was refluxed for 3 h, stirred at room temperature for 24 h, and quenched with 0.75 mL of H_2O, 0.75 mL of 15% NaOH, and 2.25 mL of H_2O. After the salts were washed with ether and dried over $MgSO_4$, the ether solution was cooled to 0 °C and treated with 0.5 mL of diethylamine, and a solution of 1.60 g of I_2 in ether was added dropwise until the yellow color persisted (about 90% of the solution was added). After filtration, washing with 50 mL of 10% $Na_2S_2O_3$ and 50 mL of H_2O, drying with $MgSO_4$, and concentration gave 0.52 g (68%) of **2** as a white solid, mp 103-106 °C. Empirical formula ($C_{14}H_{24}N_4$) was established by high-resolution mass spectroscopy: ^1H NMR ($CDCl_3$) δ 4.14 (br s, 4 H), 2.10-1.20 (m, 20 H); ^{13}C NMR δ 58.2 (d), 30.0 (t), 26.7 (t), 17.2 (t).

7-(Dimethylamino)-7-azabicyclo[2.2.1]heptane (6) was obtained in low yield by reductive methylation[18] of **5** prepared by the method of Dervan[6] and purified by preparative VPC. Empirical formula ($C_8H_{16}N_2$) was established by high-resolution mass spectroscopy: ^1H NMR ($CDCl_3$) δ 3.1 (m, 2 H), 2.5 (s, 6 H), 1.72-2.08 (m), 1.16-1.44 (m).

7-Phthalimido-7-azabicyclo[4.1.0]hept-2-ene (8) was prepared by the method of Hoesch.[7b] A slurry of 10.0 g (61.7 mmol) of *N*-aminophthalimide (**7**), 14.85 g (185 mmol) of 1,3-cyclohexadiene, 34.3 g (248 mmol) of K_2CO_3, and 30 mL of methylene chloride was mechanically stirred in a 250-mL three-necked flask while 25 g (185 mmol) of freshly recrystallized $Pb(OAc)_4$ was added in spatula-tip portions over 1.75 h. Methylene chloride was added as necessary to keep the slurry stirring. After 0.5 h of further stirring, the slurry was filtered, washed with methylene chloride, and stripped to a yellow residue. Filtration of a chloroform solution of this material through an alumina plug helps clean up later steps and gave 14.8 g of crude material. Recrystallization (hexane) gives a light yellow powder: mp 39-40 °C; ^1H NMR ($CDCl_3$) δ 7.75 (m, 2 H), 7.60 (m, 2 H), 6.25 (m, 1 H), 5.9 (m, 1 H), 3.15 (m, 1 H), 2.9 (q, 1 H), 2.4-2.65 (m, 1 H), 2.0-2.3 (m, 2 H), 1.6-1.8 (m, 1 H).

7-Phthalimido-7-azabicyclo[2.2.1]hept-2-ene (9).[7b] A mixture of 12.0 g of unrecrystallized **8** from the above reaction (50 mmol) was refluxed in 250 mL of xylene under N_2 for 48 h and stripped to a residue containing 10-20% **4**, 40-50% **8**, and 10-20% *n*-phthalimidopyrrole by ^1H NMR spectroscopy. Chromatography on a 500 × 7.5 cm column of preparative silica gel (60 PF) in CH_2Cl_2 separated **9**, which was recrystallized from hexane at -78 °C to give material melting at 118-122 °C: ^1H NMR ($CDCl_3$) δ 7.7-7.8 (m, 2 H), 7.6-7.7 (m, 2 H), 6.15 (t, 2 H), 4.95 (br s, 2 H), 2.0 (d, 2 H), 1.15 (q, 2 H).

7-Phthalimido-7-azabicyclo[2.2.1]heptane (10). Hydrogenation of 0.94 g (3.9 mmol) of **9** in 50 mL of ethyl acetate over 1.55 g of 5% $Pd/BaCO_3$ at atmospheric pressure took 1.5 h to take up the theoretical amount of H_2. After filtration, solvent removal gave 0.95 g of crude material, which was crystallized from hexane to give 0.67 g of bright yellow **10**: mp 102-104 °C; ^1H NMR ($CDCl_3$) δ 7.7-7.8 (m, 2 H), 7.6-7.7 (m, 2 H), 4.75 (t, 2 H), 1.8-2.0 (m, 4 H), 1.4 (m, 4 H).

Azo-7-azabicyclo[2.2.1]heptane (11). A mixture of 0.424 g (1.75 mmol) of **10** and 6 mL of hydrazine hydrate was stirred at room temperature. Solution of **10** occurred after 5 min, and after stirring an additional 10 min, the mixture was extracted with 4 × 10-mL portions of ether, and the ether was dried over NaOH pellets and stripped to give 0.095 g (48%) of **5** as a semisolid. This material was cooled to 0 °C in 5 mL of ether, treated with an excess of ethylamine, and stirred while 0.216 g (0.851 mmol) of I_2 in 10 mL of ether was added dropwise over 1.5 h. The mixture was filtered, washed with 15 mL of 10% $Na_2S_2O_3$, 15 mL of H_2O, dried over K_2CO_3, and concentrated to a solid residue, which was crystallized from acetonitrile to give 0.080 g (43%) of **11**. Empirical formula ($C_{12}H_{20}N_4$) was established by high-resolution mass spectroscopy: ^1H NMR (CD_3CN) δ 3.95 (br s, 4 H), 1.55 (m, 8 H), 1.30 (d, 8 H); ^{13}C NMR (CD_3CN) δ 58.91, 28.41.

7-Chloro-7-azabicyclo[2.2.1]heptane (13). The method of Coleman[19] was used to convert 0.50 g (3.7 mmol) of **12**·HCl[8] to 0.41 g (83%) of **13**, obtained as a yellow oil after Kugelrohr distillation. Empirical formula ($C_6H_{10}ClN$) was eastablished by high-resolution mass spectroscopy: ^1H NMR ($CDCl_3$) δ 3.68 (m, 2 H), 2.05-2.47 (m, 4 H), 1.24-2.08 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 67.57 (d), 27.99 (t), 27.27 (t).

7,7'-bi-7-azabicyclo[2.2.1]heptane (14). A 1.9 M *tert*-butyllithium solution (1.25 mL, 2.35 mmol) was added dropwise to a solution of 0.309 g (2.35 mmol) of **13** in 10 mL of dry THF at -78 °C. After being stirred for 1 h at -78 °C, the solution was allowed to warm to room temperature over 22 h. Concentration and Kugelrohr distillation gave 0.24 g of residue, which was sublimed at 3 Torr (80 °C bath temperture) to give 0.15 g (66%) of **14**, mp 111.5-112 °C. Empirical formula ($C_{12}H_{20}N_2$) was established by high-resolution mass spectroscopy: ^1H NMR ($CDCl_3$) δ 3.23 (m, 4 H), 1.92-2.28 (m, 4 H), 1.48-1.84 (m, 4 H), 1.10-1.36 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 60.79 (d), 28.27 (t), 27.93 (t).

Electrochemistry was done as previously described,[16] and low-temperature ^{13}C NMR experiments employed a JEOL FX-200 instrument. AM1 calculations were carried out on a VAX-8600, by using QCPE 506.

Acknowledgment. We thank the National Science Foundation for partial financial support of this work under Grants CHE-8025111 and CHE-8415077.

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Calixarenes. 22. Synthesis, Properties, and Metal Complexation of Aminocalixarenes

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Abstract: Calix[4]arene (**2**), readily accessible from *p-tert*-butylcalix[4]arene (**1**), is shown to react smoothly with formaldehyde and secondary amines to yield Mannich bases (**3**), which can be converted to the corresponding quaternary salts (**4**). Treatment of the quaternary salt with 2 equiv of a nucleophile (the first equivalent acting as a base) yields a para substituted calix[4]arene via a putative calixarene *p*-quinone methide intermediate. By means of this sequence of reactions a variety of functionalized calixarenes (**6**) have been prepared, including those carrying CN, OCH_3, N_3, SEt, $CH(CO_2Et)_2$, $CH(NO_2)CO_2Et$, and imidazolyl functions. Of particular interest are *p*-(2-aminoethyl)calix[4]arene (**7b**), obtained by reduction of *p*-(cyanomethyl)calix[4]arene (**6a**), and the amino calixarenes obtained directly from the Mannich reaction. On the basis of NMR, IR, and UV measurements, the aminocalixarenes are shown to exist as zwitterions in polar organic solvents and as aminophenols in nonpolar solvents. The interaction of the *p*-bromobenzenesulfonate of *p*-(2-aminoethyl)calix[4]arene (**11**) with several metal ions, including Ni^{2+}, Cu^{2+}, Pd^{2+}, Co^{2+}, and Fe^{2+}, has been investigated. The spectral and chemical characteristics of these complexes are interpreted as indicating that **11** is more flexible than had been anticipated, behaving more like four independent ethylamine moieties than a single trialkylenetetramine moiety.

Synthesis of Functionalized Calixarenes: the *p*-Quinone Methide Route. Calixarenes are cavity-containing macrocyclic compounds that have attracted our interest because of their potential for forming host-guest complexes and, if appropriately functionalized,

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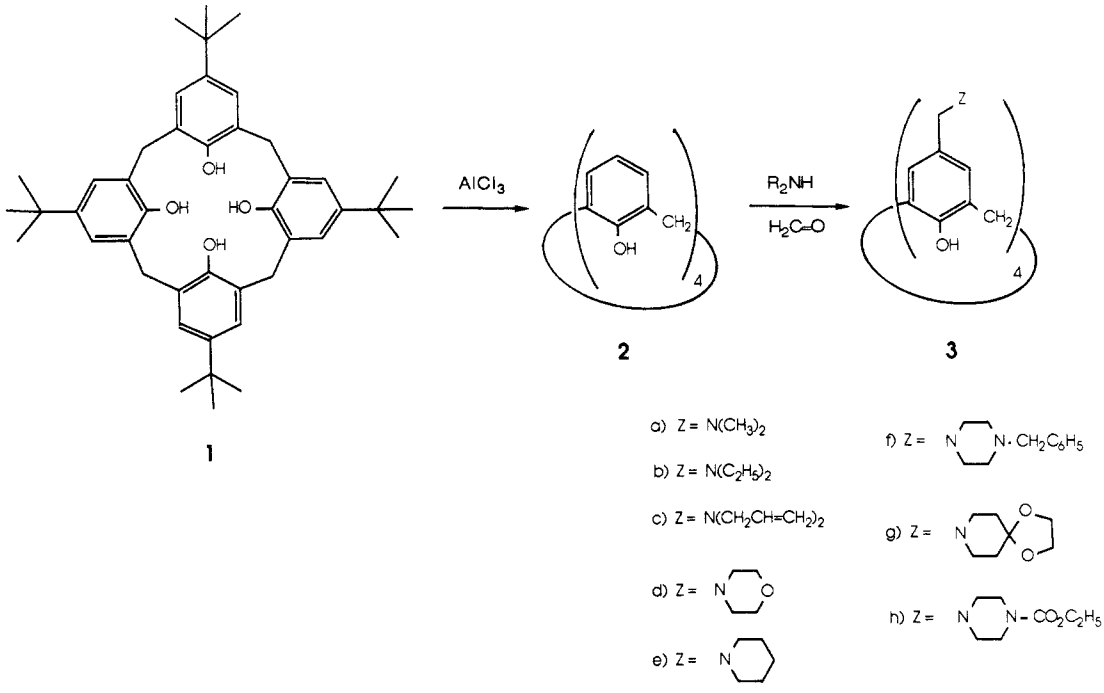

Figure 1. Synthesis of calixarene Mannich bases.

acting as enzyme mimics.[1] In previous papers in this series we have discussed the preparation of functionalized calixarenes by means of the direct substitution route[2] and the para Claisen rearrangement route.[3,4] The present method utilizes a *p*-quinone methide pathway and makes available an expanded variety of functionalized calixarenes, including a number of amino-calixarenes.

p-tert-Butylcalix[4]arene (**1**) can be easily prepared in good yield by the base-induced condensation of *p-tert*-butylphenol and formaldehyde.[5] Aluminum chloride catalyzed removal of the *tert*-butyl groups proceeds in excellent yield,[3,4] making calix[4]-arene (**2**) a readily available starting material for the introduction of functional groups onto the calixarene framework. Since calixarenes are phenols and should be expected to undergo the reactions that are characteristic of this class of compounds, it was anticipated that the Mannich reaction with formaldehyde and a secondary amine would proceed without event (Figure 1). There are, in fact, numerous accounts in the literature[6] of successful applications of this process to simple phenols, but our initial attempts to achieve aminomethylation with **2** failed. The cause of the failure was eventually determined to be due to conditions that were too strenuous, leading to polymeric mixtures. When milder conditions were employed, involving treatment of a THF–acetic acid solution of **2**, formaldehyde, and the appropriate secondary amine at room temperature for a day, 70–90% yields of Mannich bases (**3**) were realized.

One of the principal synthetic applications of Mannich bases involves their conversion to the corresponding quaternary ammonium salt followed by treatment with a nucleophile to effect an S_N2 displacement of the amino moiety.[7] With phenolic Mannich bases the nucleophilic displacement is thought to proceed via an intermediate quinonemethide. The intermediacy of *o*-quinone methides has been inferred in several cases from the results of trapping experiments with agents such as vinyl ethers, which engage in a cycloaddition reaction to yield coumarans;[8] *p*-quinone methides themselves have been isolated as such in certain instances.[9] Employing the general protocol described in the literature, the Mannich bases (**3**) were treated with methyl iodide to produce the quaternary ammonium compounds (**4**), which were not isolated but were allowed to react directly with a nucleophile, yielding the substitution products (**6**) (Figure 2). That the *p*-quinone methide (**5**) is an intermediate is indicated by the fact that when the phenol **3a** is protected as a *p*-bromobenzenesulfonate and then treated with methyl iodide followed by sodium cyanide, no reaction occurs even after many hours. Under comparable conditions the quaternary ammonium compound from the free phenol (**3a**) reacts with cyanide to yield **6a** smoothly and rapidly.

The *p*-quinone methide route provides a particularly short pathway to a variety of functionalized calixarenes. For example, the preparation of *p*-(2-aminoethyl)calix[4]arene (**7b**) via the *p*-Claisen rearrangement route[3] has been previously described wherein the resulting *p*-allylcalix[4]arene is oxidized to the aldehyde, the aldehyde is reduced to the alcohol, the alcohol is converted to the bromide, the bromines are replaced by azide groups, and the azide groups are reduced to amino groups to yield **7b**. This same compound has now been prepared simply by reduction of **6a**, making it considerably more readily available, and its lower homologue, *p*-(aminomethyl)calix[4]arene (**7a**), is also easily accessible via the *p*-quinone methide route by reduction of the azide **6c**. The *p*-quinone methide route provides an easy way to introduce carboxyl groups onto the calixarene framework, because enolates from diethyl malonate and ethyl α-nitroacetate react smoothly with the quaternary compounds to yield **6f** and **6g**, respectively. Hydrolysis and decarboxylation of **6f** produces *p*-(carboxyethyl)calix[4]arene (**8a**), and hydrolysis of **6g** yields *p*-(2-nitro-2-carboxyethyl)calix[4]arene (**8b**). Compound **8b** is particularly interesting as a precursor to a calixarene carrying α-amino acid moieties, although attempts to reduce **8b** to the corresponding amine have so far been unsuccessful. Also disappointing have been attempts to effect nucleophilic substitution of the quaternized Mannich bases with acetylides. Neither 1-

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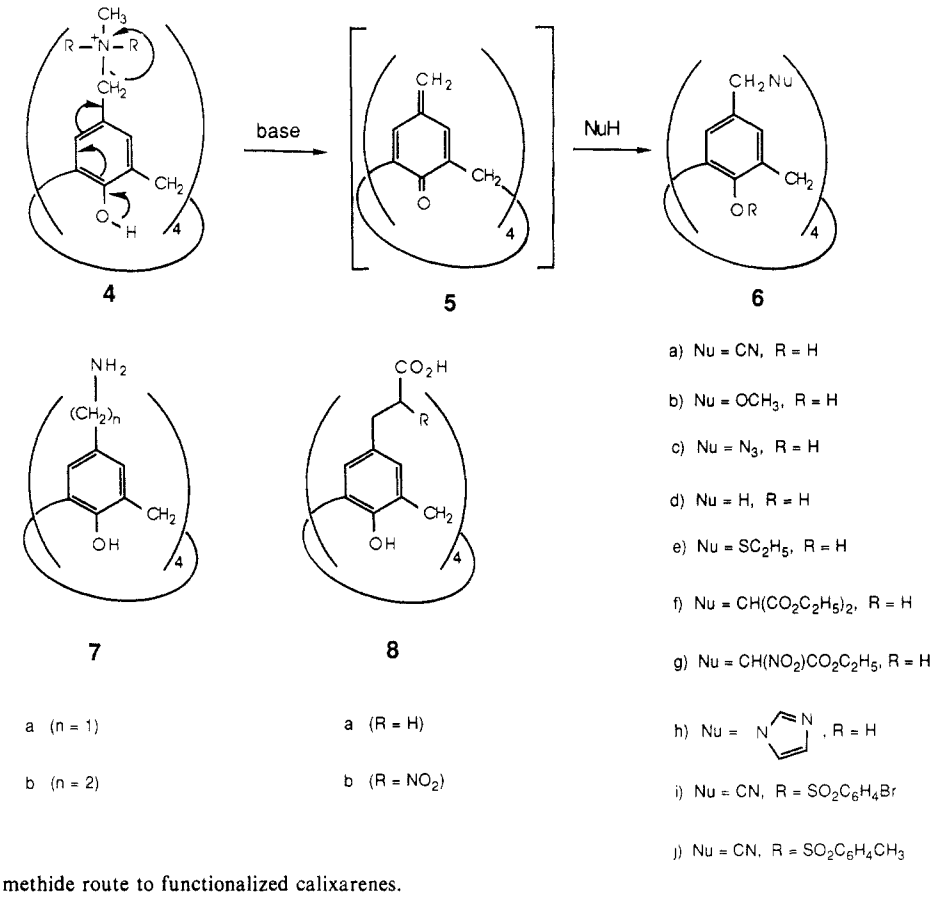

Figure 2. *p*-Quinone methide route to functionalized calixarenes.

lithioethyne nor 1-lithiohexyne reacted smoothly with **4**, mixture being produced in both cases. Although spectral evidence indicates that the desired acetylene-containing calixarenes are present, pure materials could not be isolated. These reactions were carried out in DMSO solution, and it appears that the anion from DMSO competes with the acetylide, resulting in a mixture of products containing both of these nucleophiles in various arrays around the calixarene ring. Fortunately, this complication is absent with the more weakly basic anions such as cyanide, methoxide, azide, sulfide, and malonate. Of course, too weak a base will not react, although even imidazole, under somewhat more strenuous conditions, affords good yields of the interesting tetraimidazolyl compound **6h**.

The reaction of **4** with sodium borohydride in which *p*-methylcalix[4]arene is the expected product was only partly successful, complicated by hydride displacement on the methyl groups of the quaternary salt to yield the parent amine **3a**. Nevertheless, sufficient quantities of **6d** were isolated to allow its purification and characterization. This compound is of historical interest, because it was the first calixarene to be synthesized by a "rational" procedure. Hayes and Hunter[10] employed a stepwise synthesis to build up a *linear* tetramer protected at one of its ortho positions by bromine and containing a hydroxymethyl group at the other ortho position. Removal of the bromine followed by acid catalysis then yielded the *cyclic* tetramer, *p*-methylcalix[4]arene, which was tacitly assumed at the time to provide a proof of structure for the products that Zinke and co-workers[11] had obtained from the base-induced condensation of formaldehyde with *p*-substituted phenols, including *p*-cresol, although no direct comparison of materials was made. Later investigation,[12] however, showed that although *p-tert*-butylphenol yields a tractable product, which, under certain conditions, is mainly the cyclic tetramer, *p*-cresol yields a far less tractible mixture from which pure cyclic oligomers have yet to be isolated. Thus, the present synthesis is the first direct connection between the Hayes and Hunter stepwise preparation and the Zinke-type preparation of *p*-methylcalix[4]arene, albeit the latter via *p-tert*-butylcalix[4]arene as an intermediate.

Table I. Coalescence Temperatures and Free Energies of Activation for the Conformational Inversion of Calix[4]arenes Carrying Amine-Containing Substituents in the Para Position

substituent	deuteriated solvent	T_c, °C	δ, CH_2 Protons H_a	H_b	$\Delta G^{\ddagger}$, kcal/mol
(dimethylamino)-methyl	chloroform	52	4.24	3.48	15.7
	bromobenzene	46	4.23	3.35	15.4
	CH_3CN	67	4.37	3.21	16.2
	pyridine	40	5.14	3.51	14.7
	DMF	71	4.37	3.18	16.3
	CF_3CO_2H	27			
	DMSO	82	4.27	3.18	16.9
(*N*-benzylpiperazino)-methyl	chloroform	57	4.20	3.49	16.0
	DMSO	85	4.24	3.12	17.1
2-aminoethyl	DMSO	90	4.23	3.10	17.3
imidazolinomethyl	DMSO	62	4.22	3.10	15.9

NMR, IR, and UV Spectral Properties of *p*-(Aminoalkyl)calix[4]arenes. The conformational behavior of *p*-alkylcalix[4]arenes has been studied in considerable detail[13] by means of ^1H NMR spectroscopy, and the coalescence temperature for the cone–cone interconversion has been shown to be dependent (inter alia) on

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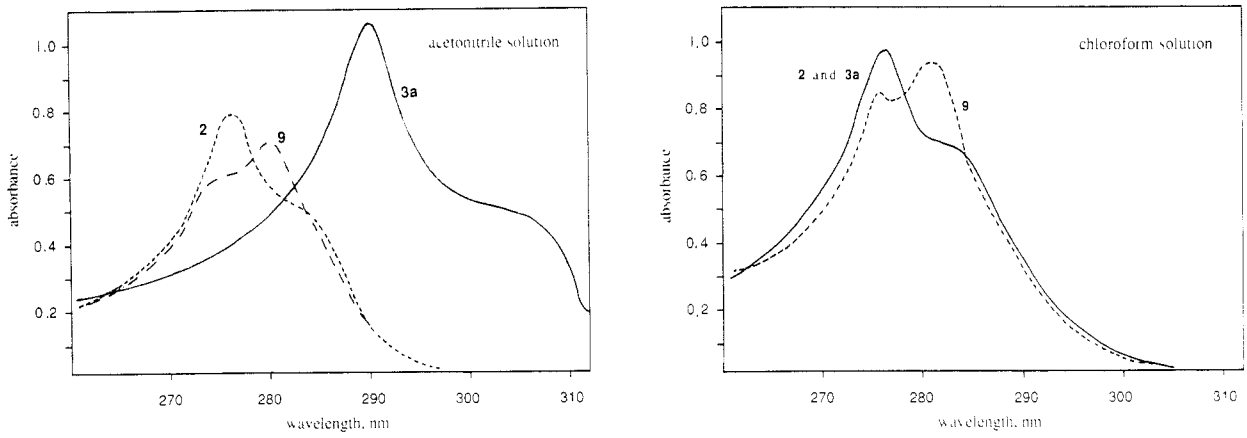
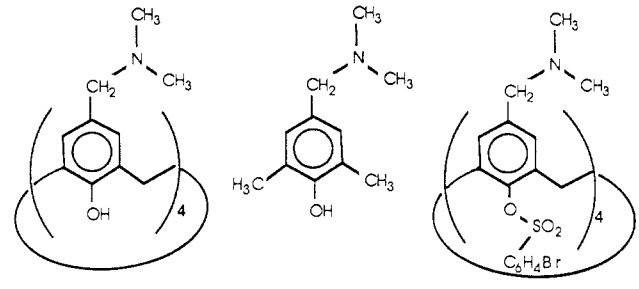


Figure 3. UV spectra of **2**, **3a**, and **9** in chloroform and acetonitrile solution.

the *p*-substituent as well as the solvent. For example, *p*-*tert*-butylcalix[4]arene has T_c = 52 °C in chloroform, 18 °C in DMSO, and 15 °C in pyridine, corresponding to $\Delta G^{\ddagger}$ values of 15.7, 13.8, and 13.7 kcal/mol; *p*-allylcalix[4]arene has T_c = 37 °C in chloroform and 10 °C in acetonitrile, corresponding to $\Delta G^{\ddagger}$ values of 15.0 and 13.5 kcal/mol; *p*-(1,1,3,3-tetramethylbutyl)-calix[4]arene has T_c = 30 °C in chloroform and −13 °C in pyridine corresponding to $\Delta G^{\ddagger}$ values of 14.6 and 12.4 kcal/mol. In contrast, the coalescence temperatures and the $\Delta G^{\ddagger}$ values that are observed for calix[4]arenes carrying amino-containing substituents in the *para* positions, as shown in Table I, are generally higher, the difference being especially notable in the more polar solvents such as pyridine, acetonitrile, and DMSO. A similar increase in coalescence temperature is observed when an amine is added to an acetonitrile or acetone solution of a calixarene. For example,[14] the T_c for *p*-allylcalix[4]arene is increased from 10 to 36 °C upon the addition of *tert*-butylamine in acetonitrile solution, although there is essentially no change in chloroform solution. The increased T_c in acetonitrile is ascribed to an intermolecular proton transfer that produces a calixarene anion and a *tert*-butylammonium cation. In similar fashion, the four aminocalixarenes shown in Table I can form a calixarene anion and an ammonium cation, the only difference being that in this case the process is intramolecular and the product is a zwitterion.

The fact that the T_c values are higher in acetonitrile and DMSO than in chloroform suggests that the aminocalix[4]arenes have increased zwitterionic character in the more polar solvents, a conclusion that finds further corroboration in the comparison of the NMR characteristics of *p*-[(dimethylamino)methyl]calix-[4]arene (**3a**), 4-[(dimethylamino)methyl]-2,6-dimethylphenol (**9**), and the *p*-bromobenzenesulfonate of *p*-(dimethylamino)-methyl]calix[4]arene (**10**). In DMSO solution the δ values for the *N*-methyl protons are 2.18 for **3a**, 2.08 for **9**, and 1.93 for **10**, as shown in Table II. Since **10** has no phenolic groups, it is assumed that its amino groups are unprotonated and that the δ 1.93 resonance represents that of CH_3 attached to a neutral nitrogen. Thus, with respect to **10**, the CH_3N resonances of **3a** and **9** are shifted 0.25 and 0.15 ppm downfield, respectively, indicating that both have zwitterionic character but with that of **3a** greater than **9**. This is commensurate with the greater acidity of the calixarene as compared with its monomeric phenol counterpart, as has been shown, for example, for *p*-nitrocalix-[4]arene, which is 7 or more orders of magnitude more acidic than *p*-nitrophenol[15] in aqueous solution. What is assumed to be *complete* protonation of **3a**, **9**, and **10** was achieved by adding a large excess of trifluoroacetic acid, producing δ values of 2.64, 2.68, and 2.64, respectively. In similar fashion, comparisons of the CH_2 resonances for compounds **3a**, **9**, and **10**, alone and in the presence of trifluoroacetic acid, lead to the same conclusion, viz. that both **3a** and **9** have zwitterionic character but **3a** more so than **9**. When this same series of measurements was carried out with chloroform solutions of **3a**, **9**, and **10**, the values obtained showed approximately the same downfield shifts of the CH_3 and CH_2 protons of **3a** and **9** relative to **10**, suggesting that in this solvent **3a** is no more zwitterionic than **9**.

Table II. Chemical Shifts (δ) of the CH_3 and CH_2 Protons of **3a**, **9**, and **10**



3a **9** **10**

	DMSO	DMSO	DMSO
CH_3	2.18	2.08	1.93
CH_2	3.27	3.18	2.97
	$CDCl_3$	$CDCl_3$	$CDCl_3$
CH_3	2.18	2.19	2.05
CH_2	3.20	3.29	2.99
	DMSO (with TFA)	DMSO (with TFA)	DMSO (with TFA)
CH_3	2.63	2.68	2.63
CH_2	4.05	4.12	4.16

p-Alkylcalix[4]arenes show concentration independent OH stretching bands in the IR spectra at ca. 3200 cm^{-1}, indicative of strong intramolecular hydrogen bonding. The infrared spectra of *p*-aminoalkylcalix[4]arenes (KBr pellet) show a broad band extending from 2500 to 3200 cm^{-1}, characteristic of a tertiary amine salt and commensurate with a zwitterionic structure.

The UV spectra of *p*-[(dimethylamino)methyl]calix[4]arene (**3a**), calix[4]arene (**2**), and 4-[(dimethylamino)methyl]-2,6-dimethylphenol (**9**) in chloroform and in acetonitrile solution are shown in Figure 3. In chloroform solution all three spectra are quite similar in character, showing absorption maxima at ca. 275 and 285 nm; indeed, those of the two calixarenes are almost superimposable on one another. In acetonitrile solution, however, the spectrum of the aminocalixarene **3a**, displaying a major peak at 290 nm and a shoulder at 310 nm, is different from that of the simple calixarene or the monomeric aminophenol. Previous work in this laboratory[16] has shown that the UV spectrum of an acetonitrile solution of an alkylcalix[4]arene changes upon addition

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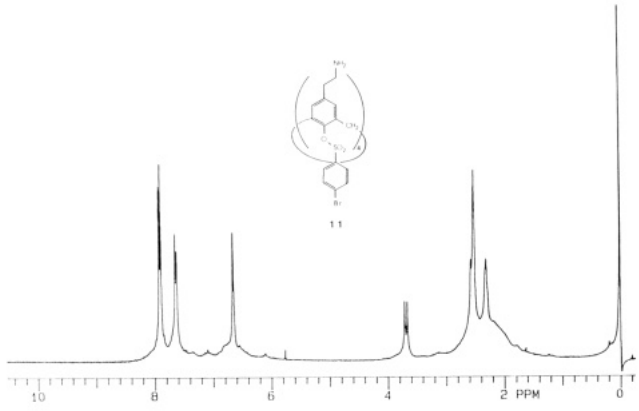


Figure 4. 300-MHz ^{1}H NMR spectrum of **11** in DMSO-d_6.

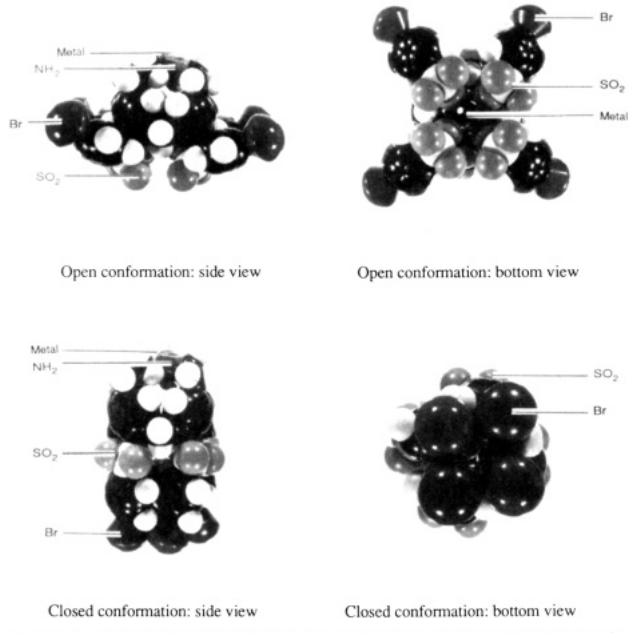


Figure 5. Space-filling CPK models of the "open" and "closed" conformations of a **11**·metal complex.

of an amine, the λ_{max} moving to a longer wavelength. This is ascribed to the formation of the calixarene monoanion, and it suggests that **3a** similarly exists as a calixarene monoanion, in this case a zwitterion.

Metal Binding Properties of *p*-(2-Aminoethyl)calix[4]arene. One of the reasons for undertaking the synthesis of *p*-(2-aminoethyl)calix[4]arene (**7b**) was to explore its potential for acting as an oxygen carrier in the presence of certain metal ions, the premise being that an octahedral complex would form in which the amino groups of **7b** occupy four equatorial sites around a metal ion; an external ligand such as an amine occupies a fifth (apical) site, leaving the sixth (apical) site pointing *into* the cavity of the calixarene and accessible only to molecules small enough to pass through the annulus at the "lower rim" of the calixarene. Although this goal has yet to be realized, none of the metal ion complexes that were investigated showing any oxygen affinity, the results of this study may provide the guidelines for the eventual construction of an oxygen-carrying calixarene.

All of the metal ion complexation studies were carried out with the tetra-*p*-bromobenzenesulfonate of *p*-(2-aminoethyl)calix[4]arene (**11**) to insure a rigid cone conformation and to obviate any involvement of the phenolic hydroxyl groups in the interaction with the metal ion. That the calixarene is in the cone conformation is indicated by the ^{1}H NMR spectrum, shown in Figure 4, which contains a pair of doublets arising from the CH_2 protons and unique for the cone conformation, one centered at δ 3.77 and the other at δ 2.47 (underneath resonances from $ArCH_2CH_2N$). Unfortunately, there is no NMR pattern that allows the conformation of the [(*p*-bromophenyl)sulfonyl]oxy groups to be established in comparable fashion. The ArH resonances of the [(*p*-bromophenyl)sulfonyl]oxy ring appear as a pair of sharp doublets, commensurate either with a fixed, and symmetrical, conformation or with a rapidly interconverting set of conformations. Two conformations of **11** (complexed with a metal) are illustrated by the CPK models shown in Figure 5, one an "open" form in which the [(*p*-bromophenyl)sulfonyl]oxy groups radiate outward from the lower rim of the calix and the other a "closed" form in which these same groups align themselves proximate to one another in a face-to-face fashion. Of course, numerous conformations intermediate between these two extremes are possible.

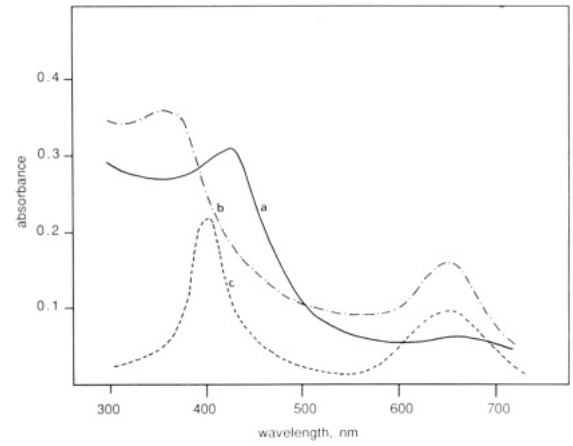
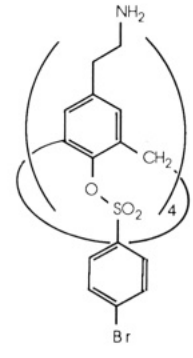


Figure 6. Visible absorption spectra: (a) Ni(II)–**11** complex in THF solution, (b) Ni(II)–**11** complex in THF in presence of $LiClO_4$, (c) $(isoquinoline)_2Ni(NO_3)_2$ complex in aqueous solution.

Nickel Complexes. Treatment of **11** with an equimolar quantity of $Ni(ClO_4)_2 \cdot 6H_2O$ in THF produces a greenish yellow solution whose spectrum possesses absorption maxima at 380 and 650 nm, as shown by curve a in Figure 6. Upon addition of lithium perchlorate to this solution, the color changes from greenish yellow to yellow, and the spectrum displays a single major absorption at 420 mm, as shown by curve b in Figure 6. This behavior is rather similar to that of triethylenetetraamine (trien) with Ni(II), which was shown by Jorgensen[17] to produce an equilibrium mixture of (a) a yellow, low-spin, diamagnetic square-planar species $[Ni(trien)]^{2+}$ with an absorption maximum at 443 nm and (b) a blue, high-spin, diaquo octahedral species $[Ni(trien)(H_2O)_2]^{2+}$ with absorption maxima at 352 and 550 nm; the equilibrium is shifted in favor of the square-planar species by increasing the ionic strength of the solution. The ^{1}H NMR spectrum of the greenish yellow species obtained from **11** showed only broad bands, suggestive of the presence of a paramagnetic ion; the IR spectrum contained bands at 1100 and 640 cm^{-1}, indicative of the presence of uncoordinated perchlorate ion. Thus, the combined UV and ^{1}H NMR spectral evidence supports the structure of the greenish yellow Ni^{2+} complex as being a hexa-



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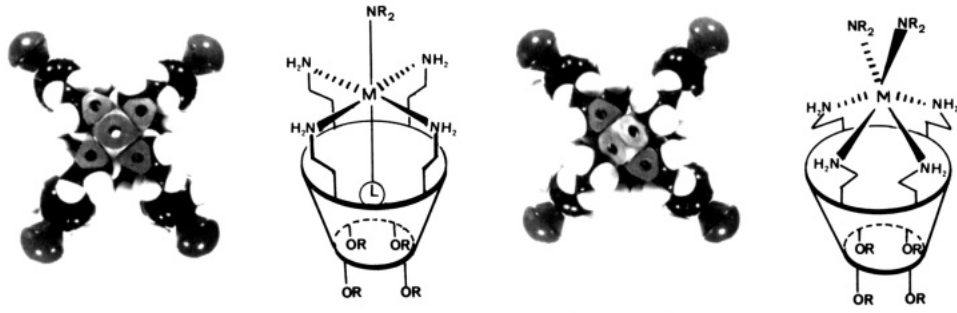

Structure A showing one *endo*-calix site on metal

Structure B showing two *exo*-calix sites on metal

Figure 7. CPK models and stylized representations of two configurations of the hexacoordinate, octahedral complex of **11** with a metal ion.

coordinate, octahedral species, and the UV spectral evidence supports the structure of the yellow Ni^{2+} complex as being a tetracoordinate, square-planar species. Although the working premise of this investigation was that the octahedral complexes of **11** should possess the structure A illustrated in Figure 7, CPK models indicate that structure B can also exist in which *both* the fifth and sixth coordination sites are *external* to the cavity. The inability to regenerate the greenish yellow, octahedral species from the yellow, square-planar species by the addition of excess imidazole might be taken as support of structure A in favor of structure B, the former requiring that one of the imidazoles be inside the calix. Additional support for the octahedral geometry of the **11**-Ni(II) complex is provided by a comparison with the $(isoquinoline)_2Ni(NO_3)_2$ complex, which is known to have an octahedral configuration[18] and which has a spectrum rather similar to that of the greenish yellow complex of **11**-Ni(II), as shown by curve c in Figure 6.

Copper Complexes. A mixture of equimolar amounts of **11** and $Cu(ClO_4)_2 \cdot 6H_2O$ in THF produces a green solution, which displays an absorption band at 625 nm and a small shoulder at 540 nm, as shown in curve a in Figure 8. Upon the addition of imidazole to this solution the green color persists, but the major absorption band becomes sharper and moves to 650 nm and the shoulder at 540 nm disappears, as shown in curve b in Figure 8. When the THF solution of the Cu(II)–**11** complex is refluxed the 650-nm band slowly disappears and is ultimately replaced after 6 h by a band at 540 nm, as represented by curve c in Figure 8. In comparison, the initially formed complex of *N,N'*-bis(2-aminoethyl)-1,3-propanediamine (2,3,2-tet) and $Cu(ClO_4)_2 \cdot 6H_2O$ in methanol is reddish violet, showing an absorption maximum at 523 nm that changes to 578 nm upon the addition of a ligating agent such as imidazole. The structures of these 2,3,2-tet complexes have been established[19] as square-planar and square-pyramidal, respectively, although an octahedral complex cannot be unequivocally excluded as a possibility. Barbucci and co-workers have reported a square-pyramidal [Cu(trien)(SCN)](NCS) complex,[20] which shows a 625-nm absorption band in DMF and nitrobenzene, and a trigonal bipyramidal [Cu(trien)(SCN)](CNS) complex,[21] which shows a broad absorption band at 833 nm. On the basis of these data it is postulated that the Cu(II)–**11** complex having the 540-nm absorption band represents the square-planar species and that the one having the 650-nm absorption band represents the square-pyramidal species. When $CuCl_2 \cdot H_2O$ instead of $Cu(ClO_4)_2 \cdot 6H_2O$ is used, a complex is produced that possesses an absorption band at 740 nm, characteristic of the known octahedral complex $(isoquinoline)_2Cu(NO_3)_2$[18] and Cu(EDTA).[22]

Palladium Complexes. Treatment of a THF solution of $Pd(CH_3CN)_2Cl_2$, prepared from $PdCl_2$,[23] with **11** produces a copious white precipitate that is separable by filtration but that resists purification by recrystallization. The IR spectrum of this material shows no absorption near 2300 cm^{-1} (indicating the absence of CN) but reveals the presence of two NH stretching bands, one at 3580 cm^{-1} and the other at 3280 cm^{-1}. The ^1H NMR spectrum shows two equally intense resonances from the Ar H of the calixarene ring (a single resonance in the parent compound) and two equally intense sets of pairs of doublets from the bridge CH_2 groups of the calixarene (one set in the parent compound). On the basis of these data the postulated structure is that of a complex containing two N–Pd covalent bonds and two N–Pd coordinate bonds, similar to that observed in porphyrin compounds.[24]

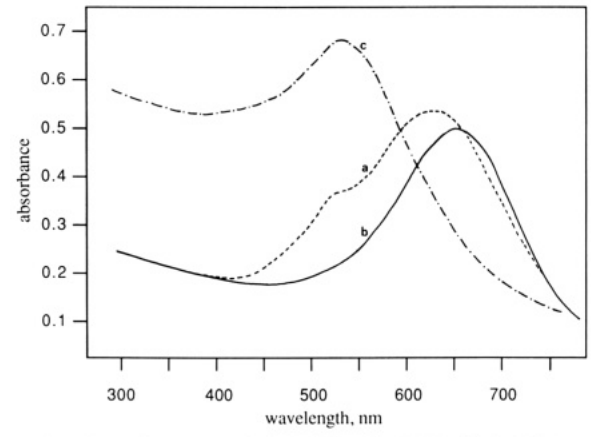

Figure 8. Absorption spectra: (a) Cu(II)–**11** in THF, (b) Cu(II)–**11** and excess imidazole in THF, (c) Cu(II)–**11** in THF after 6 h of reflux.

Cobalt Complexes. Treatment of a THF solution of **11** with an equimolar amount of $CoCl_2$ in an inert atmosphere produces a blue solution, the spectrum of which displays a major band at 630 nm and shoulders at 599 and 660 nm, as shown by curve b in Figure 9. On the basis of data reported in the literature for Co(II)–amine complexes,[25] it is postulated that the Co(II)–**11** complex is a mixture of tetrahedral and octahedral species, the octahedral complex possessing weak absorption bands in the 460–560-nm region (pale orange-pink) and the tetrahedral complex giving rise to the stronger absorption (intense blue-violet). There is little similarity between these spectra and those of the known square-pyramidal Co(II) complexes.[26]

A solution of $CoCl_2$ in THF is deep blue, shows a broad absorption band at 684 nm, and is stable to oxidation to Co^{3+}. When a few equivalents of pyridine or 100 or more equivalents of 2,6-lutidine are added to this solution, the absorption band is shifted to shorter wavelength and is greatly increased in intensity, but the solution remains resistant to oxidation. Addition of lesser

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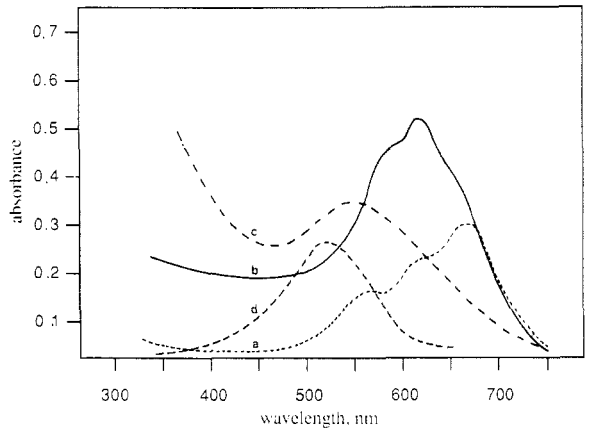

Figure 9. Absorption spectra: (a) $CoCl_2$ in THF, (b) $CoCl_2$–**11** in THF, (c) $Co(OAc)_2$–**11** in THF, (d) $Co(OAc)_2$–**11** in CH_3OH.

amounts of 2,6-lutidine, however, results in the formation of a green solution and the separation of a precipitate. The spectrum of the green solution shows a large increase in absorption in the UV, characteristic of a Co^{3+} species.[27] It is postulated that with pyridine or with an excess of 2,6-lutidine a hexacoordinate Co^{2+} species predominates, which is resistant to oxidation, but that with smaller amounts of the more weakly coordinating 2,6-ligand a pentacoordinate species is present, which has been suggested[28] to have enhanced sensitivity to attack by O_2. Like $CoCl_2$ in THF, alone or in the presence of pyridine, the $CoCl_2$–**11** complex in THF is stable to oxidation. Upon the addition of several equivalents of imidazole, *N*-methylimidazole, or a small amount of water, however, the color almost immediately changes from blue to a very pale yellow, a change that can also be induced by the addition of oxidizing agents such as KIO_4. Thus, while **11** coordinates the Co^{2+} in a geometry that resists oxidation, displacement of one or more of the ligands of **11** by an external nucleophile produces a much more easily oxidized species, possibly one that is pentacoordinate.

Somewhat different results are observed when $Co(OAc)_2 \cdot 4H_2O$ is mixed with **11** in THF or CH_3OH, giving rise in the first instance to a violet solution with an absorption maximum at 549 nm and in the second instance to a red solution with an absorption maximum at 518 nm, as represented by curves c and d in Figure 9. In both cases the formation of an octahedral complex is indicated by the position of λ_{max}. When the violet solution is exposed to air for 24 h, it changes to a pale yellow, indicative of oxidation to a Co^{3+} species and suggesting that the octahedral complex is more susceptible to oxidation than is the tetrahedral complex.

Iron Complexes. Treatment of a THF solution of anhydrous $FeCl_2$ with **11** in an inert atmosphere produced a brown solid, which was separated by filtration. A solution of this material in DMSO containing *N*-methylimidazole showed a featureless visible spectrum that did not change upon exposure to oxygen. Had an iron–dioxygen species been formed it would have been expected to show an absorption maximum near 520 nm, which should have disappeared upon flushing the solution with N_2 or lowering the partial pressure of O_2.[29] The ^1H NMR spectrum of the $FeCl_2$–**11** complex shows only broad resonances in which the Ar H peaks are shifted downfield (δ 7.4 in the complex; δ 6.6 in the parent calixarene) and in which a peak appears at ca. δ 6 (ascribed to NH). Exposure of this solution to oxygen does not change the ^1H NMR spectrum, corroborating the fact that an oxygen complex is not forming. Upon the addition of a drop of D_2O to the solution, a marked change occurs in the ^1H NMR spectrum in which the ArH resonances move back to δ 6.9 and two broad singlets at δ 2.9 and 2.6 appear (arising from the CH_2 protons). Close examination of this spectrum reveals that it is essentially identical with that of **11**·HCl, suggesting that the complex has reacted with D_2O to release Fe(II), generate DCl, and form the hydrochloride.

Table III. Extraction of Picrate Salts with Various Amines

ligand	fraction of cation extracted, %				
	Li^+	Na^+	K^+	Rb^+	Cs^+
11	85	84	84	84	85
2-aminoethylbenzene	2	3	3	2	3
p-bromobenzenesulfonate of (2-aminoethyl)benzene	20	21	19	21	21
p-bromobenzenesulfonate of calix[4]arene	1	1	1	1	1
6-cetyl-1,4,7,11-tetraazaundecane	97	99	99	97	97
(2-aminoethyl)benzene + *p*-bromobenzenesulfonate of (2-aminoethyl)benzene	9	10	11	11	8

The goal of constructing an aminocalixarene capable of interacting reversibly with O_2 has not yet been achieved, none of the metal complexes that are described above showing any tendency in this direction. While this may be the result of an annulus that is too small to allow the entry of oxygen at the "lower rim" of the calixarene, it is more likely due, at least in part, to the lack of rigidity of the polyamine, which leads to less stable complexes than had been anticipated. There appears to be little, if any, "macrocyclic effect"[30] with **11**, the four aminoethyl groups acting essentially independently of one another and more comparable to 4 equiv of ethylamine than 1 equiv of a trialkylenetetramine or cyclam. Work is currently under way in an attempt to increase the rigidity of the aminocalixarene **11** by introducing spanner groups between the nitrogens.

Extraction and Ion Transport Studies. Considerable attention has been devoted over the last decade to the transport of metal ions across membranes, a membrane often being interpreted as a nonaqueous barrier separating two aqueous phases.[31] In the present work the U-tube method of measurement was employed in which a $CHCl_3$ solution containing an aminocalixarene (5×10^{-1} M) was placed in the bottom of the assembly, deionized water was placed in one side (receiving phase), and a 0.01 M solution of picric acid (source phase) was placed in the other side. The amount of metal picrate transported from the source phase to the receiving phase was measured by UV–vis spectroscopy. Only small amounts of transport were noted, however, and even after long periods of time much less transport occurred than with the *p*-alkylcalixarenes.[31] For example, Li^+, which showed the highest value, was transported only to the extent of 0.4% after 290 h, and after the same length of time K^+ and Cs^+ showed only 0.05% transport.

The aminocalixarenes were more effective in straight extracation experiments, although with none of the compounds that were investigated were any ion selectivities noted. Extraction experiments were typically performed by equilibrating 5 mL of a 7×10^{-5} M solution of the metal picrate in water with 5 mL of a 2×10^{-4} M solution of the tetraamine in CH_2Cl_2, the equilibration being facilitated by agitation for 5 min on a shaker. The extraction yield (R, %) was determined by measuring the amount of metal ion in the aqueous layer before and after the extraction, furnishing the data shown in Table III. Although the *p*-bromobenzenesulfonate of *p*-(2-aminoethyl)calix[4]arene (**11**) is considerably more effective than its monomeric analogue, it is significantly less so than a triethylenetetraamine carrying a cetyl group to render it soluble in CH_2Cl_2. Thus, the extraction data, like the spectral

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(31) Cf. for example, (a) the work of Izatt and co-workers on the ion transport properties of the *p-tert*-butylcalixarenes (Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Brown, P. R.; Izatt, S. R.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1782. Izatt, S. R.; Hawkins, R. T.; Christensen, J. J.; Izatt, R. M. *Ibid.* **1985**, *107*, 63) and (b) the work of Shinkai and co-workers on the construction of a calixarene-based uranophile (Shinkai, S.; Koreishi, H.; Ueda, K.; Arimura, T.; Manabe, O. *J. Am. Chem. Soc.* **1987**, *109*, 6371).

data, indicate that **11** provides a considerably less preorganized system for metal complexation than do certain polyamines such as triethylenetetramine.

Experimental Section[32]

Mannich Reactions. 5,11,17,23-Tetrakis[(dimethylamino)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (3a). To a solution of 15.9 g (0.0395 mol) of calix[4]arene (**2**) in 360 mL of THF were added 45 mL of acetic acid, 22.5 g (0.2 mol) of 40% aqueous dimethylamine, and 16.2 g (0.2 mol) of 37% aqueous formaldehyde. The reaction mixture was stirred for 24 h at room temperature, the solvents were removed under vacuum, and the residue was dissolved in 250 mL of water. The aqueous solution was extracted two times with 200 mL of ether and neutralized with 10% K_2CO_3 solution, and the precipitate that formed was removed by suction filtration. The product was dried under vacuum and then recrystallized from chloroform to give 19.1 g (78%) of white needles: mp 160 °C dec; ^{1}H NMR (DMSO-d_6) δ 6.85 (s, 8, Ar H), 4.25 and 3.16 (pair of d, 8, J = 12 Hz, $ArCH_2Ar$), 3.27 (s, 8, $ArCH_2N$), 2.18 (s, 24, NCH_3); ^{13}C NMR (DMSO-d_6) δ 154.1, 129.9, 128.4, and 125.2 (Ar), 62.5 ($ArCH_2N$), 44.0 (NCH_3), 32.5 ($ArCH_2Ar$). Anal. Calcd for $C_{40}H_{52}N_4O_4 \cdot {}^1/_8CHCl_3$: C, 72.19; H, 7.80; N, 8.40. Found: C, 72.10; H, 7.84; N, 8.42. A sample dried for 120 h at 109 °C turned pale yellow and gave even lower analytical values for carbon content.

5,11,17,23-Tetrakis[(dimethylamino)methyl]-25,26,27,28-tetrakis[[(*p*-bromophenyl)sulfonyl]oxy]calix[4]arene (*p*-Bromobenzenesulfonate of 3a). To a solution of 3.26 g (5 mmol) of **3a** in 120 mL of THF was added 4 g of NaH (60% oil dispersion, 100 mmol). The reaction mixture was stirred for 30 min, treated with 6.12 g (24 mmol) of *p*-bromobenzenesulfonyl chloride, and allowed to remain at room temperature for 10 h. The solvent was then removed under vacuum, and the residue was treated with 100 mL of ice–water and 100 mL of $CHCl_3$. The organic layer was separated, dried over Na_2SO_4, and evaporated to give a residue, which was triturated with hexane and recrystallized from acetone–isopropyl alcohol to give 6.96 g (92%) of pale yellow crystals: mp 187–189 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 16, Br–Ar H), 6.55 (s, 8, Ar H), 3.78 and 2.49 (pair of d, 8, $ArCH_2Ar$), 2.99 (s, 8, $ArCH_2N$), 2.05 (s, 24, NCH_3); ^{13}C NMR ($CDCl_3$) δ 143.7, 136.6, 134.9, 134.2, 132.3, 130.8, 129.6, and 129.3 (Ar), 63.3 ($ArCH_2N$), 44.9 (NCH_3), 31.0 ($ArCH_2Ar$). Anal. Calcd for $C_{64}H_{64}N_4O_{12}S_4Br_4$: C, 50.26; H, 4.19. Found: C, 50.16; H, 4.07.

5,11,17,23-Tetrakis[(dimethylamino)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (3b) was prepared by the procedure described for **3a**, with diethylamine, and was obtained in 72% yield as a colorless solid: mp ca. 134 °C dec; ^{1}H NMR ($CDCl_3$) δ 10.59 (br s, 4, OH), 6.92 (s, 8, Ar H), 4.38 and 3.26 (pair of d, 8, $ArCH_2Ar$), 3.44 (s, 8, $ArCH_2N$), 2.58 (q, 16, NCH_2), 1.06 (t, 24, CH_3); ^{13}C NMR (DMSO-d_6) δ 154.6, 130.2, and 128.4 (Ar), 56.4 ($ArCH_2Ar$), 10.8 (CH_3). Anal. Calcd for $C_{48}H_{68}N_4O_4 \cdot {}^1/_4CHCl_3$: C, 72.92; H, 8.56; N, 7.05. Found: C, 73.01; H, 8.56; N, 7.05.

5,11,17,23-Tetrakis[(diallylamino)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (3c) was prepared by the procedure described for **3a**, with diallylamine, and was obtained in 76% yield as a colorless solid: mp 74–76 °C; ^{1}H NMR ($CDCl_3$) δ 9.70–8.75 (br s, 4, OH), 6.99 (s, 8, Ar H), 5.85 (m, 8, CH=), 5.12 (m, 16, H_2C=), 4.20 and 3.48 (pair of d, 8, $ArCH_2Ar$), 3.35 (s, 8, $ArCH_2N$), 3.01 (d, NCH_2C=); ^{13}C NMR ($CDCl_3$) δ 147.7, 135.6, 132.4, 129.3, 128.0, and 117.3 (Ar and C=C), 57.0 and 56.3 ($ArCH_2N$ and NCH_2C), 31.9 ($ArCH_2Ar$). Anal. Calcd for $C_{56}H_{68}N_4O_4 \cdot {}^1/_4CHCl_3$: C, 75.84; H, 7.64; N, 6.29. Found: C, 75.60; H, 7.75; N, 5.98.

5,11,17,23-Tetrakis(*N*-piperidinomethyl)-25,26,27,28-tetrahydroxycalix[4]arene (3e) was prepared by the method described for **3a**, with piperidine, and was obtained in 79% yield as a colorless solid: mp ca. 162 °C dec; ^{1}H NMR (DMSO-d_6) δ 6.84 (s, 8, Ar H), 4.27 and 3.15 (pair of d, 8, J = 12 Hz, $ArCH_2Ar$), 3.30 (s, 8, $ArCH_2N$), 2.48 (br s, 16, NCH_2), 1.50 and 1.39 (m, 24, $CH_2CH_2CH_2$); ^{13}C NMR (DMSO-d_6) δ 155.0, 130.4, 129.0, and 127.6 (Ar), 62.0 and 53.2 ($ArCH_2N$ and NCH_2), 32.6 ($ArCH_2Ar$), 26.9 and 23.4 (CH_2CH_2). Anal. Calcd for $C_{52}H_{68}N_4O_4 \cdot {}^1/_6CHCl_3$: C, 75.24; H, 8.17; N, 6.73. Found: C, 75.03; H, 8.17; N, 6.18.

5,11,17,23-Tetrakis(*N*-piperidinomethyl)-25,26,27,28-tetrakis[[(*p*-bromophenyl)sulfonyl]oxy]calix[4]arene (*p*-bromobenzenesulfonate of 3e) was prepared by the procedure described for **3a** and was obtained in 91% yield as colorless crystals: mp 221–223 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 and 7.64 (pair of d, 16, J = 10 Hz, Ar H), 6.47 (s, 8, Ar H), 3.73 and 2.46 (pair of d, J = 14 Hz, $ArCH_2Ar$), 2.99 (s, 8, $ArCH_2N$), 2.11 (br s, 16, NCH_2), 1.48 and 1.38 (2 br s, 24, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 143.8, 136.0, 134.9, 134.4, 132.4, 131.0, 130.0, and 129.3 (Ar), 63.0 ($ArCH_2N$), 54.3 (NCH_2), 31.1 ($ArCH_2Ar$), 25.9 and 24.3 ($CH_2CH_2CH_2$). Anal. Calcd for $C_{76}H_{80}N_4O_{12}S_4Br_4$: C, 54.03; H, 4.74; N, 3.32. Found: C, 53.97; H, 4.61; N, 3.09.

5,11,17,23-Tetrakis(*N*-morpholinomethyl)-25,26,27,28-tetrahydroxycalix[4]arene (3d) was prepared by the procedure described for **3a**, with morpholine, and was obtained in 78% yield as a colorless solid: mp ca. 170 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 8, Ar H), 4.22 and 3.52 (pair of d, 8, J = 14 Hz, $ArCH_2Ar$), 3.69 (br s, 16, CH_2O), 3.26 (s, 8, $ArCH_2N$), 2.38 (br s, 16, CH_2N); ^{13}C NMR (DMSO-d_6) δ 154.6, 130.2, 129.0, and 124.2 (Ar), 67.8, 62.1, and 52.5 (NCH_2, CH_2O and $ArCH_2N$), 32.4 ($ArCH_2Ar$). Anal. Calcd for $C_{48}H_{60}N_4O_8 \cdot {}^1/_3CHCl_3$: C, 67.44; H, 6.98; N, 6.51. Found: C, 67.59; H, 7.14; N, 6.50.

5,11,17,23-Tetrakis(*N*-morpholinomethyl)-25,26,27,28-tetrakis[[(*p*-bromophenyl)sulfonyl]oxy]calix[4]arene (*p*-bromobenzenesulfonate of 3d) was prepared by the method described for **3a** and was obtained in 85% yield as colorless crystals: mp 263–265 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 and 7.69 (pair of d, 16, J = 9 Hz, BrArH), 6.54 (s, 8, Ar H), 3.83 and 2.55 (pair of d, 8, J = 12 Hz, $ArCH_2Ar$), 3.66 (br s, 16, OCH_2), 3.08 (s, 8, $ArCH_2N$), 2.22 (s, 16, NCH_2); ^{13}C NMR ($CDCl_3$) δ 144.0, 135.3, 135.2, 134.4, 132.5, 131.0, 130.0, and 129.5 (Ar), 66.8, 62.6, and 53.5 ($CH_2NCH_2CH_2O$), 31.2 ($ArCH_2Ar$). Anal. Calcd for $C_{72}H_{72}N_4O_{16}S_4Br_4$: C, 50.94; H, 4.25; N, 3.30. Found: 50.98; H, 4.20; N, 3.18.

5,11,17,23-Tetrakis[(*N'*-benzyl-*N*-piperazino)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (3f) was prepared by the procedure described for **3a**, with *N*-benzylpiperazine, and was obtained in 70% yield as colorless crystals: mp 134–136 °C; ^{1}H NMR ($CDCl_3$) δ 10.0–9.5 (br s, 4, OH), 7.30 (m, 20, Ar H), 6.96 (s, 8, Ar H), 4.10 and 3.49 (pair d, 8, $ArCH_2Ar$), 3.51 and 3.25 (2 s, 16, $ArCH_2N$), 2.45 (br s, 32, NCH_2CH_2N); ^{13}NMR ($CDCl_3$) δ 147.7, 138.0, 131.5, 129.6, 129.1, 128.1, 127.9, and 126.9 (Ar), 63.0, 62.4, 53.0, and 52.9 (4 NCH_2), 31.6 ($ArCH_2Ar$). Anal. Calcd for $C_{76}H_{88}N_8O_4$: C, 77.55; H, 7.48; N, 9.52. Found: C, 77.06; H, 7.53; N, 9.15.

5,11,17,23-Tetrakis[(1,4-dioxo-8-azaspiro[4.5]decanyl)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (3g) was prepared by the procedure described for **3a**, with 1,4-dioxo-8-azaspiro[4.5]decane, and was obtained in 73% yield as colorless crystals: mp ca. 165 °C dec; ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 8, Ar H), 4.21 and 3.50 (pair of d, 8, $ArCH_2Ar$), 3.94 (s, 16, OCH_2), 3.28 (s, 8, $ArCH_2N$), 2.45 (br s, 16, NCH_2), 1.73 (t, 16, CH_2C); ^{13}C NMR ($CDCl_3$) δ 147.8, 132.2, 129.6, and 128.0 (Ar), 107.4 (OCO), 64.2, 62.1, and 51.3 (OCH_2, NCH_2, and NCH_2Ar), 34.8 and 31.8 ($ArCH_2Ar$ and CH_2C). Anal. Calcd for $C_{60}H_{76}N_4O_{12}$: C, 68.97; H, 7.28; N, 5.36. Found: C, 68.29; H, 7.26; N, 4.71.

5,11,17,23-Tetrakis[(*N'*-carbethoxy-*N*-piperazino)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (3h) was prepared by the procedure described for **3a**, with ethyl 1-piperazinocarboxylate, and was obtained in 82% yield as a white solid: mp ca. 130 °C dec; IR (KBr) 1700 cm^{-1} (NC=O); ^{1}H NMR ($CDCl_3$) δ 10.3–9.8 (br s, 4, OH), 6.99 (s, 8, Ar H), 4.13 (q, 8, OCH_2), 4.23 and 3.51 (pair of d, 8, $ArCH_2Ar$), 3.26 (s, 16, $CONCH_2$), 3.27 (s, 8, $ArCH_2N$), 2.33 (s, 16, NCH_2), 1.25 (t, 12, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.4 (C=O), 148.1, 131.2, 129.5, and 128.1 (Ar), 62.3, 61.2, 52.7, and 43.6 ($ArCH_2N$, NCH_2CH_2N, and OCH_3). Anal. Calcd for $C_{60}H_{80}N_8O_{12}$: C, 65.22; H, 7.25; N, 10.14. Found: C, 65.03; H, 7.48; N, 9.62.

***p*-Quinone Methide Reactions. 5,11,17,23-Tetrakis(cyanomethyl)-25,26,27,28-tetrahydroxycalix[4]arene (6a).** To a solution containing 16.3 g (0.025 mol) of **3a** in 220 mL of DMSO was slowly added 9.57 mL (0.15 mol) of CH_3I. After the reaction mixture was stirred for 30 m at room temperature, 15 g (0.3 mol) of NaCN was added, and the mixture was heated for 2 h at 80 °C in an atmosphere of N_2. The solution was cooled, treated with 1 L of ice water, acidified with 2 N HCl, filtered, and air-dried. The crude product was recrystallized from CH_3CN to yield 12.8 g (88%) of **6a** as a pale yellow solid: mp >414 °C; IR (KBr) 3140 (OH), 2245 cm^{-1} (CN); ^{1}H NMR (DMSO-d_6) δ 10–9 (br s, 4,

(32) The melting points of all compounds melting above 250 °C were taken in sealed and evacuated capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) with use of a 500 °C thermometer calibrated against a thermocouple. Proton nuclear magnetic resonance spectra (^{1}H NMR spectra) were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Infrared spectra were determined on a Perkin-Elmer 283B spectrometer. UV–vis spectra were determined on a Bausch and Lomb Spectronic 1001 spectrometer. Microanalyses were done by MicAnal Laboratories (now Desert Laboratories), Tucson, AZ. Flash chromatography[33] was carried out with E. Merck silica gel (230–400 mesh ASTM) on columns 50 mm in diameter filled to a height of 6 in. Elution rates were 2 in/min; fractions of 50 mL were collected. Analytical samples were dried at least 36 h at 100–140 °C and 1–2 mm of pressure. In a number of instances, however, solvent of crystallization was retained, considerably affecting the elemental analysis. In such cases best fits between the analytical values and the appropriate fractional increment of solvent were sought, leading in some instances to seemingly adventitious amounts of solvents.

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

OH), 7.04 (s, 8, Ar H), 3.89 (br s, 8, $ArCH_2Ar$), 3.74 (s, 8, $ArCH_2CN$); ^{13}C NMR (DMSO-d_6) δ 149.7, 128.7, 128.4, 123.0, and 119.3 (Ar and CN), 30.7 and 21.6 ($ArCH_2Ar$ and $ArCH_2CN$). Anal. Calcd for $C_{36}H_{28}N_4O_4$: C, 74.48; H, 4.83; N, 9.66. Found: C, 74.26; H, 4.80; N, 9.61.

5,11,17,23-Tetrakis(cyanomethyl)-25,26,27,28-tetrakis[[(*p*-bromophenyl)sulfonyl]oxy]calix[4]arene (6i). To a solution of 2.90 g (5 mmol) of **6a** in 100 mL of THF was added 3.2 g (80 mmol) of NaH (60% oil dispersion). After 30 min, 6.40 g (26 mmol) of *p*-bromobenzenesulfonyl chloride was introduced, and the mixture was stirred for 3 h at room temperature. After 3 h the solvent was removed by evaporation, the residue was treated with 100 mL of $CHCl_3$ and 100 mL of ice water, and the organic layer was separated and washed three times with 100-mL portions of water. The $CHCl_3$ solution was dried over Na_2SO_4 and then evaporated to leave a crude product that was washed with hexane and then subjected to column chromatography (eluant, 1:1 acetone–hexane). The product so obtained was recrystallized from acetone–hexane to give 4.96 g (66%) of colorless crystals: mp 188–190 °C; IR (KBr) 2250 (CN), 1380 and 1190 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 7.77 (s, 16, BrArH), 6.60 (s, 8, Ar H), 3.81 and 2.55 (pair d, 8, $ArCH_2Ar$), 3.54 (s, 8, $ArCH_2CN$); ^{13}C NMR ($CDCl_3$) δ 144.5, 135.8, 133.9, 132.8, 130.8, 129.9, 128.8, and 128.6 (Ar), 117.6 (CN), 31.1 ($ArCH_2Ar$), 22.8 ($ArCH_2CN$). Anal. Calcd for $C_{60}H_{40}N_4O_{12}S_4Br_4$: C, 49.45; H, 2.75; N, 3.85. Found: C, 49.33; H, 2.72; N, 3.76.

5,11,17,23-Tetrakis(cyanomethyl)-25,26,27,28-tetrakis[(*p*-tolylsulfonyl)oxy]calix[4]arene (6j). Via the procedure described above, 2.9 g, of **6a** was treated with *p*-toluenesulfonyl chloride to yield **6j** as a colorless solid: mp 152–155 °C; ^1H NMR ($CDCl_3$) δ 7.79 and 7.39 (pair d, 16, J = 7.8 Hz, SO_3ArH), 6.54 (s, 8, Ar H), 3.85 and 2.44 (pair d, 8, J = 14.7 Hz, $ArCH_2Ar$), 3.52 (s, 8, $ArCH_2CN$), 2.50 (s, 12, $ArCH_3$); ^{13}C NMR ($CDCl_3$) δ 145.8, 145.6, 136.5, 132.3, 130.2, 130.0, 129.0, and 128.2 (Ar), 118.1 (CN), 31.2 ($ArCH_2Ar$), 23.1 and 22.0 ($ArCH_2CN$ and $ArCH_2Ar$). Anal. Calcd for $C_{64}H_{52}N_4O_{12}S_4 \cdot {}^1/_2CHCl_3$: C, 61.62; H, 4.18; N, 4.46. Found: C, 62.46; H, 4.08; N, 4.43.

5,11,17,23-Tetrakis(methoxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (6b). Via the method described for **6a**, 1.63 g of **3a** was treated with 1.0 mL of CH_3I and 1.4 g of $NaOCH_3$ to yield 1.23 g (62%) of **6b** as colorless crystals: mp 214–216 °C; ^1H NMR (DMSO-d_6) δ 9.70 (br s, 4, OH), 7.04 (s, 8, Ar H), 4.15 (s, 8, $ArCH_2O$), 3.85 (br s, 8, $ArCH_2Ar$), 3.19 (s, 12, OCH_3); ^{13}C NMR (DMSO-d_6) δ 149.2, 130.8, 128.2, and 128.1 (Ar), 73.8 ($ArCH_2O$), 57.5 (OCH_3), 30.8 ($ArCH_2Ar$). Anal. Calcd for $C_{36}H_{40}O_8$: C, 72.00; H, 6.67. Found: C, 72.10; H, 6.74.

5,11,17,23-Tetrakis(azidomethyl)-25,26,27,28-tetrahydroxycalix[4]arene (6c). Via the procedure described for **6a**, 1.63 g of **3a** was treated with 1.0 mL of CH_3I and 1.6 g of NaN_3 to yield 1.0 g (62%) of **6c** as a pale yellow solid: mp ca. 152 °C dec; IR (KBr) 2100 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 10.05 (br s, 4, OH), 7.01 (s, 8, Ar H), 4.24 and 3.56 (two br s, 8, $ArCH_2Ar$), 4.14 (s, 8, $ArCH_2N_3$); ^{13}C NMR ($CDCl_3$) δ 148.7, 129.3, 128.9, and 128.3 (Ar), 54.1 ($ArCH_2N_3$), 31.9 ($ArCH_2Ar$). Anal. Calcd for $C_{32}H_{28}N_{12}O_4$: C, 59.63; H, 4.35; N, 26.09. Found: C, 59.79; H, 4.18; N, 23.74.

5,11,17,23-Tetramethyl-25,26,27,28-tetrahydroxycalix[4]arene (6d). Via the procedure described for **6a**, 1.63 g of **3a** was treated with 1.0 mL of CH_3I and 1.9 g of $NaBH_4$ to yield 0.85 g of crude product. A pure sample of **6d** was obtained by flash chromatography[33] (eluant, 2:1 $CHCl_3$–heptane) followed by recrystallization from $CHCl_3$ to give 0.41 g (34%) of **6d** as a white solid: mp ca. 380 °C sublimes; ^1H NMR ($CDCl_3$) δ 10.12 (s, 4, OH), 6.83 (s, 8, Ar H), 4.32–3.21 (pair broad s, 8, $ArCH_2Ar$), 2.17 (s, 12, CH_3); ^{13}C NMR ($CDCl_3$–DMSO-d_6) δ 146.1, 131.0, 129.2, and 128.1 (Ar), 31.2 ($ArCH_2Ar$), 20.0 ($ArCH_3$). Anal. Calcd for $C_{32}H_{32}O_4$: C, 80.00; H, 6.67. Found: C, 79.91; H, 6.61.[34]

5,11,17,23-Tetrakis[(ethylthio)methyl]-25,26,27,28-tetrahydroxycalix[4]arene (6e). To a solution of 1.63 g (2.5 mmol) of **3a** in 40 mL of DMSO was added 0.95 mL (15 mmol) of CH_3I. After 30 min, a solution prepared by adding 0.58 g of Na to 1.55 g of ethyl mercaptan in 14 mL of EtOH was added, and the reaction mixture was heated at 70 °C for 5 h in a N_2 atmosphere. The crude product, obtained in conventional fashion, was purified by chromatography (eluant, 1:1 acetone–hexane) followed by recrystallization to give 0.95 g (53%) of colorless crystals: mp 160–161 °C; ^1H NMR ($CDCl_3$) δ 10.15 (s, 4, OH), 7.00 (s, 8, Ar H), 4.19 and 3.50 (2 br s, 8, $ArCH_2Ar$), 3.52 (s, 8, $ArCH_2S$), 2.40 (q, 8, J = 7.4 Hz, SCH_2), 1.22 (t, 12, J = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 147.6, 132.0, 129.2, and 128.0 (Ar), 35.1 ($ArCH_2S$), 31.6 ($ArCH_2Ar$), 25.2 (SCH_2), 14.2 (CH_3). Anal. Calcd for $C_{40}H_{48}O_4S_4$: C, 66.67; H, 6.67. Found: C, 66.54; H, 6.67.

(34) This product was described by Hayes and Hunter[10] as a light brown solid that did not melt below 300 °C, that showed IR bands characteristic of 1:2:4:6 aromatic substitution, and that possessed an elemental analysis corresponding to a hemihydrate.

5,11,17,23-Tetrakis(2-carboxyethyl)-25,26,27,28-tetrahydroxycalix[4]arene (8a). To a solution of 3.26 g (5 mmol) of **3a** in 80 mL of DMSO, 1.90 mL (30 mmol) of CH_3I was added. After the mixture was stirred for 30 min, sodium diethyl malonate, prepared from 1.20 g of Na, 7.28 g of diethyl malonate, and 28 mL of EtOH, was added, and the reaction mixture was heated for 2 h at 80 °C in an atmosphere of N_2. The solution was then cooled, poured onto 200 mL of ice water, acidified with 2 N HCl, and worked up in the usual fashion to give 5.50 g (99%) of **6f** as a crude product. Hydrolysis and decarboxylation of **6f** were effected by dissolving it in 100 mL of DMSO and 30 mL of concentrated HCl and heating at 120 °C for 10 h in an atmosphere of N_2. The mixture was then cooled, poured onto 500 mL of ice water, stirred for 10 m, and filtered. The precipitate was recrystallized from acetone–ethyl acetate to give 2.42 g (69%) of **8a** as colorless crystals: mp ca. 224 °C dec; IR (KBr) 3190 (OH), 1705 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 11.4–10.6 (br s, 8, OH), 6.96 (s, 8, Ar H), 4.4–3.2 (br s, 8, $ArCH_2Ar$), 2.59 and 2.43 (pair t, 16, J = 7.3 Hz, $ArCH_2CH_2CO_2H$); ^{13}C NMR (DMSO-d_6) δ 173.9 (CO_2H), 147.3, 133.5, 128.4, and 128.3 (Ar), 35.2, 30.7, and 29.7 (CH_2CH_2 and $ArCH_2Ar$). Anal. Calcd for $C_{40}H_{40}O_{12}$: C, 67.42; H, 5.62. Found: C, 66.77; H, 5.75.

5,11,17,23-Tetrakis(2-nitro-2-carbethoxyethyl)-25,26,27,28-tetrahydroxycalix[4]arene (6g). A 3.26-g (5-mmol) sample of **3a** was converted to the quaternary salt with CH_3I and treated with sodium ethyl nitroacetate (prepared from 1.2 g of Na and 6.65 g of ethyl nitroacetate in 28 mL of EtOH) in the manner described above to give 4.25 g (88%) of **6g** as an almost colorless product: mp 96–99 °C; IR (KBr) 3200 (OH), 1750 (C=O), 1560 and 1370 cm^{-1} (NO_2); ^1H NMR (DMSO-d_6) δ 10.1–9.1 (br s, 4, OH), 6.98 (s, 8, Ar H), 5.86 (t, 4, $CHNO_2$), 4.11 (q, 8, OCH_2), 4.1–3.5 (br s, 8, $ArCH_2Ar$), 3.20 (m, 8, $ArCH_2$), 0.96 (t, 12, CH_3); ^{13}C NMR (DMSO-d_6) δ 164.3 (CO_2), 148.8, 129.2, 128.5, and 126.7 (Ar), 88.5 and 62.6 (CH_2NO_2 and CH_2O), 34.7 and 30.6 ($ArCH_2$, $ArCH_2Ar$), 13.3 (CH_3). Anal. Calcd for $C_{48}H_{52}N_4O_{20}$: C, 57.37; H, 5.18; N, 5.58. Found: C, 57.92; H, 5.36; N, 5.42.

5,11,17,23-Tetrakis(*N*-imidazolinomethyl)-25,26,27,28-tetrahydroxycalix[4]arene (6h). A 3.26-g (5-mmol) sample of **3a** was converted to the quaternary salt with CH_3I and treated with 5.20 g (76 mmol) of imidazole in the manner described above for the preparation of **3a** to give 2.68 g (72%) of white needles: mp ca. 170 °C dec; ^1H NMR (DMSO-d_6) δ 8.21, 7.32, and 7.19 (3 s, 12, Im H), 6.82 (s, 8, Ar H), 4.94 (s, 8, $ArCH_2Ar$), 4.22 and 3.12 (pair d, 8, $ArCH_2Ar$); ^{13}C NMR (DMSO-d_6) δ 154.5, 136.6, 130.3, 127.2, 126.5, 125.9, and 120.0 (Im and Ar), 50.0 ($ArCH_2N$), 32.4 ($ArCH_2Ar$). Anal. Calcd for $C_{44}H_{40}N_8O_4 \cdot 1.5C_3H_8O$ and $\cdot 1.CH_3OH$: C, 68.59; H, 6.47; N, 12.93. Found: C, 68.64; H, 5.98; N, 12.93. The isopropyl alochol resonances appear in the ^1H NMR spectrum.

Miscellaneous Reactions. 5,11,17,23-Tetrakis(2-aminoethyl)-25,26,27,28-tetrahydroxycalix[4]arene (7b). To a suspension of 1.45 g (2.5 mmol) of *p*-(cyanomethyl)calix[4]arene (**6a**) in 50 mL of THF was added 50 mL of a 1.0 M solution of B_2H_6 in THF. The mixture was heated at reflux in an atmosphere of N_2 for 8 h, and an additional 30 mL of diborane solution was added. Refluxing was continued overnight, the solution was then cooled, and the solvents were removed by evaporation. The residue was treated with a mixture of 20 mL of H_2O, 100 mL of CH_3OH, and 20 mL of concentrated HCl and refluxed for 1 h. The solvents were removed under reduced pressure, and the residue was treated with 200 mL of acetone. The crude product was collected by filtration and recrystallized from CH_3OH–$CHCl_3$ to yield 1.54 g (83%) of **6a**·4HCl as almost colorless crystals: mp ca. 160 °C dec; ^1H NMR (DMSO-d_6) δ 10.00–10.4 (br s, 4, OH), 8.25 (s, 12, NH_3Cl), 7.01 (s, 8, Ar H), 3.4 and 4.2 (2 br s, 8, $ArCH_2Ar$), 2.92 (br s, 8, CH_2N), 2.69 (t, 8, $ArCH_2C$); ^{13}C (DMSO-d_6) δ 149.02, 129.25, 129.0, and 128.3 (Ar), 32.1 and 30.9 ($ArCH_2CH_2N$ and $ArCH_2Ar$). Anal. Calcd for $C_{36}H_{48}N_4O_4Cl_4 \cdot 3/4CHCl_3$: C, 53.03; H, 5.87; N, 6.73. Found: C, 53.34; H, 5.93; N, 6.71. The free amine (**6a**) was obtained by neutralizing the amine salt in water, but it slowly decomposed upon standing in air: ^1H NMR (DMSO-d_6) δ 6.73 (s, 8, Ar H), 4.54 and 3.20 (pair d, 8, $ArCH_2Ar$), 2.68 and 2.43 (2 br t, 16, $ArCH_2CH_2N$).

5,11,17,23-Tetrakis(2-aminoethyl)-25,26,27,28-tetrakis[[(*p*-bromophenyl)sulfonyl]oxy]calix[4]arene (11). A solution of 3.64 g (2.5 mmol) of the *p*-bromobenzenesulfonate of *p*-(cyanomethyl)calix[4]arene (**6i**) in 100 mL of dry THF was reduced with diborane in the manner described above for **7b** to yield a crude product that was dissolved in CH_2Cl_2 and treated with gaseous HCl to yield the salt. Recrystallization from CH_3OH–$CHCl_3$ gave 3.00 g (74%) of **11**·4HCl as white needles: mp ca. 185 °C dec; ^1H NMR (DMSO-d_6) δ 7.93 and 7.65 (pair d, 16, BrArH), 6.95 (s, 8, Ar H), 5.0–3.5 (br s, 12, NH_3), 3.72 and 2.65 (pair d, 8, $ArCH_2Ar$), 2.92 (t, 8, CH_2N), 2.68 (t, 8, $ArCH_2$); ^{13}C NMR (DMSO-d_6) δ 142.0, 136.0, 134.8, 133.5, 132.5, 130.2, 129.2, and 128.8 (Ar), 39.1, 31.0, and 30.0 ($ArCH_2CH_2N$ and $ArCH_2Ar$). Anal. Calcd for $C_{60}H_{60}N_4O_{12}Br_4Cl_4S_4 \cdot 1.5CHCl_3$ and $0.5CH_3OH$: C, 41.04; H, 3.53; N,

3.09. Found: C, 41.05; H, 3.54; N, 3.02. Resonances for CH_3OH and $CHCl_3$ appear in the ^1H NMR spectrum.

The free amine was prepared by stirring the amine salt with 100 mL of CH_2Cl_2 and 100 mL of 10% aqueous K_2CO_3 for 2 h. The organic phase was separated, washed with water, and dried over Na_2SO_4. Evaporation of the solvent left 2.45 g (67%) of a white powder: mp ca. 150 °C soften; ^1H NMR ($CDCl_3$) δ 7.73 (s, 16, BrArH), 6.40 (s, 8, Ar H), 3.77 and 2.47 (pair d, 8, $ArCH_2Ar$), 2.69 (t, 8, $ArCH_2C$), 2.39 (t, 8, CH_2N), 2.0-1.8 (br s, 8, NH_2); ^{13}C NMR ($CDCl_3$) δ 142.9, 137.7, 134.9, 134.0, 132.3, 130.7, and 129.2 (Ar), 43.3, 39.1, and 31.1 ($ArCH_2CH_2N$ and $ArCH_2Ar$). Anal. Calcd for $C_{60}H_{56}N_4O_{12}S_4Br_4 \cdot CH_2Cl_2$: C, 47.01; H, 3.73; N, 3.59. Found: C, 47.37; H, 3.58; N, 3.52. The resonance for CH_2Cl_2 was observed in the ^1H NMR spectrum.

4-[(Dimethylamino)methyl]-2,6-dimethylphenol (9) was prepared from 2.44 g (0.02 mol) of 2,6-dimethylphenol, 3.38 g (0.03 mol) of 40% aqueous dimethylamine, 2.43 g (0.03 mol) of 37% aqueous HCHO, and 2 mL of acetic acid and was obtained in 86% yield as colorless crystals after recrystallization from hexane: mp 116-117 °C (lit.[35] mp 120-122 °C); ^1H NMR ($CDCl_3$) δ 6.87 (s, 2, Ar H), 6.0 (br s, 1, OH), 3.31 (s, 2, $ArCH_2N$), 2.22 and 2.18 (2 s, 12, NCH_3 and $ArCH_3$); ^{13}C NMR ($CDCl_3$) δ 151.7, 129.6, and 123.6 (Ar), 63.8 and 45.1 ($ArCH_2N$ and NCH_3), 16.1 ($ArCH_3$).

Palladium Complex of 11. A 0.259-g sample of $[Pd(CH_3CN)_2Cl_2]$ (0.001 mol) was dissolved in 20 mL of warm CH_3CN, 0.415 g (0.002 mol) of $AgClO_4$ in 5 mL of CH_3CN was added, and the mixture was stirred at room temperature for 1 h. The AgCl was removed by filtration, and the filtrate was added to 1.47 g (0.001 mol) of **11** in 30 mL of THF with stirring. After 2 h a copious white precipitate had formed, which was collected by filtration, triturated with 20 mL of THF, and dried under vacuum for 5 days at 69 °C to give 1.12 g (71%) of a gray powder: mp ca. 209 °C dec; IR (KBr) 3550 and 3280 (NH), 1380 and 1190 cm^{-1} (SO_2); ^1H NMR (DMSO-d_6) δ 7.94 and 7.58 (pair d, 16, BrArH), 7.27 and 6.94 (2 s, 8, Ar H), 3.80, 3.71, 2.80, and 2.65 (two pair d, 8, $ArCH_2Ar$), 3.04 (br s, 16, $ArCH_2CH_2Ar$), 5.00 and 2.21 (2 br s, 6, NH and NH_2). Anal. Calcd for $C_{60}H_{54}N_4S_4Br_4Pd$: C, 45.69; H, 3.43; N, 3.55. Found: C, 45.01; H, 3.38; N, 3.21.

6-Cetyl-1,4,8,11-tetraazaundecane was prepared as described in the literature[36] and obtained as a waxy solid; mp 98-100 °C (lit.[36] mp 98-100 °C).

Acknowledgment. We are indebted to the National Institutes of Health (Grant GM-23534) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous financial support of this work.

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The Tunichromes. A Class of Reducing Blood Pigments from Sea Squirts: Isolation, Structures, and Vanadium Chemistry

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Received November 2, 1987

Abstract: Marine tunicates ("sea squirts") display a remarkable propensity to sequester and reduce vanadium (or iron) in specialized blood cells termed vanadocytes (or ferrocytes). Characterization of the reducing blood pigments designated as tunichromes (TC's) suggested a plausible mechanism for accomplishing this. TC refers to a class of hydroxy-Dopa-containing peptides whose purification entailed several unusual chromatographic techniques, all performed anaerobically. The first TC characterized from *Ascidia nigra* (*An*-1) is one such modified tripeptide (**1a**).[4] The structural elucidation of two other major TCs from *Ascidia nigra* (*An*-2 and *An*-3), as well as two additional TC's from an iron-sequestering tunicate, *Molgula manhattensis* (*Mm*-1 and *Mm*-2), is reported here. Aqueous *An*/V complexation reactions exhibited a preferred stoichiometry of 2-3:1. Moreover, *A. nigra* blood cells afforded a green fraction possessing the spectroscopic features of an *An*/V complex. These and other findings regarding tunichrome-vanadium complexation chemistry are presented.

Organisms possess a variety of mechanisms for sequestering metal ions. One such metal, vanadium, displays a wide spectrum of biochemical properties.[5] Animal feeding studies suggest that vanadium may be essential for normal mammalian growth and development, yet, this conclusion awaits definitive verification,[6] and a physiological role in humans has not been established. To date, only two low molecular weight vanadium complexes have been isolated from natural sources;[7,8] both are from fungi and are unlikely to reflect vanadium interactions present in mammalian systems.[7-10] With the discoveries that vanadium is found at the active sites of an alternative nitrogenase from the Gram-negative bacterium *Azotobacter chroococcum*[9] and a bromoperoxidase from the marine algae *Ascophyllum nodosum*,[11] true biological roles for vanadium are now manifest.

In the animal kingdom, certain species of the marine organisms known as tunicates (phylum *chordata*) accumulate vanadium to 0.15 M, a level 10^7-fold greater than that present in sea water.[12] Other species sequester iron specifically. A widespread view is

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