Calixarenes. 16. Functionalized Calixarenes: The Direct Substitution Route

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The base-induced condensation of *p*-phenylphenol and formaldehyde is shown to yield *p*-phenylcalix[6]arene **3** and *p*-phenylcalix[8]arene **5** as isolable products but no detectable amount of *p*-phenylcalix[4]arene **1**, contrary to earlier reports. As an alternative to *p*-phenylcalix[4]arene as a "deep cavity" compound, *p*-benzoylcalix[4]arene **27** and *p*-(4'-hydroxybenzoyl)calix[4]arene **29** are proposed, and their syntheses by AlCl₃-catalyzed aroylation of the methyl ether of calix[4]arene **14** are described. Methods are given for introducing various groups into the para position of the calix[4]arene ring system, including bromo, lithio, carboxyl, carbomethoxy, and cyano, thus making available a variety of functionalized calixarene molecules.

The 1944 report by Zinke and Ziegler[1] that *p-tert*-butylphenol and formaldehyde react under certain conditions to form a cyclic tetramer was followed 4 years later by another paper[2] stating that the reaction is a general one and works, inter alia, with *p*-phenylphenol. When we

1, *n* = 4
2, *n* = 5
3, *n* = 6
4, *n* = 7
5, *n* = 8
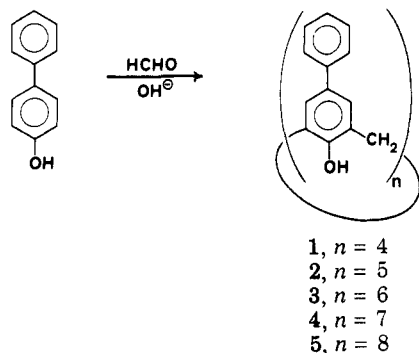
became interested in building enzyme mimics these cyclic oligomers, which we have named calixarenes,[3,4] attracted our attention. The cyclic tetramer that Zinke thought to be the product of condensation of *p*-phenylphenol and formaldehyde seemed particularly intriguing because of its deep cavity. However, when subsequent investigation revealed that the reaction of *p-tert*-butylphenol yields a variety of cyclic oligomers,[5] the cyclic tetrameric structure that had been assigned to the product from *p*-phenylphenol required verification. This provided the starting point for the work reported in the present paper.

p-Phenylphenol–Formaldehyde Condensation. A number of procedures have been described for the prep-

aration of calixarenes via the condensation of phenols and formaldehyde. The original Zinke procedure[1] is a several step process that involves (a) treating a para substituted phenol with aqueous formaldehyde and NaOH at 50–55 °C for 45 h, (b) heating the reaction mixture at 110–120 °C for 2 h, during which time the water evaporates to leave a friable solid, (c) acidifying the residue, and (d) suspending the resin in linseed oil and heating at 220 °C for several hours. A simpler method, which we have referred to as the "Munch procedure" or the "Petrolite procedure"[6] is a one-step process that involves refluxing a mixture of a para substituted phenol, paraformaldehyde, and a very small amount of an alkali hydroxide in xylene for 4 h or more. Several variations on these two themes have been reported, including the substitution of diphenyl ether–biphenyl eutectic (Dowtherm) for linseed oil in the Zinke procedure[7] and the use of a larger amount of base in the Petrolite procedure.[5] In the case of the *p-tert*-butylphenol–formaldehyde condensation previous work in our laboratory has shown[5] that the ring size of the calixarene that is formed is a function of the procedure that is used, viz., the Zinke–Cornforth procedure can yield cyclic tetramer as the major product in some cases, the Petrolite procedure yields cyclic octamer, and a modified Petrolite procedure yields cyclic hexamer. More recent work,[8] however, has revealed that this outcome is far from general and that different para-substituted phenols behave in quite different ways; the behavior of *p-tert*-butylphenol does not necessarily predict that of *p*-phenylphenol, contrary to the inferences in the Zinke papers.

In the present work we use a modified Zinke–Cornforth procedure for synthesizing the *p*-phenylcalixarenes. Chromatographic separation of the CHCl₃ soluble fraction of the crude product yielded ca. 10% of *p*-phenylcalix[6]arene **3** as a white powder with a melting point very close to that reported[9] for *p*-phenylcalix[4]arene **1**, and it

(1) Zinke, A.; Ziegler, E. *Chem. Ber.* **1944**, *77B*, 264.
(2) Zinke, A.; Zigeuner, G.; Hossinger, K.; Hoffmann, G., *Monatsh.* **1948**, *79*, 438.
(3) Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, *43*, 4905.
(4) For general reviews of the calixarenes, see: (a) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161. (b) Gutsche, C. D. "Topics in Current Chemistry"; Vol 123, Boschke, F. L., Ed.; Springer-Verlag: Berlin and Heidelberg, 1984: Vol. 123, p 1.
(5) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

(6) Buriks, R. S.; Fauke, A. R.; Munch, J. H. U.S. Patent 4 259 464, 1981.
(7) Cornforth, J. W.; D'Arcy Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Br. J. Pharmacol.* **1955**, *10*, 73.
(8) Gutsche, C. D.; Chen, S. I., unpublished observations.

was initially though that the cyclic tetramer had, indeed been synthesized. However, TLC and spectral comparisons with an authentic sample of 1 that had been prepared by a convergent stepwise procedure[9] showed the two compounds to be different, and a mixed melting point determination further confirmed this fact. The product obtained from the modified Zinke–Cornforth procedure was assigned the cyclic hexameric structure on the basis of osmometric molecular weight determinations of the methyl ether 6 and the allyl ether 7[10] as well as the ^{1}H NMR and ^{13}C NMR spectral characteristics of these compounds, which are commensurate with a symmetrical structure.
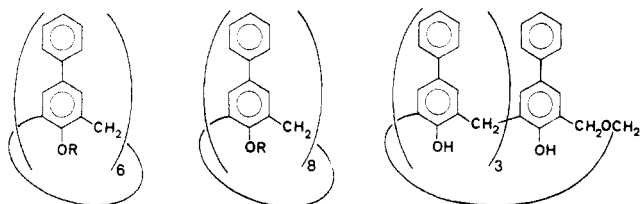
6, R = CH₃
7, R = CH₂CH=CH₂
8, R = COCH₃

9, R = CH₃
10, R = Si(CH₃)₃
11, R = COCH₃

12

When the same procedure was carried out but with the addition of half as much NaOH (0.075 equiv per phenolic residue) prior to the final heating in diphenyl ether, a 50% yield of crude product was obtained which produced ca. 14% of *p*-phenylcalix[8]arene 5, melting at 421–423 °C after recrystallization. The cyclic octameric structure was assigned on the basis of an osmometric molecular weight determination on the octaacetate 11 coupled with the ^{1}H NMR and ^{13}C NMR spectral characteristics of the methyl ether 9 and the trimethylsilyl ether 10.

We also investigated the Petrolite procedure as a possible means for preparing *p*-phenylcalixarenes. The crude product, obtained in ca. 50% yield, was separated by Soxhlet extraction into a THF-soluble and a THF-insoluble fraction. From the THF-insoluble fraction a small amount of *p*-phenylcalix[8]arene was obtained, while the THF-soluble fraction failed to yield any crystallizable materials. In an attempt to gain further insight into the composition of the product obtained from the condensation carried out by the Petrolite procedure, the total crude reaction mixture was methylated via the Stoochnoff and Benoiton procedure.[11] TLC analysis of this material showed five components to be present, one corresponding to the methyl ether of the cyclic hexamer (6), one corresponding to the methyl ether of the cyclic octamer (9), and one corresponding to the methyl ether of *p*-phenyldihomooxacalix[4]arene (12).[12] A fourth component with an R_f value slightly higher than that of the cyclic hexamer may be the cyclic heptamer.[13] A fifth component with an R_f value of 0 is probably a mixture of linear oligomers.

(9) Gutsche, C. D.; No, K. H., *J. Org. Chem.* 1982, *47*, 2708.
(10) The behavior of the allyl ether 7 on melting was interesting. The material softened, bubbled, and shrank at 283–284 °C but did not completely melt until 407–409 °C, the same mp as 6 and possibly the result of the extrusion of allene from the molecule.
(11) Stoochnoff, B. A.; Benoiton, N. L. *Tetrahedron Lett.* 1973, 21.
(12) We are indebted to Dr. Elliot Kaplan for preparing a pure sample of *p*-phenyldihomooxacalix[4]arene.
(13) A series of Japanese patents have appeared which describe the preparation of *p*-phenylcalix[6]arene 2 (Jpn. Kokai Tokkyo Koho JP 59 104 331 [84 104 331], 1984; *Chem. Abstr.* 1984, *101*, 191410*v*, 720), *p*-phenylcalix[7]arene 3 (Jpn. Kokai Tokkyo Koho JP 59 104 332 [84 104 332], 1984; *Chem. Abstr.* 1984, *101*; 191409*b*, 720), and *p*-phenylcalix[8]arene 4 (Jpn. Kokai Tokkyo Koho JP 59 104 333 [84 104 333], 1984; *Chem. Abstr.* 1984, *101*, 19141*w*, 720) by a process that appears to closely resemble the Petrolite procedure. Although the characterization data for the compounds in these patents are sparse, the isolation of the cyclic heptamer indicates its presence in at least some of the reaction mixtures from the *p*-phenylphenol–formaldehyde condensation.

Thus, both the Zinke–Cornforth and the Petrolite procedures yield small but ponderable amounts of the cyclic hexamer and cyclic octamer (and, possibly, the cyclic heptamer[13]), but no evidence has been adduced for the presence any cyclic tetramer (1) or cyclic pentamer (2) in the condensation mixtures. This stands in stark contrast to the *p*-tert-butylphenol–formaldehyde condensation, where procedures have now been developed for obtaining cyclic tetramer, cyclic hexamer, and cyclic octamer in yields exceeding 50%.[5,14]

Synthesis of Calix[4]arenes with Functional Groups at the Para Position.

The availability of *p*-tert-butylcalix[4]arene in high yield[15] and the facility with which its *tert*-butyl groups can be removed[15,16] makes calix[4]arene 13 an attractive starting material for the preparation of various para-substituted calix[4]arenes. Although introduction of functional groups into the calixarene ring via electrophilic substitution were stated in earlier communications to fail, successful nitration of calix[4]arene[17a] and sulfonation of calix[6]arene[17b] have recently been reported. Acylation under Friedel–Crafts conditions results in O-acylation rather than para acylation,[16] and the resulting esters fail to undergo further reaction at the para position. Therefore, attention was turned to ethers of calix[4]arene in the hope that they would undergo electrophilic substitution at the para position. The methyl ether 14 was obtained in good yield by treatment of 13 with NaH in THF/DMF followed by CH₃I,[11] and the benzyl ether 21[18] was obtained in similar fashion with benzyl bromide. The trimethylsilyl ether 24[19] was obtained through the use of bis(trimethylsilyl)acetamide. Treatment of 14 with *N*-bromosuccinimide[20] produced the methyl ether of *p*-bromocalix[4]arene 15[21–23] in 90% yield. The benzyl ether 21 behaves in analogous fashion, furnishing the benzyl ether of *p*-bromocalix[4]-

(14) Gutsche, C. D.; Iqbal, M.; Stewart, D. S., unpublished results.
(15) Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* 1982, *104*, 2652.
(16) Gutsche, C. D.; Lin, L.-g., *Tetrahedron*, in press.
(17) (a) Nam, K. C., unpublished observations. (b) Shinkai, S.; Mori, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* 1984, 5315.
(18) In contrast to the methyl ether, the benzyl ether is conformationally fixed (on the NMR time scale) at room temperature and exists in a cone conformation, as evidenced by a pair of doublets arising from the methylene hydrogens.
(19) In contrast to the trimethylsilyl ether of *p*-tert-butylcalix[4]arene,[15] which exists in the cone conformation, 16 exists in the partial cone conformation. The tetrakis(trimethylsilyl)ether 24 forms with considerable difficulty, and from a reaction mixture that was refluxed for a shorter time it was possible to isolate a tris(trimethylsilyl) ether 25.
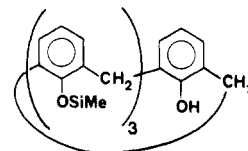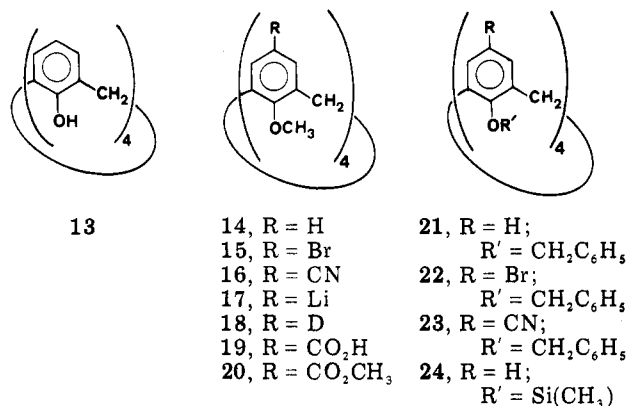

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(20) Djerassi, C. *Chem. Rev.* 1948, *43*, 271.
(21) Bromination of 14 with other reagents was less successful. With Br₂ in CS₂/CH₃CO₂H a mixture of five products was obtained. Heating 14 with Br₂ in CHCl₃/CH₃CO₂H and Fe metal for 20 h at 40 °C yielded a two-component mixture from which some 15 could be isolated, although in varying amounts. The accompanying low R_f impurities were not easily separated from 15. These showed strong OH stretching bands in the IR and are probably products of demethylation, presumably the result of the formation of FeBr₃ and its subsequent action as a Lewis acid catalyst. Demethylation has been observed with 14 in attempted Friedel–Crafts reactions.[16]
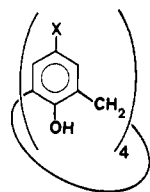(22) The *p*-bromo ether 15 is conformationally less flexible than the parent ether 14. At room temperature the ^{1}H NMR spectrum of 15 shows a well-resolved pattern of resonances arising from the methylene hydrogens that is commensurate with a partial cone conformation,[25] whereas the room temperature ^{1}H NMR spectrum of 14 shows a broad resonance characteristic of a more rapidly interconverting system; only at lower temperature does the spectrum of 14 change to the highly structured pattern.

arene in comparable yield. The trimethylsilyl ether **24**, on the other hand, gave a mixture of products that we think is the result of partial bromination and the cleavage of some of the trimethylsilyl ether linkages.

13

14, R = H;
15, R = Br
16, R = CN
17, R = Li
18, R = D
19, R = CO$_2$H
20, R = CO$_2$CH$_3$

21, R = H;
    R' = CH$_2$C$_6$H$_5$
22, R = Br;
    R' = CH$_2$C$_6$H$_5$
23, R = CN;
    R' = CH$_2$C$_6$H$_5$
24, R = H;
    R' = Si(CH$_3$)

Treatment of **15** with CuCN in refluxing *N*-methylpyrrolidinone[26,27] resulted in a three-component mixture from which the methyl ether of *p*-cyanocalix[4]arene **16** could be separated by chromatography. In similar fashion the benzyl ether **21** yielded the benzyl ether of *p*-cyanocalix[4]arene **23**. Conversion of the bromocalixarene **15** to the corresponding lithio compound **17** was achieved by treatment with *n*-butyllithium in THF for 1 h at −78 °C. That complete metal–halogen exchange had occurred was shown by hydrolyzing the product and obtaining the methyl ether of calix[4]arene (**14**) as the major product, accompanied by only very small amounts of two other materials. In similar fashion, deuterolysis of **17** yielded the tetradeuterio compound **18** as the major product, accompanied by small amounts of two other materials. The lithiation of the benzyl ether of *p*-bromocalix[4]arene **22** was also investigated; however, mixtures of products were obtained, and complete reaction was not achieved, possibly because of the precipitation of partially lithiated materials from the reaction mixture. Treatment of the tetralithio compound **17** with CO$_2$ produced a material that formed a thick, soapy solution in water from which a white powder could be obtained upon acidification. The spectral char-

acteristics of this product are commensurate with those expected for the methyl ether of *p*-carboxycalix[4]arene (**19**), but the broad melting range of the crude material was not significantly changed after recrystallization. Therefore, the carboxylic acid **19** was treated with diazomethane, and the three component mixture that was formed was chromatographed to yield a compound whose chemical and spectral properties are commensurate with structure **20**.

Synthesis of "Deep Cavity" Calixarenes. Failing to obtain *p*-phenylcalix[4]arene **1** directly from a phenol-formaldehyde condensation process, it was hoped that it might be possible to introduce the phenyl groups into the para positions of the calix[4]arene ring system. Our one attempt to achieve this, however, was unsuccessful when treatment of **14** with phenylzinc chloride in the presence of diisopropylaluminum hydride and Cl$_2$Pd[P(C$_6$H$_5$)$_3$]$_2$ in THF/ether[28] yielded only recovered starting material. Rather than continuing to pursue this route as a method for extending the length of the cavity of a calix[4]arene, attention was turned to the introduction of aroyl groups onto the para positions. This proved to be more successful. Treatment of **14** with benzoyl chloride and AlCl$_3$ results in complete para benzoylation, but, concomitantly, a certain amount of demethylation occurs which is followed by benzoylation of the resulting hydroxyl functions.[29] To obtain a pure sample of the methyl ether of *p*-benzoylcalix[4]arene **26** it is necessary to treat the crude product with aqueous base to hydrolyze the benzoates and then treat with CH$_3$I to remethylate the hydroxyl functions. Although this procedure afforded a 32% yield of crude product, crystallization produced only 5% of a pure sample with spectral and analytical characteristics commensurate with structure **26**. That the crude material contains more of **26**, however, is indicated by the isolation of the dimethyl ether of *p*-benzoylcalix[4]arene **30** in 22% yield from a reaction mixture in which the hydrolysis and remethylation steps were omitted. *p*-Anisoyl chloride proved to be slightly more effective than benzoyl chloride, producing a 58% yield of crude material from which a 9% yield of the methyl ether of *p*-anisoylcalix[4]arene **28** was isolated.

The conversion of the methyl ethers to the corresponding phenols proved to be rather difficult. Reaction of **26** with BBr$_3$[30] resulted in little or no demethylation, and trimethylsilyl iodide[31] or HBr/CH$_3$CO$_2$H gave a very complex mixture. However, when **26** was refluxed with a twofold excess of C$_2$H$_5$SNa in DMF for 3 h,[32] a product was obtained whose spectral characteristics are those expected for a compound of structure **27**. That the calix[4]arene structure has been retained is indicated by the temperature-dependent ^{1}H NMR spectrum which shows a singlet resonance arising from the methylene protons at ca. 50 °C and a pair of doublets at lower temperatures (coalescence temperature 33 °C). A similar treatment of **28** appears to result in complete demethylation, but the temperature-dependent ^{1}H NMR of the product shows only a pair of unsymmetrical humps at low temperature

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(23) Removal of the methyl groups of **15** was effected with BBr$_3$ at room temperature, affording *p*-bromocalix[4]arene **31** in 84% yield as a white powder. Crystallization from pyridine gave a material melting above 480 °C and possessing the correct empirical formula for **31**. It

31, X = Br
32, X = Cl

showed a temperature-dependent ^{1}H NMR pattern for the methylene hydrogens (coalescence temperature 2 °C), confirming the fact that the calix[4]arene structure remains intact during the demethylation. The high melting point of this material is significant because Moshfegh and co-workers[24] have reported the preparation of a compound with mp 239–242 °C to which they assigned the *p*-chlorocalix[4]arene structure **32**. It is highly unlikely that there would be a dramatic difference in melting point between the *p*-bromo and *p*-chloro compounds, and it must be concluded that the material reported by Moshfegh et al. is not a calixarene.

(24) Moshfegh, A. A.; Mazandarani, B.; Nahid, A.; Hakimelahi, G. H. *Helv. Chim. acta.* **1982**, *65*, 1229.

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

(26) Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522. Jones, T. H.; Blum, M. S. *Synth. Commun.* **1981**, *11*, 889.

(27) Newman, M. S.; Boden, H. *J. Org. Chem.* **1961**, *26*, 2525.

(28) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

(29) Methods for effecting benzoylation were studied in some detail. Using benzoyl chloride with AlCl$_3$ as the catalyst, incomplete benzoylation resulted when lower temperatures and/or shorter times were used, while higher temperatures and/or longer times resulted in even more extensive demethylation and decomposition. Benzoyl chloride with I$_2$ as the catalyst gave only recovered starting material. Demethylation rather than benzoylation occurred with benzoyl chloride and SnCl$_4$ or AlCl$_3$ in CH$_3$NO$_2$/tetrachloroethane. With benzoic acid and polyphosphoric acid at 90 °C only partial benzoylation was achieved, and when sulfolane was added as a cosolvent the extent of demethylation increased. Benzoic acid and HF gave only recovered starting material.

(30) Tashiro, M.; Yoshiya, H.; Fukata, G. *J. Org. Chem.* **1982**, *47*, 4425.

(31) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

(32) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327.
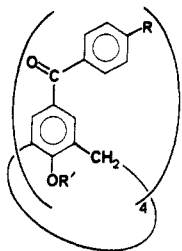
26, R = H; R' = CH₃
27, R = H; R' = H
28, R = OCH₃; R' = CH₃
29, R = OH; R' = H

30

rather than the pair of doublets that is characteristic of the calix[4]arene system. It is possible that this is due to intramolecular hemiketal formation resulting from the interaction of a pair of 4'-hydroxyl groups with a pair of carbonyl groups when the compound is in a "1,3-alternate" conformation, as illustrated by structure **33**. Space-filling molecular models indicate that **33** is a strain-free structure. The four methylene groups in **33** occur as two pairs of equivalent sets and could account for the observed NMR behavior.

33
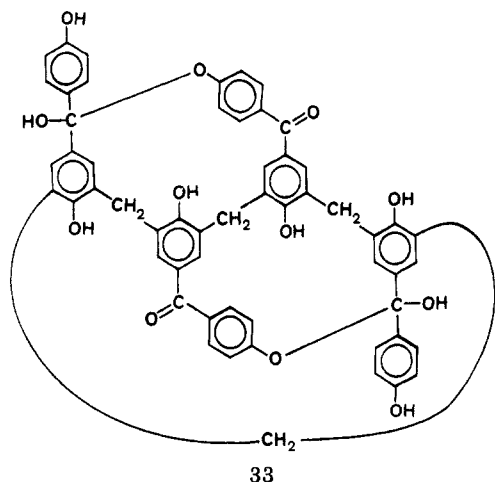
p-Phenylcalix[4]arene, an example of a deep cavity calixarene, has previously been synthesized by a convergent stepwise procedure,[9] but the yields are low; the product is difficult to obtain in amounts conducive to further synthetic elaboration. As an alternative to *p*-phenylcalix[4]arene, the syntheses of *p*-aroylcalix[4]arenes are described in this paper. It should be pointed out, however, that the shapes and conformational attributes of the *p*-aryl- and *p*-aroylcalix[4]arenes are quite different in certain respects. While both kinds of compounds experience the characteristic calix[4]arene conformational inversion, with the "cone" conformation being the preferred form in nonpolar solvents, the *p*-aroylcalix[4]arenes have additional conformational possibilities arising from rotation at the carbonyl group. Four of these are illustrated in Figure 1 and are designated as the "open calix" (structure A), "closed calix" (structure B), "spiral calix" (structure C), and "stacked" (structure D) conformations. The stacked conformation is particularly intriguing in that it aligns four aryl groups along an axis, allowing them the possibility of "communicating" with one another. It remains for a future study to elucidate the solid state and solution state con-

formational preferences of these compounds and to determine their complexation potentialities.

Experimental Section[33]

5,11,17,23,29,35-Hexaphenyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (3). A 34-g (0.20 mol) sample of *p*-phenylphenol was dissolved in 80 mL of 3 N NaOH/CH₃OH (0.24 mol) in a 250-mL round-bottomed flask equipped with a condenser. To this was added 46 mL of 37% formaldehyde (formalin), and the solution was refluxed for 1 h. The condenser was removed, and the solution was stirred at 110 °C for an additional 2 h, during which time most of the solvent evaporated to leave a viscous residue. The residue was cooled, acidified with 250 mL of 2 N HCl, and the yellow precipitate was collected by suction filtration, washed with water, and allowed to dry under suction overnight to yield 42 g of a yellow powder. A 28-g sample of this material was placed in a 1-L round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, and thermometer. To this were added, with stirring, 100 mL of diphenyl ether and 1.04 mL of 50% NaOH (0.020 mol; 0.15 equiv per mol of *p*-phenylphenol), and the solution was rapidly heated to 210–220 °C and held at this temperature for 2.5 h. The reaction mixture was cooled, 300 mL of ether was added, and the solution was stirred overnight. A tan precipitate was collected, triturated with 300 mL of boiling acetic acid for 1 h, washed with water, and dried under suction overnight. It was then extracted with 100 mL of hot CHCl₃, and the extract was subjected to flash chromatography (1:1 CHCl₃/hexanes as eluant) to give a white powder. This was recrystallized from CHCl₃/CH₃OH to give 3.57 g (10%) of **3** as a white powder: mp 408–410 °C; IR (KBr) 3200 cm⁻¹ (OH stretching); ¹H NMR (CDCl₃) δ 10.3 (s, 4, OH), 7.2–7.6 (m, 28, Ar H), 4.1 (s, 8, Ar CH₂Ar); ¹³C NMR (CDCl₃) δ 149.23, 140.75, 135.44, 128.66, 128.47, 127.59, and 127.00 (Ar), 32.65 (CH₂).
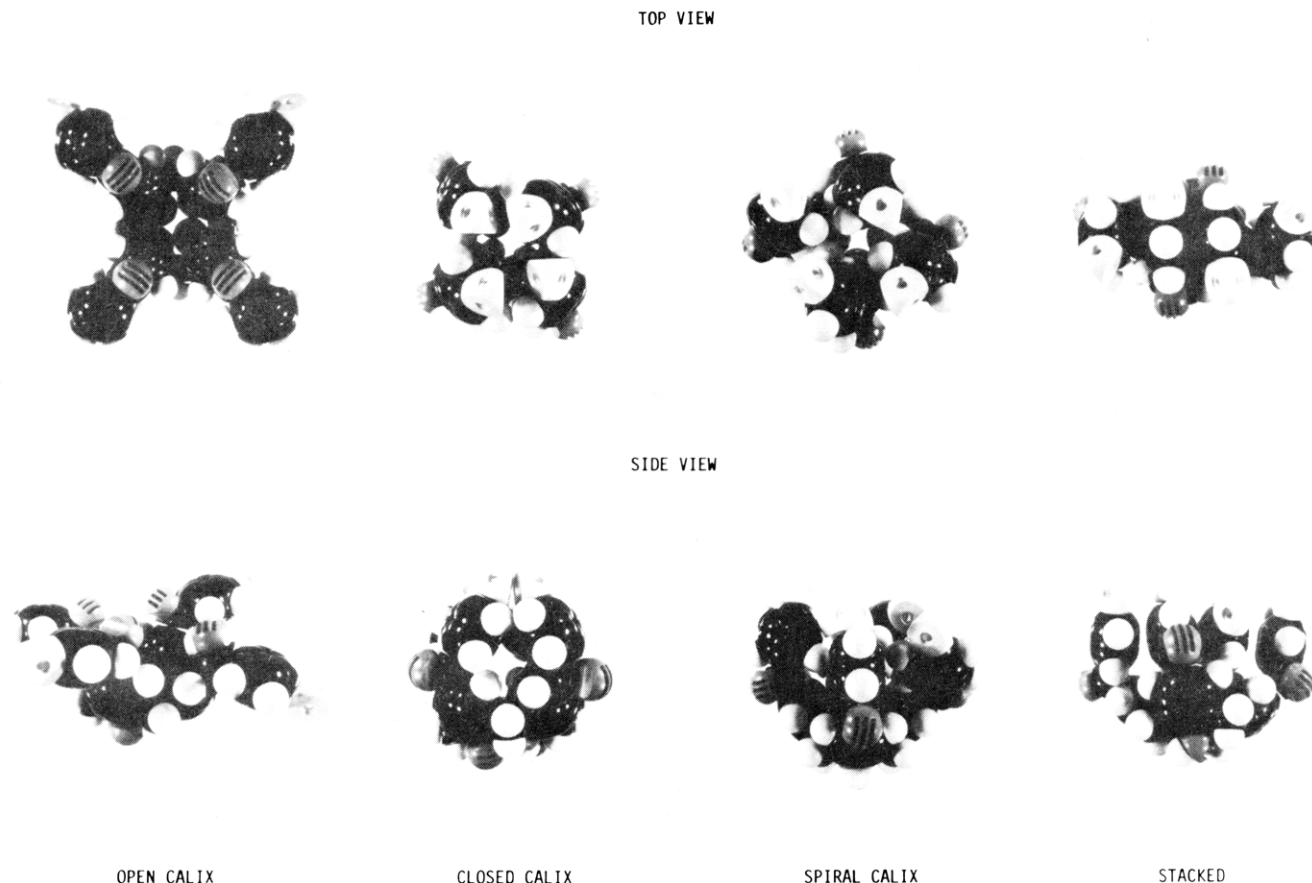
5,11,17,23,29,35,41,47-Octaphenyl-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (5). A 34-g (0.20 mol) sample of *p*-phenylphenol was treated in the same fashion as described above for the preparation of **2** except that 0.52 mL of 50% NaOH (0.01 mol; 0.075 equiv per mol of *p*-phenylphenol) was used prior to the heating in diphenyl ether. The crude product was triturated with boiling acetic acid and then with 300 mL of CHCl₃. The residue was extracted into hot pyridine, and the pyridine-soluble material was crystallized from pyridine/dioxane to give 2.5 g (7%) of material in the first crop, mp 421–423 °C, and 2.5 g (7%) in a second crop, mp 399–401 °C. The spectra of the two compounds were identical: IR (KBr) 3210 cm⁻¹ (OH stretching); ¹H NMR (pyridine-*d*₅) δ 10.0 (s, 8, OH), 7.2–7.7 (m, 56, Ar H), 4.4 (s, 16, ArCH₂Ar).

Condensation of *p*-Phenylphenol and Formaldehyde via the Petrolite Procedure. A slurry of 68 g (0.40 mol) of *p*-phenylphenol, 18 g (0.60 mol) of paraformaldehyde, 0.80 mL (0.008 mol) of 10 N KOH in 300 mL of xylene was placed in a 500-mL round-bottomed flask equipped with a condenser and a Dean–

(33) 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) using a 500 °C thermometer calibrated against a thermocouple. Infrared (IR) spectra were determined on a Perkin-Elmer 283B spectrometer. Proton nuclear magnetic resonance spectra (¹H NMR spectra) were recorded on a Hitachi Perkin-Elmer R-24B spectrometer or a JEOL FX-100 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Osmometric molecular weight determinations[34] were made on a Wescan Model 232A apparatus using concentrations of ca. 10⁻³ M in CHCl₃ solution. Microanalyses were carried out by Industrial Testing Laboratories, St Louis, MO, and MicAnal Laboratories, Tucson, AZ. Thin-layer chromatographic analyses were carried out on silica gel plates (absorbant thickness 250 μm). Flash chromatography[35] was carried out with E. Merck silica gel (230–400 mesh ASTM) on columns of 80-mm diameter (for more than 5 g of sample), 50-mm diameter (for 1–5 g of sample), and 30-mm diameter (for less than 1 g of sample)) filled to a height of 6 in. Elution rates were 2 in./min; fractions of 50 mL were collected from the two larger columns and of 20–30 mL from the smallest column. Analytical samples were dried for at least 36 h at 140 °C and 1–2 mm of pressure. In a number of instances, however, solvent of crystallization was retained, considerably affecting the elemental analyses. In such cases best fits between the analytical values and appropriate fractional increments of solvent were sought, leading sometimes to seemingly adventitious amounts of solvent.

(34) We are indebted to Alice Gutsche for carrying out the osmometric molecular weight determinations.

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

TOP VIEW

SIDE VIEW

OPEN CALIX   CLOSED CALIX   SPIRAL CALIX   STACKED

⬛ represents the 4' substituents (H in **27**, OH in **29**) and are included
— in the molecular models to highlight the conformational differences

Figure 1. Space-filling molecular models of the cone conformation of a *p*-aroylcalix[4]arene in four conformations involving rotation around the carbonyl group.

Stark water trap. The mixture was stirred, heated rapidly to reflux, and refluxed for 4 h. After $^1/_2$ h the reactants had completely dissolved, and after 1 h a precipitate began to form. The precipitate obtained from the cooled reaction mixture was washed with 50 mL of xylene and dried to yield 29.2 g (43%) of a white powder. After an 18-h trituration with THF in a Soxhlet apparatus, 17.8 g of THF-insoluble material remained, mp 360–370 °C. Recrystallization from pyridine/dioxane yielded 3.2 g (4.4% overall) of **5** as a white powder; mp 422–424 °C. The THF-soluble fraction was a mixture of materials from which no pure compounds were isolated.

5,11,17,23,29,35-Hexaphenyl-37,38,39,40,41,42-hexamethoxycalix[6]arene (6). A 0.165-g (0.15 mmol) sample of the cyclic hexamer **3** was dissolved in 13 mL of dry THF and 1 mL of DMF, treated with 1.25 g (8.8 mmol) of CH$_3$I and 0.11 g (4.4 mmol) of NaH, and refluxed for 6 h. The crude product was recrystallized twice from CHCl$_3$/CH$_3$OH to yield 0.093 g (53%) of **6** as colorless microcrystals: mp 289–290 °C; ^{1}H NMR (CDCl$_3$) δ 7.2 (br s, 42, ArH), 4.0 (s, 12, ArCH$_2$Ar), 3.4 (s, 18, OCH$_3$); ^{13}C NMR (CDCl$_3$) δ 155.95, 140.85, 136.22, 134.85, 128.27, 127.73, 126.86, and 126.71 (Ar), 60.23 (OCH$_3$), 30.75 (CH$_2$); osmometric M_r (CHCl$_3$, 37 °C) 1180 (calcd 1178). Anal. Calcd for C$_{84}$H$_{72}$O$_6$: C, 85.68; H, 6.11. Found: C, 86.20; H, 6.07.

5,11,17,23,29,35-Hexaphenyl-37,38,39,40,41,42-hexakis(allyloxy)calix[6]arene (7). Following the procedure described above, a 0.200-g sample of **3** was treated with allyl bromide to yield 0.15 g (61%) of **7** as colorless microcrystals after two recrystallizations from CHCl$_3$/CH$_3$OH: mp 286–288 °C; ^{1}H NMR (CDCl$_3$) δ 7.1–7.4 (m, 42, Ar H), 4.2–6.0 (br m, 42, allyl), 4.0 (s, 12, ArCH$_2$Ar); ^{13}C NMR (CDCl$_3$, 50 °C) δ 154.78, 140.65, 136.46, 134.70, 133.24, 128.66, 127.98, 126.71, and 118.23 (Ar and C=C), 74.08 (CH$_2$C=C), 31.09 (CH$_2$); osmometric M_r (CHCl$_3$, 37 °C) 1340 (calcd 1334); Anal. Calcd for C$_{96}$H$_{84}$O$_6$: C, 86.45; H, 6.30. Found: C, 86.13; H, 6.03.

5,11,17,23,29,35-Hexaphenyl-37,38,39,40,41,42-hexaacetoxycalix[6]arene (8). A 0.500-g (0.46 mmol) sample of **3** was dissolved in 25 mL of dry pyridine, treated with 0.430 g (5.5 mmol) of acetyl chloride, and stirred overnight at room temperature to yield a crude product as a yellow solid, which was recrystallized three times from acetic acid to afford 0.24 g (39%) of **8** as a white powder: mp 359–362 °C (softening at 350 °C); ^{1}H NMR (CDCl$_3$) δ 7.30 (br s, 42, Ar H), 3.64 (br s, 12, ArCH$_2$Ar), 1.80 (br s, 12, COCH$_3$); ^{13}C NMR (CDCl$_3$) δ 168.62 (C=O), 140.06, 139.38, 132.75, 128.66, 127.98, 127.10, and 125.93 (Ar), 31.48 (CH$_2$), 19.88 (CH$_3$); osmometric M_r (CHCl$_3$, 37 °C) 1330 (calcd 1344); Anal. Calcd. for C$_{90}$H$_{72}$O$_{12}$: C, 80.34; H, 5.39. Found: C, 79.94; H, 5.42.

5,11,17,23,29,35,41,47-Octaphenyl-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene (9). A 1.0-g (0.06 mmol) sample of the cyclic octamer **5** was methylated as described above for the cyclic hexamer to give a light yellow powder after one recrystallization from CHCl$_3$/CH$_3$OH. A second recrystallization from acetic acid yielded 0.5 g (46%) of **9** as a fluffy, white powder: mp 210–212 °C; ^{1}H NMR (CDCl$_3$) δ 7.17 (br s, 56, Ar H), 4.1 (s, 16, ArCH$_2$Ar), 3.45 (s, 24, OCH$_3$); ^{13}C NMR (CDCl$_3$) δ 156.15, 140.65, 136.65, 134.22, 128.47, 127.69, and 126.71 (Ar), 60.72 (OCH$_3$), 30.59 (CH$_2$); Anal. Calcd for C$_{112}$H$_{96}$O$_8$: C, 85.68; H, 6.11. Found: C, 85.39; H, 6.22.

5,11,17,23,29,35,41,47-Octaphenyl-49,50,51,52,53,54,55,56-octakis[(trimethylsilyl)oxy]calix[8]arene (10). A 0.500-g (0.34 mmol) sample of **5** was dissolved in 15 mL of dry CH$_3$CN, treated with 1.10 g (5.5 mmol) of bis(trimethylsilyl)acetamide, and refluxed for 10 h in an inert atmosphere. The crude white product was recrystallized from hexane to give 0.34 g (49%) of **10** as very small, colorless crystals: mp 289–291 °C; ^{1}H NMR (benzene-d_6) δ 6.8–7.9 (m, 56, Ar H), 4.25 (s, 16, ArCH$_2$Ar), 0.18 (s, 72, OSi(CH$_3$)$_3$); ^{13}C NMR (benzene-d_6) δ 151.98, 141.50, 135.36, 131.00, and 126.54 (Ar), 33.21 (CH$_2$), 1.19 (Si(CH$_3$)$_3$); Anal. Calcd for C$_{104}$H$_{144}$O$_8$Si$_8$: C, 75.54; H, 7.13. Found: C, 75.61; H, 7.45.

5,11,17,23,29,35,41,47-Octaphenyl-49,50,51,52,53,54,55,56-octaacetoxycalix[8]arene (11). A 0.500-g (0.34 mmol) sample of **5** was treated with acetyl chloride and pyridine as described above to yield 0.60 g (97%) of a crude yellow product that showed three spots upon TLC analysis. Recrystallization from benzene/ethanol or from $CHCl_3$/ethanol failed to yield a pure material, so flash chromatography was used to obtain 0.09 g (30%) of **11** as a pale yellow powder: mp 230–265 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.23–7.67 (m, 56, Ar H), 3.76 (s, 8, $ArCH_2Ar$), 1.84 (s, 12, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 168.44 (C=O), 147.09, 140.12, 139.18, 132.52, 128.72, 127.31, and 126.96 (Ar), 32.01 (CH_2), 20.02 (CH_3); osmometric M_r ($CHCl_3$, 37 °C), 1760 (calcd 1792). Anal. Calcd for $C_{120}H_{96}O_{16}\cdot C_2H_5OH$: C, 79.65; H, 5.55. Found: C, 79.76; H, 5.64.

25,26,27,28-Tetrahydroxycalix[4]arene (13) was obtained by $AlCl_3$-catalyzed removal of the *tert*-butyl groups from *p-tert*-butylcalix[4]arene as described elsewhere[15] and obtained as colorless crystals with mp 312–315 °C (lit.[15] 315–318 °C).

25,26,27,28-Tetramethoxycalix[4]arene (14) was obtained by methylation of **13** as previously described[25] and obtained in 64% yield as white needles melting at 234–236 °C (lit.[25] mp 234–235 °C).

5,11,17,23-Tetrabromo-25,26,27,28-tetramethoxycalix[4]arene (15). (A) Via *N*-Bromosuccinimide. To a solution of 2.00 g (4.20 mmol) of **14** in 100 mL of methyl ethyl ketone was added 5.01 g (37 mmol) of *N*-bromosuccinimide, and the yellow solution was stirred at room temperature for 24 h. The mixture was then stirred with 75 mL of 10% $NaHSO_3$ and worked up to yield 2.95 g (95%) of a light yellow powder. Recrystallization from $CHCl_3$/CH_3OH yielded 2.73 g (82%) of white crystals: mp 269–270 °C; ^{1}H NMR ($CDCl_3$) δ 7.36, 7.24, 7.20, 7.01, 6.85, and 6.52 (m, 8, Ar H), 4.31, 4.18, 4.05, 3.91, 3.75, 3.66, 3.55, and 3.04 (m, 20, OCH_3 and $ArCH_2Ar$); ^{13}C NMR (Me_2SO-d_6, 150 °C) δ 156.13, 134.83, 130.49, and 113.38 (Ar), 59.29 (OCH_3), 30.87 (CH_2); Anal. Calcd for $C_{32}H_{28}O_4Br_4$: C, 48.27; H, 3.55. Found: C, 48.29; H, 3.37.

(B) Via Bromine. A 0.25-g (0.53 mmol) sample of **14** in 20 mL of $CHCl_3$ to which a catalytic amount of Fe metal was added was treated, with stirring, with 0.27 mL (5.3 mmol) of Br_2 in 5 mL of acetic acid over a period of 25 m. After an additional 35 m the reaction was quenched by pouring it into 50 mL of 10% $NaHSO_3$. The crude product was recrystallized three times from $CHCl_3$/CH_3OH to give 0.19 g (50%) of a pale yellow powder, mp 249–251 °C, possessing spectral properties identical with those of the material obtained via *N*-bromosuccinimide. It was not possible to consistently reproduce the yield reported above, and sometimes the product contained as many as five components.

5,11,17,23-Tetrabromo-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (22). 25,26,27,28-Tetrakis(benzyloxy)calix[4]arene was prepared by a published procedure[25] and obtained in 65% yield as colorless needles, mp 135–136 °C (lit.[25] mp 135–136 °C). Bromination of a 4.7-g sample with *N*-bromoacetamide by the procedure described above yielded a crude product that was crystallized from acetone/CH_3OH to yield 6.0 g (91%) of a light yellow powder: mp 211–215 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (s, 20, Ar H), 6.64 (s, 8, Ar H), 4.83 (s, 8, OCH_2Ar), 4.04 and 3.86 (s, 4, $ArCH_2Ar$), 2.81 and 2.66 (s, 4, $ArCH_2Ar$); ^{13}C NMR ($CDCl_3$) δ 154.15, 136.75, 131.00, 129.83, and 115.50 (Ar), 76.71 (OCH_2Ar), 30.99 ($ArCH_2Ar$); Anal. Calcd. for $C_{52}H_{44}O_4Br_4$: C, 61.11; H, 4.00. Found: C, 61.43; H, 4.07.

25,26,27,28-Tetramethoxymethylcalix[4]arene. A solution of 0.53 g (1.25 mmol) of calix[4]arene in 30 mL of dry THF and 5 mL of DMF was treated with 0.29 g (12 mmol) of NaH and 0.95 mL (12.5 mmol) of chloromethyl methyl ether. The reaction mixture was refluxed 5.5 h and worked up to give colorless needles after recrystallization from CH_3OH: mp 216–218 °C; ^{1}H NMR ($CDCl_3$) δ 7.3–6.2 (m, 12, Ar H), 5.2–3.1 (m, 28, OCH_3 and $ArCH_2Ar$); ^{13}C NMR ($CDCl_3$) δ 154.90, 153.91, 143.80, 136.75, 133.83, 133.05, 132.97, 130.02, 128.95, 128.47, 122.81, 122.32, and 122.13 (Ar), 100.88, 100.20, 99.61, 98.83, and 98.15 ($ArCH_2O$), 58.09, 57.50, 56.82, and 56.04 (OCH_3), 36.06, 35.48, 32.07, 31.48, and 30.90 (CH_2); Anal. Calcd for $C_{36}H_{40}O_8\cdot^1/_2CH_3OH$: C, 70.62; H, 6.81. Found: C, 70.72; H, 6.35.

5,11,17,23-Tetracyano-25,26,27,28-tetramethoxycalix[4]arene (16). A mixture of 0.500 g (0.64 mmol) of **15** and 0.400 g (4.5 mmol) of CuCN in 15 mL of *N*-methylpyrrolidinone contained in a 25-mL pear-shaped flask was refluxed, with stirring, in a nitrogen atmosphere for 3.5 h. The reaction mixture, which turned brown at 180 °C and became darker as the reaction proceeded, was cooled to 100 °C and poured into a solution of 1.1 g of $FeCl_3\cdot H_2O$, 5 mL of concentrated HCl, and 25 mL of H_2O. It was stirred at 100–110 °C for 1 h, during which time the solution turned from brown to green and deposited a white precipitate. The precipitate was collected and recrystallized twice from $CHCl_3$/hexane to yield 0.210 g (58%) of white needles: mp 327–329 °C; IR (KBr) 2222 cm^{-1} (CN stretching); ^{1}H NMR ($CDCl_3$) δ 7.59, 7.47, 7.25, 7.07, and 6.67 (m, 8, Ar H), 4.30–3.05 (br m, 20, OCH_3 and $ArCH_2Ar$); ^{13}C NMR ($CDCl_3$) δ 161.49, 161.15, 160.54, 137.13, 135.49, 134.67, 134.19, 133.37, 132.97, 132.62, and 132.28 (Ar), 118.15, 107.58, 106.55, and 105.87 (CN), 61.64, 60.35, and 60.00 (OCH_3), 34.75, 29.84 (CH_2); ^{13}C NMR (Me_2SO-d_6, 150 °C) δ 160.61, 134.20, 132.39, and 117.72 (Ar), 104.90 (CN), 59.92 (OCH_3), 37.01 (CH_2); osmometric M_r ($CHCl_3$, 37 °C) 630 (calcd 585). Anal. Calcd for $C_{36}H_{28}O_4N_4$: C, 74.48; H, 4.83; N, 9.66. Found: C, 74.35; H, 4.80; N, 9.59.

Lithiation and Deuteration of 15. A solution of 0.500 g (0.64 mmol) of **15** in 50 mL of dry, deoxygenated THF in an argon atmosphere was cooled to −78 °C and treated with 2.4 mL (3.8 mmol) of *n*-butyllithium in hexane. The reaction mixture was maintained at −78 °C for an additional hour, treated with 5 mL of D_2O, and warmed to room temperature. Recrystallization of the product from CH_2Cl_2/C_2H_5OH yielded 0.27 g (90%) of a light yellow powder: mp 210–228 °C; ^{1}H NMR (Me_2SO-d_6, 150 °C) δ 6.9 (s, 8, Ar H), 3.6 (s, 8, $ArCH_2Ar$), 3.5 (s, 12, OCH_3); ^{13}C NMR (Me_2SO-d_6) δ 157.09, 133.34, 130.24, 127.78, and 121.05 (Ar), 59.27 (OCH_3), 31.49 (CH_2).

5,11,17,23-Tetracarbomethoxy-25,26,27,28-tetramethoxycalix[4]arene (20). A 0.500-g sample of **15** was lithiated as described above and then treated with gaseous CO_2, bubbled through the solution for 2 h. When the reaction mixture was worked up at this point a material could be obtained in 68% yield as a white powder after recrystallization from ethyl acetate/CH_3OH: mp 383–386 °C (some shrinking at 375 °C); IR (KBr) 1690 cm^{-1} (C=O stretching); ^{1}H NMR (Me_2SO-d_6 at 150 °C) δ 8.46 (br s, 4, CO_2H), 7.82 (br s, 8, Ar H), 4.29 (br s, 8, $ArCH_2Ar$), 3.98 (s, 12, OCH_3); ^{13}C NMR (Me_2SO-d_6 at 150 °C) δ 166.17 (C=O), 160.66, 133.03, 129.71, and 124.45 (Ar), 59.34 (OCH_3), 37.80 (CH_2). However, the elemental analysis was low in the carbon value, and a subsequent TLC analysis indicated the presence of impurities. Therefore, in another experiment the crude product of carbonation was directly treated with 100 mL of ethereal diazomethane[36] to yield a crude product as a white solid. TLC analysis of this material indicated the presence of three components, and flash chromatography (3:1 hexane/acetone as eluant) yielded (fractions 23–41) a component with R_f 0.29 from which 89 mg (20%) of **20** was obtained as white microcrystals: mp 328–331 °C; IR (KBr) 1710 cm^{-1} (C=O stretching); ^{1}H NMR (Me_2SO-d_6, 150 °C) δ 7.59 (s, 8, Ar H), 3.84 (s, 20, OCH_3 and $ArCH_2Ar$), 3.66 (s, 12, CO_2CH_3). Anal. Calcd for $C_{40}H_{40}O_{12}$: C, 67.41; H, 5.62. Found: C, 67.38; H, 6.01.

25,26,27,28-Tetrakis(benzyloxy)calix[4]arene (21). Following a literature procedure,[25] a solution of 4.00 g (9.4 mmol) of **13** in 150 mL of dry THF and 30 mL of DMF was treated with 2.00 g (81 mmol) of NaH and 11 mL (94 mmol) of benzyl bromide, and the solution was refluxed for 4.5 h. The crude yellow oil was dissolved in 70 mL of $CHCl_3$, which was extracted three times with 70 mL of H_2O, dried, and evaporated to yield an orange colored product that was recrystallized two times from isopropyl alcohol to produce 4.7 g (65%) of colorless needles, mp 135–136 °C (lit.[25] 135–136 °C).

5,11,17,23-Tetrabromo-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (22). A solution of 4.70 g (6.0 mmol) of **21** and 8.3 g (60 mmol) of *N*-bromoacetamide in 200 mL of methyl ethyl ketone was stirred for 17 h at room temperature in an atmosphere of nitrogen. The reaction mixture was then treated with 100 mL of 10% $NaHSO_3$, the two-layered system was stirred for 1 h, and the organic layer was separated and worked up to yield 6.0 g (91%) of **22** as a pale yellow powder after recrystallization from acetone/CH_3OH: mp 213–215 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (s, 20, Ar H), 6.64 (s, 8, Ar H), 4.83 (s, 8, OCH_2Ar), 4.04 and 3.86 (d, 4,

(36) Moore, J. A.; Reed, D. E. *Org. Synth.* **1961**, *41*, 16.

ArCH$_2$Ar), 2.81 and 2.66 (d, 4, ArCH$_2$Ar); ^{13}C NMR (CDCl$_3$) δ 154.15, 136.75, 131.00, 129.83, and 115.50 (Ar), 76.71 (OCH$_2$Ar), 30.99 (CH$_2$). Anal. Calcd for C$_{56}$H$_{44}$O$_4$Br$_4$: C, 61.11; H, 4.00. Found: C, 61.43; H, 4.07.

5,11,17,23-Tetracyano-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (23). A solution of 1.18 g (1.07 mmol) of **22** and 0.80 g (9.00 mmol) of CuCN in 35 mL of *N*-methylpyrrolidinone was refluxed in an atmosphere of argon for 3 h. The brown solution was poured into a solution of 1.33 g of FeCl$_3$·6H$_2$O in 40 mL of 3 N HCl and stirred at 80 °C for 1 h. The beige precipitate was separated and crystallized from toluene to yield 0.500 g (53%) of **23** as colorless needles: mp 310.5–312 °C; IR (KBr) 2214 cm^{-1} (CN stretching); ^{1}H NMR (CDCl$_3$) δ 7.14–7.39 (m, 20, Ar H), 6.90 (s, 8, Ar H), 4.98 (s, 8, OCH$_2$Ar), 4.13 and 3.99 (d, 4, ArCH$_2$Ar), 2.92 and 2.78 (d, 4, ArCH$_2$Ar); ^{13}C NMR (CDCl$_3$) δ 158.48, 136.09, 135.41, 132.27, 129.74, 128.92, 128.45, 118.00, and 107.02 (Ar and CN), 77.26 (OCH$_2$Ar), 30.71 (CH$_2$). Anal. Calcd for C$_{60}$H$_{44}$O$_4$N$_4$: C, 81.45; H, 4.98; N, 6.33. Found: C, 81.73; H, 4.92; N, 6.25.

25,26,27,28-Tetrakis[(trimethylsilyl)oxy]calix[4]arene (24). A solution of 1.06 g (2.50 mmol) of calix[4]arene **13** and 3.05 g (3.70 mmol) of bis(trimethylsilyl)acetamide in 30 mL of acetonitrile was refluxed in an atmosphere protected from moisture for 6 h. A TLC analysis of the product indicated the presence of two components, so an additional 2 mL of bis(trimethylsilyl)acetamide and 40 mL of acetonitrile were added, and the solution was refluxed an additional 3 h. Filtration of the cooled solution yielded 0.51 g (29%) of **24** as a fluffy white powder: mp 221–223 °C (gas released from 125–140 °C); ^{1}H NMR (CDCl$_3$) δ 7.03, 6.96, 6.88, 6.75, 6.68, 6.11, and 5.98 (m, 12, Ar H), 4.02 and 3.86 (d, 4, ArCH$_2$Ar), 3.50 and 2.84 (d, 4, ArCH$_2$Ar), 0.24 and 0.14 (d, 36, Si(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$) δ 152.00, 149.62, 135.24, 131.63, 130.81, 130.22, 128.95, 128.71, 128.42, 120.72, 119.89, and 119.60 (Ar H), 35.33 and 31.43 (CH$_2$), 1.36 and 0.87 (CH$_3$).

25,26,27-Tris[(trimethylsilyl)oxy]-28-hydroxycalix[4]arene (25). A solution of 0.53 g (1.25 mmol) of **13** and 0.203 g (10 mmol) of bis(trimethylsilyl)acetamide in 15 mL of acetonitrile was refluxed for 6 h in an atmosphere protected from moisture. The reaction mixture was cooled, and the solvent was removed to leave 0.64 g (80%) of a white powder. Recrystallization from toluene yielded **25** as a white, fluffy powder: mp 254–256 °C; ^{1}H NMR (CDCl$_3$) δ 6.90, 6.84, 6.78, 6.58, and 5.94 (m, 12, Ar H), 4.27, 4.14, 4.07, 3.92, 3.02, 2.88, and 2.74 (m, 8, ArCH$_2$Ar), 3.34 (s, 4, OH), 0.15 and 0.00 (s, 27, Si(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$) δ 153.42, 149.91, 135.78, 132.12, 131.14, 131.00, 129.49, 129.34, 129.25, 128.37, 128.09, 127.93, 127.73, 127.54, 127.30, 121.10, 120.77, 120.69, and 119.35 (Ar), 32.06 and 31.87 (CH$_2$), 1.02 and 0.39 (CH$_3$). Anal. Calcd for C$_{37}$H$_{48}$O$_4$Si$_3$: C, 69.34; H, 7.50. Found: C, 69.33; H, 7.63.

5,11,17,23-Tetrabenzoyl-25,26,27,28-tetramethoxycalix[4]arene (26). A solution of 1.20 g (2.5 mmol) of 25,26,27,28-tetramethoxycalix[4]arene (**14**) in 25 mL of CH$_2$Cl$_2$ was cooled to −46 °C in a dry ice–cyclohexanone bath and treated, dropwise, over a period of 40 min with a solution of 2.00 g (15 mmol) of AlCl$_3$ and 8.50 g (60 mmol) of benzoyl chloride in 25 mL of CH$_2$Cl$_2$. The cooling bath was removed, and the reaction mixture was stirred at 0 °C for 29 h and then at room temperature for 24 h. The reaction was quenched by stirring overnight with 100 mL of 1 N NaOH. The organic layer was separated, washed, and evaporated to give a yellow oil, which was redissolved in 40 mL of THF and 30 mL of ethanol. This was treated with 2.5 mL of 50% NaOH, and the solution was refluxed for 4 h. Sometimes a precipitate formed when the base was added or after ca. 1 h of refluxing; it can be redissolved by adding ca. 5 mL of H$_2$O. The reaction mixture was cooled, poured into 100 mL of cold 1 N HCl, and stirred for 30 m. The oily solution was extracted twice with 75 mL of CH$_2$Cl$_2$, the solvent was removed, and the residue was dissolved in 100 mL of THF and 25 mL of DMF and treated with 5.68 g (40 mmol) of CH$_3$I and 0.96 g (40 mmol) of NaH. After refluxing for 6 h the reaction mixture was worked up to yield a a yellow oil, which upon trituration with CH$_3$OH yielded 0.72 g (32%) of a yellow powder. TLC analysis of this material (3:1 hexane/acetone as eluant) indicated the presence of three major components (R_f 0.36, 0.28, and 0.22). Flash chromatography using 3:1 hexane/acetone as eluant yielded 0.110 g (5%) of **26** as the R_f 0.22 material: mp 302–304 °C; IR (KBr) 1652 cm^{-1} (C=O stretching); ^{1}H NMR (CDCl$_3$) δ 7.2–6.9 (br m, 28, Ar H), 4.0–3.2 (br m, 20, ArCH$_2$Ar and OCH$_3$); ^{13}C NMR (CDCl$_3$) δ 209.38 and

195.81 (C=O), 161.47, 161.06, 136.95, 136.66, 133.56, 132.86, 132.04, 131.57, 131.34, 130.23, 129.64, 128.24, and 127.77 (Ar), 61.73 and 59.56 (OCH$_3$), 35.98 and 30.54 (CH$_2$). Anal. Calcd for C$_{60}$H$_{48}$O$_8$·^{1}/$_2$CH$_2$Cl$_2$: C, 77.36; H, 5.23. Found: C, 77.37; H, 5.29.

5,11,17,23-Tetrabenzoyl-25,26,27,28-tetrahydroxycalix[4]arene (27). A mixture containing 0.13 g (0.15 mmol) of **26**, 0.11 g (1.75 mmol) of C$_2$H$_5$SH, and 0.042 g (1.75 mmol) of NaH in 13 mL of DMF was refluxed for 3 h in an atmosphere of nitrogen. The reaction mixture, which became dark brown after heating for 1 h, was cooled, poured into 50 mL of 4 N HCl, and stirred for 2 h. The beige precipitate was collected by filtration, washed with H$_2$O, dried, and recrystalized three times from ethyl acetate to yield 0.05 g (40%) of **27** as pale tan microcrystals: mp 332–334 °C (some shrinking at 181 and 201–206 °C); IR (KBr) 3280 (OH stretching), 1660 and 1648 cm^{-1} (C=O stretching); ^{1}H NMR (CDCl$_3$) δ 10.1 (br s, 4, OH), 7.8–7.4 (m, 28, Ar H), 4.1 (br s, 8, ArCH$_2$Ar); ^{13}C NMR (CDCl$_3$) δ 194.82 (C=O), 152.47, 137.43, 132.34, 132.11, 129.83, 128.37, and 127.78 (Ar H), 31.37 (CH$_2$). Anal. Calcd for C$_{56}$H$_{40}$O$_8$: C, 80.00; H, 4.76. Found: C, 79.67; H, 4.95.

5,11,17,23-Tetraanisoyl-25,26,27,28-tetramethoxycalix[4]arene (28). A 1.20-g (2.5 mmol) sample of 25,26,27,28-tetramethoxycalix[4]arene (**14**) was treated with 2.0 g (15 mmol) of AlCl$_3$ and 8.11 g (60 mmol) of *p*-anisoyl chloride in the manner described above for the benzoylation of **14**. The crude product, after hydrolysis and remethylation, amounted to 1.46 g (57%) of a white powder which was shown by TLC analysis to contain two major components. Flash chromatography followed by recrystallization yielded 0.23 g (9%) of **28** as a colorless powder: mp 194–197 °C; IR (KBr) 1650 cm^{-1} (C=O stretching); ^{1}H NMR (CDCl$_3$) δ 7.3–6.4 (m, 24, Ar H), 4.5–3.1 (m, 32, OCH$_3$ and ArCH$_2$Ar); ^{13}C NMR (CDCl$_3$) δ 194.53 (C=O), 162.30, 160.60, 157.44, 136.43, 133.81, 133.16, 132.40, 132.11, 131.82, 131.00, 130.35, 129.59, 129.30, 129.13, 128.83, 123.04, 121.81, and 112.74 (Ar), 60.91, 59.63, 59.10, and 55.30 (OCH$_3$), 35.81 and 30.43 (CH$_2$). Anal. Calcd for C$_{64}$H$_{56}$O$_{12}$: C, 75.59; H, 5.51. Found: C, 75.72; H, 5.41.

5,11,17,23-Tetrakis(4-hydroxybenzoyl)-25,26,27,28-tetrahydroxycalix[4]arene (29). A 0.20-g (0.20 mmol) sample of **28** was treated with 0.20 g (3.2 mmol) of C$_2$H$_5$SH and 0.075 g (3.2 mmol) of NaH as described above for the preparation of **27**. The crude product was recrystallized two times from acetone/benzene to yield 0.06 g (28%) of a white powder, mp ca. 216 °C, which showed a single spot on TLC analysis (R_f 0.24 with 1.5:1 hexane/acetone as eluant).

5,11,17,23-Tetrabenzoyl-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (30). A solution of 0.24 g (1.25 mmol) of 25,26,27,28-tetramethoxycalix[4]arene (**14**) in 15 mL of CH$_2$Cl$_2$ was cooled to 0 °C and treated dropwise with a solution of 0.32 g (2.4 mmol) of AlCl$_3$ and 0.34 g (2.4 mmol) of benzoyl chloride in 10 mL of CH$_2$Cl$_2$. The solution was warmed to room temperature, stirred for 24 h, and poured into 50 mL of cold water and stirred for 1 h. The organic layer was separated, washed with 2–25 mL portions of NaHCO$_3$, dried, and evaporated to yield a white powder. Fractional recrystallization from acetone/CH$_3$OH produced 0.100 g (22%) of **30** in the first two fractions as a white powder: mp 294–296 °C; IR (KBr) 3280 (OH stretching), 1650 cm^{-1} (C=O stretching); ^{1}H NMR (CDCl$_3$) δ 8.62 (s, 2, OH), 6.85–7.78 (m, 28, Ar H), 4.38 and 4.25 (s, 4, ArCH$_2$Ar), 3.54 and 3.41 (s, 4, ArCH$_2$Ar), 4.00 (s, 12, OCH$_3$); ^{13}C NMR (CDCl$_3$) δ 195.62 (C=O), 157.67, 153.17, 145.80, 132.28, 131.60, 129.69, 128.73, 128.18, and 125.59 (Ar), 63.76 (OCH$_3$), 31.13 (CH$_2$).

5,11,17,23-Tetraacetyl-25,26,27,28-tetramethoxycalix[4]arene (20). A solution of 1.2 g (2.5 mmol) of 25,26,27,28-tetramethoxycalix[4]arene (**14**) in 60 mL of CH$_2$Cl$_2$ was cooled to −10 °C and treated dropwise with a solution of 2.05 g (15 mmol) of AlCl$_3$ and 3.5 mL (50 mmol) of acetyl chloride in 50 mL of CH$_2$Cl$_2$. The mixture was warmed to room temperature, stirred for 3 h, and worked up to give a crude white product which was shown by TLC analysis to contain three major components. Flash chromatography yielded 0.47 g (29%) of 5,11,17,23-tetraacetyl-25,26,27,28-tetramethoxycalix[4]arene as a white powder: mp 228–246 °C; IR (KBr) 1677 cm^{-1} (C=O stretching); ^{1}H NMR (CDCl$_3$ at 22 °C) δ 8.1–6.8 (br m, 8, Ar H), 4.4–2.2 (br m, 32, ArCH$_2$Ar, COCH$_3$, and OCH$_3$); ^{1}H NMR (Me$_2$SO-d_6, 150 °C) δ 7.51 (Ar H), 3.79 (ArCH$_2$Ar), 3.61 (OCH$_3$), 2.36 (COCH$_3$); ^{13}C NMR (CDCl$_3$, 22 °C) δ 196.89 (C=O), 161.72, 160.96, 136.18, 134.54,

133.27, 131.56, 130.99, 130.67, 129.40, 128.39, and 128.20 (Ar), 61.41, 60.84, and 59.19 (OCH$_3$), 34.86, 29.98, 26.18, and 25.74 (CH$_2$ and COCH$_3$); ^{13}C NMR (Me$_2$SO-d_6, 150 °C) δ 195.53 (C=O), 160.83, 133.05, 131.00, and 129.54 (Ar), 59.45 (OCH$_3$), 31.43 (CH$_2$), 25.10 (CH$_3$). Anal. Calcd for C$_{40}$H$_{40}$O$_8$·^{1}/$_4$CH$_3$SOCH$_3$: C, 72.80; H, 6.22. Found: C, 73.00; H, 6.37.

5,11,17,23-Tetrabromo-25,26,27,28-tetrahydroxycalix[4]-arene (31). A solution of 0.5 g of 5,11,17,23-tetrabromo-25,26,27,28-tetramethoxycalix[4]arene (15) in 40 mL of benzene was treated dropwise with 15 mL of BBr$_3$^{37} in CH$_2$Cl$_2$, and the mixture was stirred at room temperature for 18 h in an atmosphere protected from moisture. The reaction mixture was poured into 100 mL of H$_2$O, stirred for 1.25 h, and the organic layer was evaporated and triturated with acetone to leave 0.39 g (84%) of a white powder. Crystallization from pyridine/toluene yielded a yellow powder as the first fraction and a white powder as the second fraction: mp >480 °C; IR (KBr) 3135 cm^{-1} (OH stretching); ^{1}H NMR (pyridine-d_5) δ 9.72 (s, 4, OH), 7.25 (s, 8, Ar H), 4.0 (br

s, 8, ArCH$_2$Ar). Anal. Calcd for C$_{28}$H$_{20}$O$_4$Br$_4$·^{1}/$_4$C$_5$H$_5$N: C, 46.22; H, 2.79. Found: C, 46.46; H, 2.61.

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Calixarenes. 17. Functionalized Calixarenes: The Claisen Rearrangement Route

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Methods for the preparation of a variety of para-substituted calix[4]arenes via the Claisen rearrangement route are described. Starting with the readily available *p-tert*-butylcalix[4]arene 1, the *tert*-butyl groups are removed by an AlCl$_3$-catalyzed retro-Friedel–Crafts reaction, and the calix[4]arene 2 that is formed is converted to the tetraallyl ether 3. This compound undergoes a heat-induced Claisen rearrangement to yield *p*-allylcalix[4]arene 4, which is a useful starting material for the introduction of functional groups. Along one route, the tosylate of 4 is ozonized to the aldehyde 7, the aldehyde is reduced to the alcohol 8, the alcohol is converted to the bromide 10 and then to the azide 11, and the azide is reduced with diborane to *p*-(2-aminoethyl)calix[4]arene 12, a compound of interest as a chelating species. Along a second route, the tosylate of 4 is rearranged to *p*-(1-propenyl)calix[4]arene 16 and ozonized to *p*-formylcalix[4]arene 17 from which the oxime 18 can be prepared.

p-tert-Butylcalix[4]arene 1 has become one of the most accessible of all of the known macrocyclic cavity-containing compounds, obtainable in greater than 50% yield from the base-induced condensation of *p-tert*-butylphenol and formaldehyde.[1] Aluminum chloride-catalyzed de-*tert*-

1   2
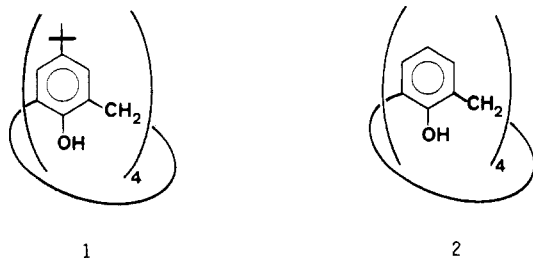
butylation has been shown to proceed in excellent yield,[2,3] making calix[4]arene 2 an extremely attactive starting material for the preparation of various para-substituted calix[4]arenes. To our surprise and disappointment, however, direct introduction of functional groups via electrophilic or nucleophilic substitution reactions has

failed in most cases. The only successes that have been achieved are the sulfonation of calix[6]arene by Shinkai and co-workers[4] and the aminomethylation of calix[4]arene in our laboratories.[5] To effect facile bromination and Friedel–Crafts acylation it is necessary to convert calix-[4]arene to an ether, such as the methyl ether, as described in the preceeding paper.[6]

Synthesis of *p*-Allylcalix[4]arene 4. Concomitant with the investigation reported in the preceding paper, we explored another route for the introduction of functional groups into the para position. The Claisen rearrangement is the prototype of the electrocyclic reaction and furnishes an extremely useful method for converting allyl phenyl ethers to *o*-allylphenols.[7] In those cases where both of the ortho positions are blocked, a two-step rearrangement occurs to yield *p*-allylphenols. Since all of the ortho positions in calix[4]arene are occupied by the methylene bridges, this would be the expected pathway of rearrangement for 25,26,27,28-tetrakis(allyloxy)calix[4]arene

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