A New Synthesis of Oxacalix[3]arene Macrocycles and Alkali-Metal-Binding Studies

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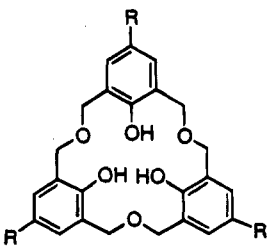
The title oxacalix[3]arene macrocycles **1** have been synthesized in yields of 12–32% by an acid-catalyzed, high-dilution condensation of 2,6-bis(hydroxymethyl)-*p*-subtituted-phenols, where R = *t*-Bu, *i*-Pr, Et, Me, and Cl. The macrocycles are isolated in high purity without chromatography, as the sodium or potassium salts of their monoanions. Metal-binding studies indicate that, like the related calixarenes, the oxacalix[3]arenes bind alkali metals only in the presence of base ($Na^+ \approx K^+ > Li^+$).

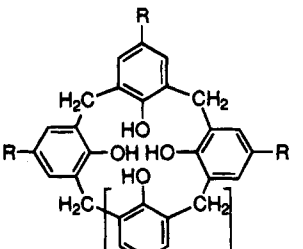
Introduction

Calixarenes and related macrocycles have received considerable attention for their host–guest chemistry and their ability to bind metals.[1] In contrast to the calix[*n*]-arenes, hexahomotrioxacalix[3]arenes **1**, abbreviated to "oxacalix[3]arenes" in this paper, have received little attention beyond reports of the isolation of the *tert*-butyloxacalix[3]arene **1a**.[2–4] In contrast to the numerous studies of metal complexation by calixarenes, there have been no studies on the metal complexing ability of the oxacalix[3]arenes.[5,6] Shinkai and co-workers have reported the complexation of alkali metals to derivatives of the oxacalix[3]arenes with alkylated phenolic oxygens.[6] Both the low yields and difficult purification reported in the literature for **1a** and the absence of other *p*-substituted oxacalix[3]arenes have limited a systematic study of the binding of metals to the oxacalix[3]arenes.[2–4]

Oxacalix[3]arenes **1** were initially reported to be formed in trace amounts during the base-catalyzed condensation of *p*-substituted phenols and formaldehyde to form phenolic resins.[2] Vicens and Gutsche and their co-workers reported that the dehydration of 2,6-bis-(hydroxymethyl)-4-*tert*-butylphenol (**3a**) in refluxing xylenes resulted in the formation of the oxacalix[3]arene **1a** along with other macrocyclic products.[3,4] Vicens and co-workers reported that macrocycles **1a** and **4a** can be isolated from the mixture of reaction products using chromatography in yields of 6% and 1%, respectively.[3] Gutche and co-workers isolated a mixture of macrocycles which included **1a** in 30% yield, and the mixture was

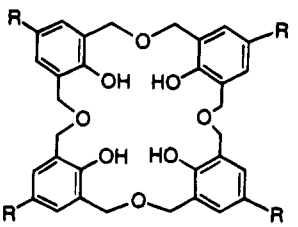


1a: R= *t*-Bu
1b: R= *i*-Pr
1c: R= Et
1d: R= Me
1e: R= Cl



calix[n]arenes
(n= 4, 6, 8)

reported to be separated by a simple recrystallization. No yield was provided for the pure **1a**.[4] Suzuki and co-workers have reported the crystal structure for **1a**.[7]



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In this paper, we report an improved synthesis of the oxacalix[3]arenes **1** and a study of the binding of alkali metals by these macrocycles. The synthesis is general and a variety of substituted oxacalix[3]arenes have been isolated. This is the first report of the synthesis of the oxacalix[3]arenes **1b–e**.

Results and Discussion

Oxacalix[3]arene Synthesis. Our attempts to reproduce the literature conditions for the synthesis of the oxacalix[3]arenes **1a** reported by Vicens and Gutsche and their co-workers resulted in the isolation of a complex mixture of macrocycles that included **1a**, the oxacalix[4]-arene **4a**, calix[4]arenes, and macrocycles possessing both CH_2 and CH_2OCH_2 linkages between the aryl rings; the latter macrocycles will be referred to as "homooxacalix-arenes" in this paper. The separation of **1a** from **4a** was not reproducible using either recrystallization or chromatography since the macrocycles exhibit similar solubil-

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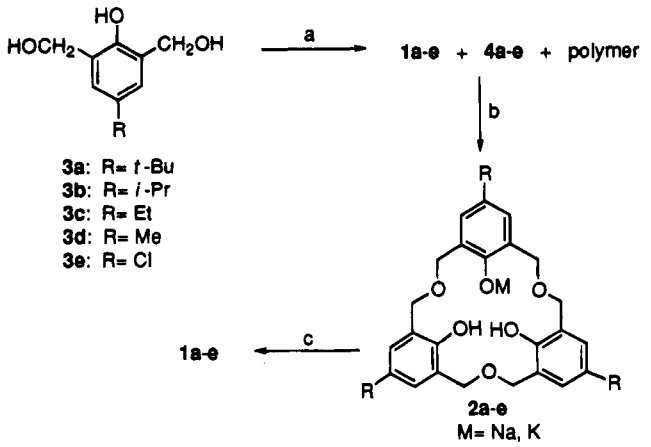
Scheme 1. Synthesis and Purification of Oxacalix[3]arenes



Key: a) refluxing DME, 0.05 - 0.5 M $MeSO_3H$, 0.025 M in **3**;
b) CH_2Cl_2, MOMe, MeOH;
c) HOAc, CH_2Cl_2

ity and chromatographic properties. By the literature routes, we were only successful in obtaining low yields of the oxacalix[3]arenes (<5%).

In contrast to the literature synthesis, we have discovered that 2,6-bis(hydroxymethyl)-4-substituted-phenols **3** (R = *t*-Bu, *i*-Pr, Et, Me, and Cl) condense under high-dilution (0.025 M in **3**), acid-catalyzed conditions in refluxing DME or CH_2Cl_2 to form a mixture of the oxacalix[3]arenes **1** and oxacalix[4]arenes **4** (Scheme 1) along with polymeric material. Calixarenes are not formed under these conditions, and only minor amounts of homooxacalixarenes are observed, depending on the acid concentration and reaction temperature. Sodium sulfate was present in the reactions to absorb the water formed during the condensation; its presence increased both the yield and the ratio of oxacalix[3]arenes to oxacalix[4]arenes.

Addition of a methanol solution of sodium methoxide or potassium *tert*-butoxide to a THF or CH_2Cl_2 solution of the crude reaction mixture results in the precipitation of only the monosodium or monopotassium salts **2** in good yield. The salts **2a–e** have been characterized by elemental analysis, FTIR, FAB mass spectral analysis, and ^1H NMR. The poor analyses obtained for the salts **2** could be due to contamination by NaOH or $NaOCH_3$ or to hydrolysis of the salts **2** during sample preparation. The mass spectral data for the salts **2** are consistent with the formation of only the monosodium and monopotassium salts; there were no higher mass peaks corresponding to the salts of the di- or trianions of the macrocycles.

The ^1H NMR of the salts **2** exhibit broadened resonances that are shifted upfield of the corresponding macrocycle signals, and no phenolic proton signal is observed. The methylene protons in **2** appear as a broadened singlet. This is in contrast with the ^1H NMR spectrum of a titanium(IV) complex of macrocycle **1a** that exhibits doublets for the methylene protons due to metal coordination to one of the macrocycle faces.[5] Since the atomic radii of Na^+ and K^+ are larger than that of Ti^{4+}, we believe that the alkali metal in the salts **2** is similarly bound out of the plane of the macrocycle. The equivalence of the macrocycle faces in the salts **2** is probably due to intramolecular or intermolecular exchange of the metal from one macrocycle face to the other, resulting in equivalent macrocycle faces on the ^1H NMR time scale.

Table 1. Oxacalix[3]arene Yields and Their Dependence on Reaction Conditions

compd	solvent	[MsOH],[a] M	[3], M	1:4[b]	yield,[c] %
1a	DME	0.05	0.025	5:1	32
	CH_2Cl_2	0.025	0.025		21
1b	DME	1.0	0.025	21:1	20[d]
	DME	0.20	0.025	12:1	30
	DME	0.20	0.025	5:1	20[e]
	DME	0.05	0.025	9:1	22
	DME	0.05	0.10	2:1	5.3
	CH_2Cl_2	0.05	0.025	17:1	10[d]
1c	DME	0.50	0.025	14:1	21[f]
1d	DME	0.50	0.025	16:1	21
	DME	0.50	0.025	16:1	19[f]
1e	DME	0.50	0.025	5:1	12[f]

[a] MsOH = methanesulfonic acid. [b] The ratio of oxacalix[3]arene **1** to oxacalix[4]arene **4** was based upon integration of the phenolic protons of the macrocycles corrected for the number of protons. [c] Unless noted otherwise, the oxacalix[3]arenes were isolated as the sodium salts of their monoanions. [d] Homooxacalixarenes were observed in the crude reaction mixture. [e] Sodium sulfate was omitted from this reaction. [f] The oxacalix[3]arenes were isolated as the potassium salts of their monoanions.

One possible intramolecular mechanism involves movement of the metal through the center of the macrocycle. A similar "through-the-annulus" mechanism has been proposed for the dynamic isomerization of O-alkylated derivatives of macrocycle **1a**.[6b]

Protonation of the macrocycle monoanion salts **2a–e** in CH_2Cl_2/acetic acid results in the isolation of the pure macrocycles **1a–e** in good yield and without chromatography. Yields of the macrocycles are listed in Table 1. Macrocycles **1a–e** have been characterized by ^1H and ^{13}C NMR, FTIR, mass spectroscopy, and elemental analyses. The ^1H and ^{13}C NMR spectra of **1a** are identical to that reported by Vicens and Gutsche and their co-workers.[3,4] The TLC, ^1H and ^{13}C NMR, and mass spectra of the isolated oxacalix[3]arenes **1** show no evidence for the presence of oxacalix[4]arenes **4** or other macrocycles. The ^1H NMR of macrocycles **1** and **4** are essentially identical except for the chemical shifts for the phenolic protons (**1**, ~8.6 ppm and **4**, ~8.1 ppm). The ratio of macrocycles **1** and **4** in crude reaction mixtures can be determined from the integrals of these phenolic signals provided that the crude product is DME and acid-free. The phenolic protons in the oxacalix[3]arenes **1** are D_2O exchangeable, but they show no exchange with H_2O or the phenolic protons of the oxacalix[4]arenes on the NMR time scale.

Dependence of Oxacalix[3]arene Formation on Reaction Conditions. The dependence of the yield of the oxacalix[3]arenes **1** and the ratio of macrocycles **1** and **4** on reaction conditions was examined. The following reaction parameters were independently varied: (1) the concentration of **3**, (2) the nature of and concentration of the acid catalyst, (3) the solvent, and (4) the reaction temperature. Yields and macrocycle ratios (**1**:**4**) for these experiments are listed in Table 1.

The yield of macrocycle **1b** and the ratio **1b**:**4b** both decreased when the concentration of **3b** was raised from 0.025 to 0.1 M in DME with methanesulfonic acid (MsOH) as the catalyst (0.05 M). It appears that the highest yields are obtained when the concentration of the starting material **3b** is in the high-dilution region (<0.05 M). The literature syntheses of **1a** utilized considerably higher concentrations of **3a** (0.24–1 M), which may explain the low **1a**:**4a** ratios (~6:1) and the low yields for these syntheses.[3,4]

The effect of the nature of the acid catalyst was examined under high-dilution conditions in **3a** (0.025 M).

Both methanesulfonic acid (MsOH) and *p*-toluenesulfonic acid (TsOH) were found to be good catalysts for the reaction. With sulfuric acid as the catalyst in DME solvent, the reaction was biphasic and only trace amounts of macrocycle **1a** were isolated (<1%). At a concentration of 0.24 M in refluxing CH_2Cl_2, trifluoroacetic acid (TFA) yielded only a trace amount of macrocycle **1a**. No macrocycle formed at higher TFA concentrations (2.4 M), and **3a** was completely consumed. At lower TFA concentrations (~0.024 M), the starting material **3a** was still present after several days. The failure of TFA as a catalyst may be due to a competition between ether formation and reaction of the trifluoroacetate anion with reaction intermediates.

The optimum MsOH concentration for the formation of the oxacalix[3]arenes was found to depend on the *p*-substituent. For **1a**, low acid concentrations (0.02 M in CH_2Cl_2 and 0.05 M in DME) were sufficient for good yields, whereas higher concentrations were required for the other macrocycles **1b–e**. At these concentrations the reaction was complete in several hours. Lower concentrations of MsOH resulted in a slow reaction (days) and a lower **1:4** ratio. With increasing acid concentration, the **1:4** ratio increased but the yields decreased. At the highest acid concentrations homooxacalixarenes were observed as minor products. The low solubility of TsOH prevented a study of its concentration dependence.

The rate of the condensation reaction was observed to be dependent on both the nature of the solvent and the reaction temperature. At room temperature in CH_2Cl_2 (0.02 M MsOH), the reaction was essentially complete in 8 h, whereas in refluxing CH_2Cl_2, the reaction was complete in less than 30 min. In DME at room temperature, the reaction was considerably slower, and it took several days for the starting material **3b** to be consumed. In contrast, **3b** was consumed in approximately 5 h in refluxing DME at 0.05 M MsOH, in 1.5 h at 0.2 M MsOH, and in 20 min at 1 M MsOH. In general, reactions were run in DME since the macrocycle yields were higher and the monomers **3** exhibited a greater solubility in this solvent. Monomers **3b–d** were essentially insoluble in CH_2Cl_2.

The yield and **1:4** ratio were greater when the reactions were run in the presence of sodium sulfate. Under the reaction conditions, sodium methanesulfonate (NaOMs) could form from the protonation of sodium sulfate by MsOH and could serve as a template for the reaction. Addition of NaOMs to a typical reaction in DME with sodium sulfate present resulted in no increase in the yield or the **1:4** ratio. The low solubility of NaOMs in DME indicates that the reaction is probably saturated in NaOMs in the absence of added NaOMs. In another experiment, sodium trifluoromethanesulfonate (NaOTf) was added to the typical reaction conditions for the preparation of **1b**, since NaOTf is considerably more soluble than NaOMs in DME. In the presence of NaOTf (0.2 M), only trace amounts of macrocycle **1b** formed along with a great number of unidentified products. No attempt was made to determine the yield (≪5%) or **1:4** ratio for this reaction. We believe that the lower yield in the absence of sodium sulfate is simply due to inhibition of the reaction by water formed during the reaction. Similar decreased yields were observed when reactions were run in wet DME. The water may decrease the yields and **1:4** ratio by disrupting the intramolecular hydrogen bonding in the acyclic precursors to macrocycle **1**.

Metal Complexation by the Oxacalix[3]arenes. The ability of macrocycles **1a–e** to bind alkali metal ions as neutral or anionic ligands was examined utilizing spectrophotometric and NMR titration methods. There have been no reports of such studies on the oxacalix[3]-arenes, however Shinkai and co-workers have reported alkali-metal-binding studies for the O-alkylated derivatives of macrocycle **1a**.[6] Two conformers exist for the O-alkylated derivatives of the oxacalix[3]arenes, where either all three O-alkyl groups are on the same face of the macrocycle, the "cone" conformer, or where one O-alkyl group is on the opposite face of the macrocycle, the "partial cone" conformer. The cone derivatives are reported to selectively bind sodium ions and *n*-butyl ammonium ions, whereas the partial cone derivatives are more selective for potassium ions.

Metal complexation to the neutral macrocycles **1** was examined by picrate extraction studies.[6,8] A solution of either macrocycle **1a** or **1e** in CH_2Cl_2 was stirred at room temperature for 24 h with an aqueous solution of lithium, sodium, or potassium picrate (10 equiv), and the absorbance of the CH_2Cl_2 layer was analyzed at 378 nm. Neither of the macrocycles exhibited a significant absorption with any of the three metal ions (Li^+, Na^+, or K^+). The small absorptions indicate that less than 0.5% of the macrocycle binds the metal picrate. This behavior is identical to that of the calix[*n*]arenes (n = 4, 6, and 8) which exhibit a negligible binding of metal picrates.[8a] The O-alkyl derivatives of **1a** are reported by Shinkai and co-workers to exhibit a substantially greater ability to bind alkali metal ions than **1a**.[6]

Metal binding to the neutral macrocycles **1a**, **1d**, and **1e** was also examined by ^1H NMR. Solutions of the three macrocycles in 1:1 DMSO-d_6/$CDCl_3$ were titrated with a DMSO-d_6 solution of a metal triflate (MOTf: M = Li, Na, K). On addition of a large amount of the MOTf (M = Li, Na, K), no significant change in the ^1H NMR resonances was observed for either macrocycle **1a** or **1d**. Only macrocycle **1e** exhibited a modest shift of the aromatic and methylene resonances on addition of NaOTf; no shift was observed on addition of LiOTf or KOTf. It appears that sodium ions are weakly bound to macrocycle **1e** under these conditions. The observation of only one methylene proton resonance for the mixture of the macrocycle **1e** and its NaOTf complex indicates that they rapidly equilibrate on the NMR time scale. As a result, it has not been possible to measure a binding constant for this complexation. The inability of macrocycles **1a–d** to bind alkali metal ions suggests that a template effect is probably not responsible for the higher yield and **1:4** ratio in the presence of sodium sulfate.

The ability of macrocycles **1** to bind alkali metal ions as anionic ligands was examined by ^1H NMR. Solutions of macrocycles **1a**, **1d**, or **1e** containing a MOTf (M = Li, Na, K) in 1:1 DMSO-d_6/$CDCl_3$ were titrated with triethylamine and analyzed by ^1H NMR. Neither macrocycle **1a** nor **1d** exhibited a shift in any of the macrocycle resonances on addition of a large amount of triethylamine. For macrocycle **1e**, addition of triethylamine resulted in a shift of the macrocycle methylene and aryl proton resonances for each of the MOTf. The single resonance observed for the mixture of macrocycle **1e** and its salts **2e** (M = Li, Na, K) indicates that they are in rapid exchange on the NMR time scale. The exchange

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process could occur through protonation of the salt **2e** by triethylammonium triflate or through an intermolecular exchange of metal ions and protons between macrocycles **1e** and the salts **2e**. A similar averaged spectrum was observed when macrocycle **1e** was added to a solution of the isolated salts **2e**. This indicates that intermolecular exchange between **1e** and **2e** is at least partially responsible for the exchange occurring during titrations. The ability of macrocycle **1e** to bind metals in the presence of triethylamine is consistent with the anticipated lower pK_a for this macrocycle compared to the *p*-alkyl-substituted oxacalix[3]arenes **1a–d**.[9] The alkali metal complexes **2a–d** of macrocycles **1a–d** can be prepared using a stronger base, i.e. hydroxide ion.

The binding of alkali metals to macrocycle **1e** in the presence of triethylamine involves two steps: (1) binding of the MOTf to the neutral macrocycle (eq 1), and (2) deprotonation of the MOTf complex of the macrocycle to form the salts **2** (eq 2). The neutral macrocycle, the alkali metal complex of the macrocycle, and the alkali metal salts **2** are abbreviated as H_3L, H_3L·MOTf, and H_2LM, respectively, in eqs 1 and 2. The overall binding constant for this system is the product ($K_s\alpha$) of the two equilibrium constants, K_s and α, as shown in eq 3.

$$H_3L + MOTf \underset{}{\overset{K_s}{\rightleftharpoons}} H_3L{\cdot}MOTf \quad (1)$$

$$H_3L{\cdot}MOTf + Et_3N \overset{\alpha}{\rightleftharpoons} H_2LM + Et_3NH^+OTf^- \quad (2)$$

$$K_s\alpha = \frac{[H_2LM][Et_3NH^+OTf^-]}{[MOTf][Et_3N][H_3L]} \quad (3)$$

$$[H_2LM] = \frac{[H_3L]_i(\delta_1-\delta)}{\delta_1-\delta_2} \quad (4)$$

The binding constants for macrocycle **1e** with MOTf were determined using eqs 3 and 4 as discussed in the experimental section. Binding constants for the alkali metals ($K_s\alpha$) were found to be Na^+ (0.39 M^{-1}), K^+ (0.32 M^{-1}), and Li^+ (0.11 M^{-1}). Thus the macrocycle monoanion **2e** shows essentially the same affinity for sodium and potassium ions and exhibits a slightly lower affinity for lithium ions. This selectivity for the binding of potassium and sodium ions is consistent with the studies of Shinkai and co-workers on O-alkylated derivatives of **1a**.[6] The modest selectivity could be due to either a stronger binding of the neutral macrocycle to NaOTf or KOTf (larger K_s) or to a greater acidity of the alkali metal complex H_3L·MOTf (larger α). The observation that NaOTf exhibits significantly stronger binding to the neutral macrocycle **1e** than KOTf indicates that the two factors are both important determinants of the binding selectivity.

Conclusion

An improved route to the oxacalix[3]arene macrocycles has been developed that provides the macrocycles in good yield and high purity without chromatography. With this new route, a family of oxacalix[3]arene macrocycles have been prepared with a range of *p*-substituents. The *p*-chlorooxacalix[3]arene macrocycle is observed to bind sodium ions in the absence of base and binds sodium ions and potassium ions with greater affinity than lithium ions in the presence of triethylamine. The more electron-rich *p*-alkyloxacalix[3]arenes exhibit binding of alkali metals only in the presence of a strong base (OH^-).

Experimental Section

General Comments. All solvents and reagents were obtained from commercial sources and used without further purification. Methanol, CH_2Cl_2, and THF were dried over molecular sieves (3 Å). EI mass spectra were recorded at an ionizing voltage of 60 eV. FAB mass spectral analyses were performed at the Midwest Center for Mass Spectrometry, University of Nebraska–Lincoln. Melting points are uncorrected. NMR spectra were referenced to TMS or to protio solvent impurity. Metal picrates were synthesized by reaction of picric acid with a stoichiometric amount of the corresponding metal hydroxide in methanol. All compounds were single components by TLC.

General Synthesis of 2,6-Bis(hydroxymethyl)phenols 3. The 2,6-bis(hydroxymethyl)-4-alkylphenols (**3a–c**) were prepared according to the general literature conditions of Freeman.[10] Literature syntheses have been reported for **3d** and **3e**.[11,12] Basic aqueous dioxane or THF solutions of the corresponding phenols, formaldehyde, and sodium hydroxide were stirred for the indicated time. The sodium salts of **3a–e** were isolated by removal of the solvent under reduced pressure and precipitation with 2-propanol. Acidification of the sodium salts with acetic acid in acetone, removal of sodium acetate by filtration, and recrystallization from ethyl acetate resulted in good yields of **3a–e**. Compound **3a** was frequently isolated as an oil. The yields, melting points, elemental analyses, and infrared and ^1H NMR spectra for **3a–e** are provided below. Each of the compounds **3a–e** was pure on the basis of thin-layer chromatography (silica gel, 1:1 ethyl acetate/cyclohexane).

4-*tert*-Butyl-2,6-bis(hydroxymethyl)phenol (3a): reaction time, 7–10 days; yield, 70%; mp 68–70 °C; IR (KBr) ν 3500–3100, 2957, 2905, 1489, 1217, 1015, and 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (s, 2H), 4.79 (s, 4H), and 1.27 (s, 9H). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.48; H, 8.60.

4-Isopropyl-2,6-bis(hydroxymethyl)phenol (3b): reaction time, 7–10 days; yield, 70%; mp 127–128 °C; IR (KBr) ν 3399, 3294, 2951, 2928, 1483, 1466, 1211, and 1014 cm^{-1}; ^1H NMR (acetone-d_6) δ 6.98 (s, 2H), 4.72 (d, 4H, J = 0.5 Hz), 2.96 (br s, 3H), 2.80 (q, 1H, J = 6.9 Hz), and 1.17 (d, 6H, J = 6.9 Hz). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.20; H, 8.27.

4-Ethyl-2,6-bis(hydroxymethyl)phenol (3c): reaction time, 7–10 days; yield, 70%; mp 89–90 °C; IR (KBr) ν 3416, 3354, 3260, 3167, 2961, 2934, 2877, 1604, 1485, 1215, 1069, 1057, and 1001 cm^{-1}; ^1H NMR (acetone-d_6) δ 6.94 ppm (s, 2H), 4.71 (s, 4H), 2.51 (q, J = 7.6 Hz, 2H), and 1.14 (t, J = 7.6 Hz, 6H). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.02; H, 7.75.

4-Methyl-2,6-bis(hydroxymethyl)phenol (3d): reaction time, 7–10 days; yield, 72%; mp 130–131 °C (lit.[11] mp 127–129, 128 °C); IR (KBr) ν 3397, 3312, 2951, 2913, 2876, 1483, 1466, 1204, 1063, and 1003 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89 ppm (s, 2H), 4.79 (s, 4H), and 2.25 (s, 3H). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.29.

4-Chloro-2,6-bis(hydroxymethyl)phenol (3e): reaction time, 15–20 days; yield, 72%; mp 163–165 °C (lit[12] mp 166–168, 159–161 °C); IR (KBr) ν 3412, 3300, 2967, 2914, 2888,

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(10) For a general procedure for the synthesis of 2,6-bis(hydroxymethyl)phenols see: Freeman, J. H. *J. Am. Chem. Soc.* **1952**, *74*, 6257.

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(12) Synthesis of **3e**: (a) Moshfegh, A. A.; Mazandarani, B.; Nahid, A.; Hakimelahi, G. H. *Helv. Chim. Acta* **1982**, *65*, 1229. (b) Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 912.

1478, 1456, 1211, 1068, and 1010 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.14 ppm (s, 2H) and 4.72 (s, 4H). Anal. Calcd for $C_8H_9O_3Cl$: C, 50.94; H, 4.81. Found: C, 50.71; H, 5.00.

Synthesis of *p-tert*-Butyloxacalix[3]arene 1a. In a 250-mL round bottom flask, 4 g of anhydrous sodium sulfate was suspended in 180 mL of DME, and 0.67 mL of MsOH (0.01 mol, 0.05 M) was added. The mixture was brought to reflux and a solution of 1.05 g of **3a** (0.005 mol, 0.025 M in **3a**) in 20 mL of DME was added. The reaction was allowed to reflux for 5 h, at which time the starting material had been consumed. Saturated sodium bicarbonate (50 mL) was added to quench the reaction, then 100 mL of water was added. Most of the DME was removed on a rotary evaporator (rotavap), and the mixture was extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $MgSO_4$ and filtered, the solvent was removed on a rotavap, and the residue was dried *in vacuo*. The solid consisted of a mixture of **1a** and **4a**. The **1a**:**4a** ratio was determined by ^1H NMR (*vide supra*).

The purification of **1a** was accomplished by its precipitation as the sodium salt **2a**. The crude solid was dissolved in dry CH_2Cl_2 (10 mL) and dry methanol (10 mL) containing 0.25 g of sodium methoxide (approximately a 3-fold excess, assuming the solid is completely **1a**) was added, and the mixture was placed in a −10 °C freezer overnight. The white precipitate was filtered and dried. Properties of **2a**: IR (KBr) ν 3368, 2957, 2866, 1487, 1364, 1213, 1078, and 880 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.91 (br s, 6H), 4.40 (br s, 12H), and 1.17 (s, 27H); MS (EI, solid) parent ion was not observed. Anal. Calcd for $C_{36}H_{47}O_6Na$: C, 74.95; H, 7.49. Found: C, 72.22; H, 7.91.

The *p-tert*-butyloxacalix[3]arene macrocycle **1a** was obtained from **2a** by stirring a suspension of the sodium salt in CH_2Cl_2 containing 100 μL of acetic acid. The opaque solution was dried over sodium sulfate and the solvent was removed on a rotavap. The resulting solid was recrystallized, if necessary, from CH_2Cl_2/MeOH. The white solid was dried *in vacuo* to provide 0.31 g (32%) of macrocycle **1a**: mp 240−242 °C; IR (KBr) ν 3369, 2957, 2868, 1486, 1210, 1080, and 879 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.57 (s, 3H), 7.13 (s, 6H), 4.73 (s, 12H), and 1.24 (s, 27H); ^1H NMR (DMSO-d_6) δ 8.35 (br s, 3H), 7.18 (s, 6H), 4.64 (s, 12H), and 1.21 (s, 27H); ^{13}C NMR (proton decoupled, $CDCl_3$) δ 153.47, 142.3, 126.85, 123.66, 71.69, 33.94, and 31.47; MS (EI, solid) m/z 576 (M^+); MS (FAB, sodium carbonate or NBA matrices[13]) m/z 599.4 ($M + Na^+$), 577.4 ($M + H^+$), 576.4 (M^+). Anal. Calcd for $C_{36}H_{48}O_6$: C, 75.07; H, 8.40. Found: C, 74.83; H, 8.48.

Synthesis of *p*-Isopropyloxacalix[3]arene 1b. The procedure for the synthesis of **1b** was similar to that of **1a** except the MsOH concentration was 0.2 M. After 1.5 h, 2 M NaOH was added to quench the bulk of the MsOH, and saturated $NaHCO_3$ was added until the pH was neutral.

The sodium salt **2b** was isolated using the same procedure as described above for **2a**. Properties: IR (KBr) ν 3376 (br), 2957, 2864, 1476, 1179, 1079, 1051, and 882 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.84 (s, 6H), 4.42 (s, 12H), 2.70 (m, 3H, J = 6.9 Hz), and 1.12 (d, 18H, J = 6.9 Hz); MS (FAB, 3-NBA or DTT/DTE matrices[13]) m/z 557 ($M + H^+$). Anal. Calcd for $C_{33}H_{41}O_6Na$: C, 71.19; H, 7.42. Found: C, 69.02; H, 6.94.

The sodium salt **2b** was protonated by the same procedure as described for **2a** to provide **1b** in 30% yield as a white solid: mp 152−154 °C; IR (KBr) ν 3354, 2959, 2870, 1487, 1179, 1084, 880, and 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.57 (s, 3H), 6.97 (s, 6H), 4.70 (s, 12H), 2.78 (m, 3H, J = 6.9 Hz), and 1.16 (d, 18H, J = 6.9 Hz); ^1H NMR (DMSO-d_6) δ 8.34 (s, 3H), 7.04 (s, 6H), 4.62 (s, 12H), 2.76 (m, 3H, J = 6.9 Hz), and 1.13 (d, 18H, J = 6.9 Hz); ^{13}C NMR (proton decoupled, $CDCl_3$) δ 153.75, 140.00, 127.80, 124.02, 71.46, 33.24, and 24.19; MS (EI, solid), m/z 534 (M^+). Anal. Calcd for $C_{33}H_{42}O_6$: C, 74.13; H, 7.92. Found: C, 73.91; H, 7.84.

Synthesis of *p*-Ethyloxacalix[3]arene 1c. The procedure for the synthesis of **1c** was identical to that of **1b** except the MsOH concentration was 0.5 M. Crystallization of the potassium salt **2c** ($M = K^+$) was accomplished by the addition of a methanol solution of potassium *tert*-butoxide to a CH_2Cl_2 solution of the crude reaction mixture. Properties of **2c**: IR (KBr) ν 3391, 3250, 2960, 2870, 1481, 1333, 1072, and 874 cm^{-1}; ^1H NMR (methanol-d_4) δ 8.37 (s, 2H), 6.99 (s, 6H), 4.61 (s, 12H), 2.56 (q, J = 7.5 Hz, 6H), and 1.17 (t, J = 7.5 Hz, 9H); MS (FAB, 3-NBA or DTT/DTE matrices[13]), m/z 531 ($M + H^+$). Anal. Calcd for $C_{30}H_{35}O_6K$: C, 67.89; H, 6.65. Found: C, 65.64; H, 6.01.

The potassium salt **2c** was protonated according to the same procedure as for **2a** to provide **1c** in a 20% yield: mp 138−142 °C; IR (KBr) ν 3326, 2897, 2858, 1610, 1487, 1356, 1202, 1078, 997, and 864 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.55 (s, 3H), 6.93 (s, 6H), 4.67 (s, 12H), 2.49 (q, J = 7.5 Hz, 6H), and 1.13 (t, J = 7.5 Hz, 9H); ^{13}C NMR (proton decoupled, $CDCl_3$) δ 154.0, 136.0, 129.7, 124.2, 71.6, 28.0, and 16.3; MS (EI, solid) m/z 492 (M^+). Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.14; H, 7.37. Found: C, 73.28; H, 6.95.

Synthesis of *p*-Methyloxacalix[3]arene 1d. The synthesis of this macrocycle was identical to that of **1c**. The potassium (M = K) or sodium (M = Na) salts **2d** were isolated in the same manner as was **2a**. Properties of **2d** (M = Na): IR (KBr) ν 3389, 2915, 2863, 1476, 1263, 1219, 1055, and 864 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.82 (s, 6H), 4.40 (s, 12H), and 2.14 (s, 9H); MS (EI, solid) parent ion was not observed. Anal. Calcd for $C_{27}H_{29}O_6Na$: C, 68.63; H, 6.19. Found: C, 66.78; H, 5.92.

Protonation of the sodium or potassium salts **2d** was accomplished by the same method as for **2a** to provide macrocycle **1d** in 19−21% yield: mp 250 °C; IR (KBr) ν 3347, 2961, 2928, 2868, 1610, 1487, 1359, 1256, 1206, 1155, 1082, 1016, 970, and 876 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.54 (s, 3H), 6.91 (s, 6H), 4.66 (s, 12H), and 2.22 (s, 9H); ^{13}C NMR ($CDCl_3$, proton decoupled) δ 153.5, 130.3, 128.9, 124.0, 71.7, and 20.3; MS (EI, solid) m/z 450 (M^+). Anal. Calcd for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.71; H, 6.49.

Synthesis of *p*-Chlorooxacalix[3]arene 1e. The synthesis of this macrocycle was identical to that of **1c**, and it was isolated as the potassium salt **2e**: IR (KBr) ν 3393, 2917, 2859, 1468, 1352, 1244, 1064, and 872 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.05 (s, 6H), 4.40 (s, 12H); MS (EI, solid) parent ion was not observed.

The potassium salt **2e** was protonated in the same manner as was **1a** in a yield of 12%: mp 215−217 °C; IR (KBr) ν 3329, 2895, 2857, 1612, 1474, 1354, 1244, 1198, 1078, 870, and 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.67 (s, 3H), 7.12 (s, 6H), and 4.65 (s, 12H); ^1H NMR (DMSO-d_6) δ 7.30 (s, 6H) and 4.59 (s, 12H); ^{13}C NMR ($CDCl_3$, proton decoupled) δ 154.6, 138.5, 130.1, 126.0, and 71.0; MS (EI, solid) m/z 512 (M^+). Anal. Calcd for $C_{24}H_{21}O_6Cl_3$: C, 56.32; H, 4.14. Found: C, 56.59; H, 3.88.

Metal Picrate-Binding Studies. An aqueous solution of lithium, sodium, or potassium picrate (5 mL, 5 mM) was stirred with a solution of **1a** or **1e** in CH_2Cl_2 (5 mL, 0.5 mM) in a closed vial at room temperature for 24 h.[8] The CH_2Cl_2 layer was allowed to separate and an aliquot was transferred to a second vial. The absorbance of the aliquot was measured at 378 nm (ϵ = 1.8 M^{-1} cm^{-1} in CH_2Cl_2), and a control experiment without macrocycle (aqueous metal picrate/CH_2Cl_2) was used as the reference. The absorbance of the macrocycle solutions was less than 0.02 absorbance units, which corresponds to a maximum concentration of 2 μM picrate in the CH_2Cl_2 layer; thus, less than 0.5% of the macrocycle binds the alkali metals (Li^+, Na^+, or K^+).

Metal Triflate-Binding Studies. NMR spectra were recorded while a solution of **1a**, **1d**, or **1e** (3−4 mM) in a mixture of 0.5 mL DMSO-d_6 and 0.5 mL $CDCl_3$ was titrated with a DMSO-d_6 solution of MOTf (M = Li, Na, K). The ^1H NMR chemical shift of the methylene and aryl protons for macrocycles **1a** and **1d** was unaffected by the addition of the MOTf up to a concentration of 30−90 mM. For macrocycle **1e**, the methylene proton signal exhibited an upfield shift (~0.1 ppm) on the addition of NaOTf, but no significant shift occurred on addition of either LiOTf or KOTf. This shift is significantly greater than the detection limit of the NMR (0.002 ppm).

Addition of triethylamine to a mixture of macrocycles **1a**, **1d**, or **1e** and MOTf (10 equiv, ~30 mM, M = Li, Na, K) in the

(13) 3-NBA: 3-nitrobenzyl alcohol. DTT: dithiothreitol. DTE: dithioerythritol.

above solvent system resulted in no change in the spectrum for macrocycles **1a** and **1d**. The methylene proton and the aryl proton signals for macrocycle **1e** exhibited an upfield shift (~0.2 ppm) on the addition of triethylamine. A spectrum of the sodium salt **2e**, prepared by the addition of the corresponding metal alkoxide (MOR: M = Li, R = Et; M = Na, R = Me; M = K, R = *t*-Bu) to the NMR tube, was used as the chemical shift (δ_2) for the pure alkali metal salt **2e**. The methylene proton signal for **2e** was used for the NaOTf and KOTf titrations. The aryl proton signal for **2e** was used for the LiOTf titration, since the methylene proton signal exhibited significant broadening on the addition of triethylamine.

The concentration of the alkali metal salt **2e** ([H_2LM]) was determined at each concentration of triethylamine using eq 4, where δ_1 is the chemical shift of a particular proton in macrocycle **1e**, δ is the chemical shift of the signal at a given concentration of triethylamine, δ_2 is the chemical shift of the corresponding signal for the alkali metal salt **2e**, and L_i is the initial concentration of macrocycle **1e**. The equilibrium concentrations of MOTf ([MOTf] = M_i−[H_2LM]), triethylamine ([Et_3N] = B_i−[H_2LM]), macrocycle ([H_3L] = L_i−[H_2LM]), and triethylammonium triflate ([$Et_3NH^+OTf^-$] = [H_2LM]), were calculated assuming a single deprotonation of the macrocycle, where M_i is the initial metal triflate concentration and B_i is the initial concentration of base added. The binding constants ($K_s\alpha$) were determined using eq 3 and the preceding equilibrium concentrations of reaction species. The reported $K_s\alpha$ values were the average of two individual experiments.

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