829 (br s, 12, ArH), 3.728 (br s, 12, ArCH_2Ar), 3.510 (s, H_2O), 3.330 (t, 6, OCH_2), 2.605 (t, 12, CH_2CO_2H), 2.421 (t, 12, ArCH$_2$C), 1.411 (m, 6, $OCCH_2$), 1.246 (br s, 18, $OCC(CH_2)_3$), 0.838 (br s, 9, CCH_3). Anal. Calcd for $C_{78}H_{96}O_{18} \cdot H_2O$: C, 69.92; H, 7.38. Found: C, 69.85; H, 7.16.

5,11,17,23,29,35-Hexakis(2′-carboxyethyl)-37(?),39(?), 41(?)-tris(carboxymethoxy)calix[6]arene (4c). A 1.00-g (9.4 × 10^{-4} mol) sample of *p*-(2-carboxyethyl)calix[6]arene (**3a**), 1.5 g (3.75 × 10^{-2} mol) of NaOH, and 2.2 g (1.6 × 10^{-2} mol) of α-bromoacetic acid were dissolved in 30 mL of water, the solution was refluxed for 24 h, another 1.5 g of NaOH and 2.2 g of α-bromoacetic acid were added, and refluxing was continued for an additional 24 h. The reaction mixture was cooled, diluted with 50 mL of water, and filtered. Acidification with dilute HCl gave a precipitate which was removed by filtration and washed several times with water and then with diethyl ether to leave 1.1 g (74%) of a colorless powder: mp >400 °C; ^{1}H NMR (DMSO-d_6) δ 6.800 (br s, 12, ArH), 4.502 (br s, 6, OCH_2CO_2H), 3.707 (br s, 12, ArCH_2Ar), 2.573 (t, 12, CCH_2CO_2H), 2.336 (t, 12, ArCH$_2$C). Anal. Calcd for $C_{66}H_{66}O_{24}$: C, 63.91; H, 5.12. Found: C, 63.94; H, 4.95.

37,38,39,40,41,42-Hexakis(carboxymethoxy)calix[6]arene (5a). A 1.2-g (1.9 × 10^{-3} mol) sample of calix[6]arene was dissolved in 20 mL of THF and 30 mL of DMF in an atmosphere of N_2,

and 1.43 g (3.6 × 10^{-2} mol) of NaH (60% dispersion in mineral oil) was added. The solution was stirred for 15 min and then treated with 3.8 g (2.2 × 10^{-2} mol) of ethyl α-bromoacetate. The solution was stirred at room temperature until foaming subsided, refluxed for 2 h, cooled, and treated with an additional 1.43 g of NaH and 3.8 g of ethyl α-bromoacetate, and refluxing was continued for another 2 h. The reaction mixture was then cooled, poured into 150 mL of ice-cold water, acidified, and extracted into $CHCl_3$, which was dried over Na_2SO_4 and evaporated to leave a dark brown oil. This was dissolved in 60 mL of THF, and 50 mL of a 10% solution of Me_4NOH was added. The reaction mixture was refluxed 24 h, cooled, and acidified, and the THF was slowly evaporated at ca. 50 °C. The resulting precipitate was collected and washed several times with water and then with $CHCl_3$ to give 0.87 g (47%) of a colorless solid: mp 310–312 °C; ^{1}H NMR (DMSO-d_6) δ 12.650 (br s, CO_2H), 7.247 (s, $CHCl_3$), 6.718 (d, 2, *m*-ArH), 6.624 (t, 1,*p*-ArH), 4.348 (s, 2, OCH_2CO_2H), 4.025 (s, 2, ArCH_2Ar), 3.40 (br s, H_2O). Anal. Calcd for $C_{54}H_{48}O_{18} \cdot CHCl_3$: C, 59.82; H, 4.47. Found: C, 60.75; H, 4.52.

49,50,51,52,53,54,55,56-Octakis(carboxymethoxy)calix[8]-arene (6a) was prepared from calix[8]arene by the procedure described above for **5a** except that hydrolysis of the ester was effected by 24 h refluxing with a 1 M solution of KOH. The product was obtained in 43% yield as a colorless solid: mp 268–270 °C; ^{1}H NMR (DMSO-d_6) δ 6.819 (m, 3, ArH), 4.362 (s, 2, OCH_2CO_2H), 4.079 (s, 2, ArCH_2Ar). Anal. Calcd for $C_{72}H_{64}O_{24}$: C, 65.85; H, 4.91. Found: C, 65.60; H, 4.92.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-(carbethoxymethoxy)calix[6]arene was prepared from *p*-*tert*-butylcalix[6]arene by the procedure described above for **5a** and was obtained in 67% yield as a colorless solid: mp 258–260 °C; ^{1}H NMR (CDCl$_3$) δ 6.982 (s, 2, ArH), 4.543 (s, 2, OCH_2CO_2H), 4.199 (q, 2, CO_2CH_2C), 4.055 (br s, 2, ArCH_2Ar), 1.247 (t, 3, CO_2CCH_3), 0.983 (s, 9, $C(CH_3)_3$). Anal. Calcd for $C_{90}H_{120}O_{18}$: C, 72.55; H, 8.12. Found: C, 72.64; H, 8.31.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-(carboxymethoxy)calix[6]arene (5b) was obtained by refluxing the ester described above for 24 h with 10% Me_4NOH and was isolated in 80% yield as a colorless solid after washing with water and boiling MeOH: mp 293–297 °C; ^{1}H NMR (DMSO-d_6/CDCl$_3$) δ 6.921 (s, 2, ArH), 4.905 (br s, CO_2H + H_2O), 4.483 (d, 1, ArCH_2Ar), 4.079 (s, 2, OCH_2CO_2H), 3.388 (d, 1, ArCH$_2$Ar), 1.073 (s, 9, $C(CH_3)_3$). Anal. Calcd for $C_{78}H_{96}O_{18} \cdot H_2O$: C, 69.94; H, 7.37. Found: C, 69.90; H, 7.48.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54, 55,56-octakis(carbethoxymethoxy)calix[8]arene was prepared from *p*-*tert*-butylcalix[8]arene by the procedure described above for **5a** and was obtained in 81% yield as a colorless solid: mp 212–214 °C; ^{1}H NMR (CDCl$_3$) δ 6.949 (s, 2, ArH), 4.163 (s, 2, OCH_2CO_2H), 4.077 (s, 2, ArCH_2Ar), 4.041 (q, 2, CO_2CH_2C), 1.094 (s, 9, $C(CH_3)_3$), 1.015 (t, 3, CO_2CH_3). Anal. Calcd for $C_{120}H_{160}O_{24}$: C, 72.55; H, 8.12. Found: C, 72.28; H, 8.28.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54, 55,56-octakis(carboxymethoxy)calix[8]arene (6b) was obtained by refluxing the ester described above for 2 h with a 5% solution of NaOH and was isolated in 88% yield as a colorless solid after washing with water and boiling MeOH: mp 347–350 °C; ^{1}H NMR (DMSO-d_6/CDCl$_3$) δ 12.940 (br s, CO_2H), 6.943 (s, 2, ArH), 4.187 (s, 2, OCH_2CO_2), 3.993 (s, 2, ArCH_2Ar), 3.612 (s, H_2O), 1.029 (s, 9, $C(CH_3)_3$). Anal. Calcd for $C_{104}H_{128}O_{24} \cdot 2H_2O$: C, 69.47; H, 7.40. Found: C, 69.69; H, 7.26. An ^{1}H NMR spectrum in CDCl$_3$ alone showed a large H_2O resonance at δ 2.6.

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(14) The melting points of all compounds above 250 °C were taken in sealed and evacuated capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) using a 500 °C thermometer calibrated against a thermocouple. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) as an internal standard. Microanalyses were carried out by Desert Laboratories, Tucson, AZ. Analytical samples were dried at least 36 h at room temperature, 140 °C, and 1–2 mm of pressure. In a number of instances solvent of crystallization (H_2O or CCl_3) was retained, considerably affecting the elemental analysis. The presence of these substances was qualitatively supported by the appearance of their characteristic resonances in the ^{1}H NMR spectra of the host compound. 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.