Synthesis of 3-Hydroxy-2-pyridinone Derivatives of 4-*tert*-Butylcalix[4]arenes: A New Class of Selective Extractants of Actinide(IV) Ions

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Organic extractants capable of selective and efficient removal of actinides, such as plutonium and americium, from aqueous process waste streams containing high concentrations of other metal ions and anions are potentially useful in radioactive waste remediation.[1] Calix[4]-arenes[2−4] that are immobilized in the cone conformation present an ideal platform for preorganization of the ligand groups on the same face of the molecule and hence for the construction of selective extractants for actinides. Recently, some reports have appeared on the synthesis of calix[4]arene extractants for actinides having four CMPO (octyl(phenyl)*N*,*N*-diisobutylcarbamoyl methylphosphine oxide)-like groups appended to the upper rim.[5−7] The authors found that these calixarene derivatives were better extractants for actinides, such as Np, Pu, and Am, than CMPO itself.[5] The synthesis of a lower rim functionalized CMPO derivative as well as a tetraiminocarboxylate calix[4]arene derivative with some preliminary actinide extraction studies has been recently published.[8] High nitrate concentration (4 M $NaNO_3$ in 1 M HNO_3) was required for efficient extraction of actinide ions into the organic layer by both the upper rim and lower rim calix CMPO derivatives. In contrast, the iminocarboxylate was an efficient extractant for thorium(IV) at pH 2 from a 0.10 M sodium nitrate solution into chloroform.[8] Another class of calixarene derivatives with phosphine oxide groups attached to the lower rim has been synthesized and shown to have high efficiency for the extraction of Th(IV) and Pu(IV) from simulated nuclear waste.[9] The syntheses and complexation properties of a number of calixarene-based tetrahydroxamate ligands developed for the selective extraction of actinide(IV) ions, as well as uranyl ion, have been disclosed.[10,11] In general, these hydroxamate systems extract both iron(III) and actinide(IV) ions efficiently under mildly acidic conditions, but exhibit little selectivity for the actinide ion.

The dibasic 3-hydroxy-2-pyridinone (3,2-HOPO) ligand, as well as its positional isomers (1,2-HOPO and 3,4-HOPO), are well-known for their strong affinity for hard trivalent and tetravalent cations.[12] The syntheses of chelators carrying this ligand moiety (mono-, di-, and trihydroxypyridinones) have been of interest due to their strong iron binding properties and potential applications in the treatment of patients suffering from iron overload diseases (Cooley's Anemia).[13−15] Also, the synthesis of a trihydroxypyridinone derivative for the complexation of gadolinium to generate useful contrast agents for MRI has been reported.[16] Desferrioxamine derivatives carrying an additional hydroxypyridininone group have been synthesized for enhanced actinide binding.[17] The synthesis of a number of other tetrahydroxypyridinones and their usefulness for in vivo clearance of plutonium have been reported.[18−20] Incorporation of the hydroxypyridinone ligands onto calixarene platforms yields a new class

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(24) In the molecular modeling of **1** using CAChe Mechanics program, the distances between the amide proton of one ligand chain and the carbonyl oxygen of the proximal amide were found to be between 2.01 and 2.22 Å and are consistent with strong hydrogen-bonding interactions. Additionally, a similar type of interstrand hydrogen-bonding network was indicated between the hydroxypyridinone groups on adjacent chains. The molecular modeling dynamics simulations of calixarene **2** indicated that there were a large number of structures with potential energies comparable to that of the lowest energy structure identified. This suggests that the ligand arms of **2** show little preorganization in absence of an alkali metal ion. The MM2 force field used by the CAChe Mechanics program utilizes augmented parameters to accommodate atoms and interactions not explicitly defined by MM2. This "augmented" MM2 parameter set was used without modification.

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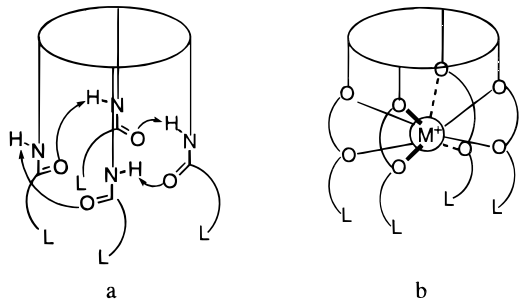
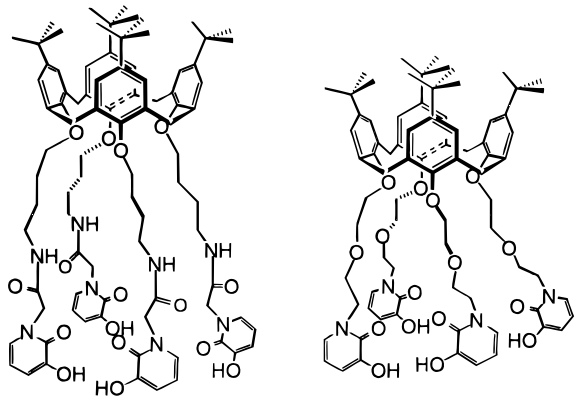


Figure 1. Potential preorganization of ligand arms through (a) hydrogen bonding in calix[4]arene extractant **1** and (b) alkali metal coordination in extractant **2**. L = 3,2-HOPO ligand.

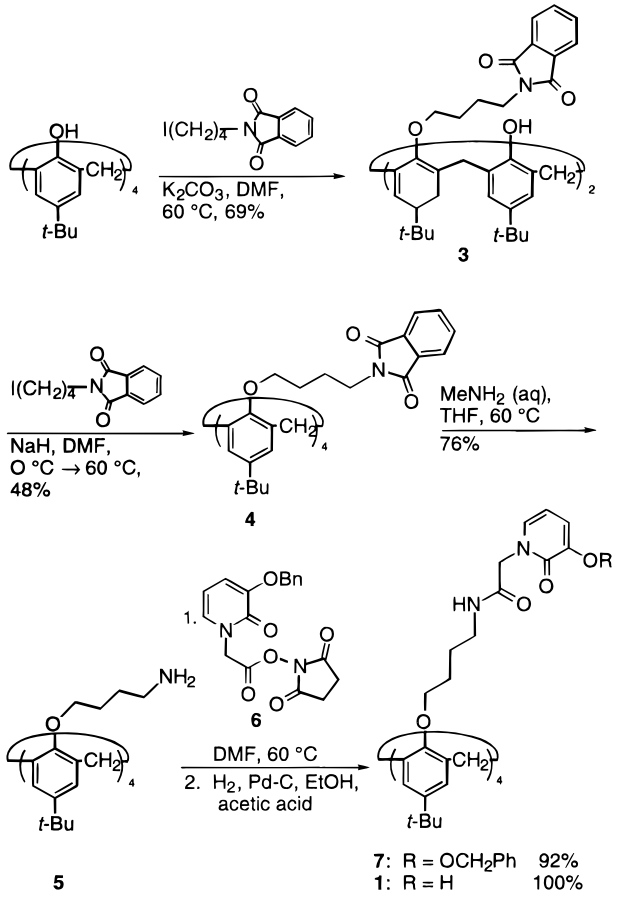
of extractants whose synthesis and complexation behavior has so far not been examined. In this paper, we report the preparation of two calixarene tetrahydroxypyridinone extractants, designed for the specific extraction of actinides, and some of their metal ion extraction properties.



It is generally accepted that selective binding of chelators to tetravalent actinide ions can be achieved by taking advantage of their higher coordination number (8 or more) and more flexible coordination geometry relative to the smaller transition metals.[21,22] While the hydroxypyridinone ligand is a strong complexant of actinide ions, the preorganization of the ligand arms on a calix[4]arene platform should also help to overcome unfavorable entropic factors in actinide complexation. We hypothesized that interstrand hydrogen bonds between an amide proton in one ligand arm with the amide carbonyl group on a proximal chain in chelator **1** would help in the preorganization of the ligand arms so as to favor actinide complexation (Figure 1a). Such examples of hydrogen bonding are well documented in supramolecular chemistry.[23] In the potentially ditopic chelator **2** (Figure 1b), it was of interest to determine if the coordination of an alkali metal cation by the four diethyleneoxy ligand chains would lead to a conformation favorable for binding An^{4+}.[24] If true, extractants of this class may be particularly useful for situations where the actinide waste stream contains moderately high concentrations of cations, such as Na^+ or K^+. A few calixarene-derived ditopic ligands have been examined for the simultaneous complexation of two cations[25] or the complexation of an anion and a cation.[26]

The tetrahydroxypyridinone **1** was prepared in a relatively straightforward manner using a short synthetic

Scheme 1



sequence that begins from commercially available *tert*-butylcalix[4]arene (Scheme 1). The distally disubstituted calixarene **3** was first prepared by alkylation of *tert*-butylcalix[4]arene with *N*-4-iodobutylphthalimide in the presence of K_2CO_3 in DMF at 60 °C. Further reaction of **3** with the same alkylating reagent at room temperature in DMF gave the cone tetraphthalimide **4** in 48% yield after careful purification by column chromatography. In our hands, this two-step procedure, rather than a one-step exhaustive alkylation in DMF, was preferable for easy isolation of the desired cone isomer **4**. The phthalimido protecting groups were then readily removed by refluxing with an excess of aqueous methylamine to give the tetraamine **5**.[27] The tetraamine **5** was then coupled to the known *N*-hydroxysuccinimide ester **6**,[28] prepared from commercially available 2,3-dihydroxypyridine in four steps, to give the protected tetrahydroxypyridinone **7**. The desired tetrahydroxypyridinone extractant **1** was obtained in excellent yield after cleavage of the O-benzyl ethers by hydrogenolysis.

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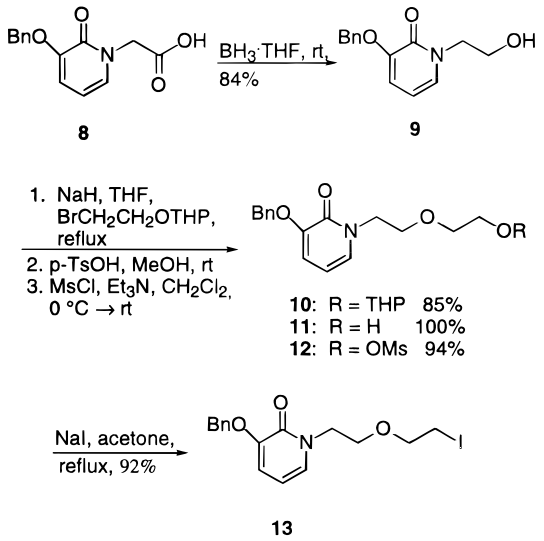
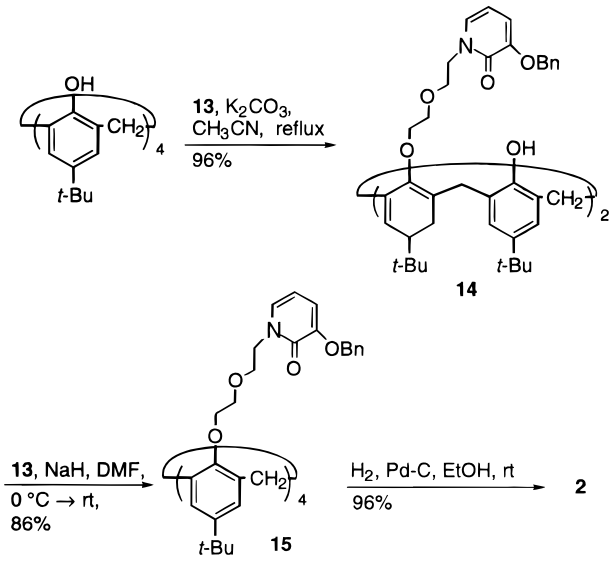
Scheme 2



Scheme 3



Our sythetic route to the chelator **2** was more convergent, but required the preparation of a suitable alkylating agent with a protected hydroxypyridinone moiety. This was accomplished in five steps that began from the known carboxylic acid **8** (Scheme 2).[28] The pyridinone carboxylic acid **8** was easily reduced with borane in THF to provide the alcohol **9** in good yield. Alkylation of the alcohol with 2-(2-bromoethoxy)tetrahydro-2*H*-pyran was slow, but proceeded effectively to give **10**. The THP protecting group was then removed using catalytic p-TsOH in MeOH to obtain the alcohol **11**. Conversion of alcohol **11** into the iodide **13** was readily accomplished in two steps (86% yield) via its mesylate **12**. In general, in this synthetic sequence, column chromatographic purification was required in only one step (in the alkylation to give **10**) and the crude products were of sufficient purity to be used directly in the next step.

With iodide **13** in hand, the tetrahydroxypyridinone **2** was prepared readily from 4-*tert*-butylcalix[4]arene in two steps (Scheme 3). The alkylation of 4-*tert*-butylcalix[4]arene with **13** using K_2CO_3 in refluxing MeCN gave the distally disubstituted calixarene **14** in excellent yield. Further reaction of **14** with alkylating agent **13** and NaH at room temperature in DMF gave the protected hydroxypyridinone cone isomer **15** in 86% yield. Hydrogenolysis of the O-benzyl ether groups gave tetrahydroxypyridinone **2** in excellent yield.

Table 1. %M^{n+} Extracted by Calixarene Ligands 1 and 2[a]

initial	Th^{4+}		Fe^{3+}		Eu^{3+}		Cu^{2+}	
pH	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
0[b]	88	>98	29	26				
1[c]	>99	>99	32	65	2	2	11	12
2[d]	>99	>99	79	99	7	1	11	8

[a] Into $CHCl_3$ from 0.10 M $NaNO_3$, [**1**] = 1.0 mM, [**2**] = 1.0 mM. [b] $[Th^{4+}]$ = 0.19 mM, $[Fe^{3+}]$ = 0.19 mM, where pH 0 is ~8.2 M HNO_3 (0.10 M $NaNO_3$). [c] $[Th^{4+}]$ = 0.19 mM, $[Fe^{3+}]$ = 0.24 mM, $[Eu^{3+}]$ = 0.23 mM, $[Cu^{2+}]$ = 0.25 mM. [d] $[Th^{4+}]$ = 0.19 mM, $[Fe^{3+}]$ = 0.24 mM, $[Eu^{3+}]$ = 0.24 mM, $[Cu^{2+}]$ = 0.25 mM.

The ability of hydroxypyridinone chelators **1** and **2** to extract Th(IV), Fe(III), Eu(III), and Cu(II) from acidic solutions (0.10 M $NaNO_3$) into chloroform was examined, and initial results are quite promising. Thorium(IV) and Eu(III) were chosen for these studies, as they are surrogates for Pu(IV) and Am(III) present in radioactive waste streams. Both calixarenes **1** and **2** are highly efficient in extracting Th(IV) into chloroform from aqueous solutions at pH values of 0, 1, and 2 (Table 1). Under comparable conditions, the extraction of Fe(III) by these ligands is less efficient and shows a significant pH dependence. It appears that the chelator **2** is more efficient than **1** for the extraction of Fe(III) in the pH range examined. Both chelators **1** and **2** are poor extractants for Eu(III) and Cu(II) into chloroform under similiar conditions. The relative efficiencies of extraction in these experiments are consistent with the relative hardness of the cations utilized in this study.

The actinide selectivity of extractants **1** and **2** was also investigated in a competitive study involving approximately equimolar quantitites of the desired ligand (0.25 mM), Fe(III) (0.24 mM), and Th(IV) (0.23 mM) at pH 1. Under these conditions, calixarene **1** removed 63% of the Th(IV) present and less than 9% of the Fe(III), displaying considerable selectivity for the larger cation. Calixarene **2**, although less efficient, was also selective for the extraction of Th(IV) (52%) over Fe(III) (15%). Further studies are needed to understand the complexation/extraction properties of these ligands and to establish the nature of the observed actinide selectivity. The influence of alkali metal ions on the extraction of actinides by the potentially ditopic extractant **2** also needs to be investigated.

In conclusion, efficient synthetic routes for two hydroxypyridinone calixarene derivatives, a new class of extractants for actinides, have been developed. Results from metal ion extraction studies indicate that both these ligands are efficient extractants for Th(IV) and Fe(III) in comparison to Eu(III) and Cu(II) in the pH range of 1−2. Morever, both **1** and **2** extract Th(IV) selectively in the presence of Fe(III) under competitive conditions at pH 1. These results clearly warrant the further development of this new class of actinide extractants for their potential application in radioactive waste remediation.

Experimental Section

General Methods. ^1H NMR (200 MHz) and ^{13}C NMR (50 or 100 MHz) spectra were recorded in $CDCl_3$ with signals recorded downfield from an internal tetramethylsilane reference unless otherwise noted. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Analytical and preparative thin-layer

chromatography was performed on silica 60/F_{254} plastic- or glass-backed plates (EM Science). Column chromatography was done on silica gel (Merck 230−400 mesh). Radial chromatography was performed on a Chromatotron (Harrison Scientific) using silica gel 60 plates. THF was freshly distilled from sodium/benzophenone. Dry DMF was obtained from Aldrich Chemical Co. in a SureSeal container.

25,26,27,28-Tetrakis(4-phthalimidobutoxy)-*p*-*tert*-butylcalix[4]arene (4). A mixture of 4-*tert*-butylcalix[4]arene (2.00 g, 3.00 mmol), *N*-(4-iodobutyl)phthalimide (4.06 g, 12.0 mmol) and K_2CO_3 (0.950 g, 6.08 mmol) in DMF (30 mL) was heated at 60 °C for 24 h. The DMF was removed in vacuo, the residue was diluted with water, and the product extracted into $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The residue was dissolved in a minimum amount of $CHCl_3$, and the crude product was precipitated by the addition of methanol. The precipitated solid was isolated by vacuum filtration and dried under vacuum. The dialkylated product **3** (2.20 g, 69%) was used in the next step without further purification: IR (KBr) 3307, 1768, 1711 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 18 H), 1.25 (s, 18 H), 2.02−2.18 (m, 8 H), 3.28 (d, J = 13.0 Hz, 4 H), 3.82−3.94 (m, 4 H), 3.97−4.08 (m, 4 H), 4.10 (d, J = 13.0 Hz, 4 H), 6.8 (s, 4 H), 7.1 (s, 4 H), 7.5 (s, 2 H), 7.6 (m, 4 H), 7.8 (m, 4 H).

To a solution of the dialkylated compound **3** (3.8 g, 3.6 mmol) in dry DMF (40 mL) under N_2 at 0 °C was added NaH (60% in oil, 433 mg, 10.8 mmol), and the reaction mixture was stirred at 0 °C until gas evolution ceased. To this mixture at 0 °C was added a solution of *N*-(4-iodobutyl)phthalimide (4.7 g, 14.4 mmol) in DMF (20 mL) via an addition funnel over a period of 20 min. The reaction was allowed to warm to room temperature, stirred for 24 h, and finally heated at 60 °C for 1 h. The reaction was then allowed to cool to room temperature and quenched with water. The DMF was removed in vacuo, the residue was diluted with water, and the product extracted into $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The crude product was purified using column chromatography (66% ethyl acetate/hexanes) to give the tetraamide **4** (2.40 g, 48%): mp 75 °C; IR (KBr) 1615, 1713, 1772, 3466 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 36 H), 1.70−1.85 (m, 8 H), 2.01−2.18 (m, 8 H) 3.10 (d, J = 12.5 Hz, 4 H), 3.77 (t, J = 7.0 Hz, 8 H), 3.92 (t, J = 7.1 Hz, 8 H), 4.37 (d, J = 12.5 Hz, 4 H), 6.75 (s, 8 H), 7.57−7.77 (m, 16 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 27.6, 31.2, 31.4, 33.8, 38.0, 74.6, 123.0, 125.0, 132.3, 133.6, 133.8, 144.3, 153.5, 168.2. Anal. Calcd for $C_{92}H_{100}N_4O_{12}$: C, 76.01; H, 6.93; N, 3.85. Found: C, 75.74; H, 6.73; N, 3.97.

25,26,27,28-Tetrakis(4-aminobutoxy)-*p*-*tert*-butylcalix[4]-arene (5). A solution of **4** (2.4 g, 1.6 mmol) in THF (10 mL) was added to 40% aqueous methylamine (150 mL) at room temperature, and the solution was heated at 60 °C for 24 h. The reaction mixture was cooled, and the solid amine was separated by vacuum filtration on a sintered glass funnel and washed with water. The crystals were dissolved in $CHCl_3$, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo to give the tetraamine **5** (1.48 g, 76%) as a white solid. The tetraamine was dried at 80 °C for 24 h under vacuum before its use in the next step: mp 192 °C; IR (KBr) 1580, 3490 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.07 (s, 36 H), 1.45−1.69 (m, 8 H), 1.93−2.10 (m, 8 H), 2.76 (t, J = 7 Hz, 8 H), 3.12 (d, J = 12.5 Hz, 4 H), 3.87 (t, J = 7 Hz, 8 H), 4.38 (d, J = 12.5 Hz, 4 H), 6.77 (s, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 30.4, 31.1, 31.2, 31.4, 33.8, 42.4, 75.0, 125.0, 133.7, 144.4, 153.5. Anal. Calcd for $C_{60}H_{92}N_4O_4 \cdot 2H_2O$: C, 74.34; H, 9.98; N 5.78. Found: C, 73.96; H, 9.58; N, 5.75.

25,26,27,28-Tetrakis{4-[2-(3-(benzyloxy)-2-oxo-1,2-dihydro-1-pyridyl)acetamido]butoxy}-*p*-*tert*-butylcalix[4]-arene (7). The NHS ester **6**[28] (3.12 g, 8.73 mmol) was added to a solution of the tetraamine **5** (1.30 g, 1.09 mmol) in DMF (30 mL) under N_2, and the reaction mixture was heated at 60 °C for 16 h. The mixture was then cooled, and the DMF was removed in vacuo. The residue was dissolved in $CHCl_3$ and washed with saturated $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was washed with acetonitrile to remove unreacted NHS ester and then recrystallized from 95% ethanol to give **7** (2.16 g, 92% yield): mp 238 °C; IR (KBr) 1597, 1653, 1715, 2362, 3065, 3311 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 36 H), 1.59−1.70 (m, 8 H), 1.92−2.07 (m, 8 H), 3.09 (d, J = 12.6 Hz, 4 H), 3.18−3.30 (unresolved q, 8 H), 3.84 (t, J = 7 Hz, 8 H), 4.32 (d, J = 12.6 Hz, 4 H), 4.49 (s, 8 H), 4.96 (s, 8 H), 5.99 (t, J = 7.2 Hz, 4 H), 6.64 (d, J = 6.8 Hz, 4 H), 6.85 (d, J = 6.8 Hz, 4 H), 6.74 (s, 8 H), 7.26−7.36 (m, 20 H), 8.38 (unresolved t, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 28.2, 31.0, 31.4, 33.8, 40.4, 51.6, 70.7, 75.0, 104.6, 115.5, 124.8, 125.0, 125.1, 127.7, 128.2, 128.6, 130.6, 133.7, 136.1, 144.3, 148.6, 153.8, 158.2, 167.5. Anal. Calcd for $C_{116}H_{136}N_8O_{16}$: C, 73.39; H, 7.22; N, 5.9. Found: C, 73.45; H, 7.37; N, 5.73.

25,26,27,28-Tetrakis{4-[2-(3-hydroxy-2-oxo-1,2-dihydro-1-pyridyl)acetamido]butoxy}-*p*-*tert*-butylcalix[4]arene (1). Palladium on carbon (10%, 0.087 g) was added to a solution of **7** (0.210 g, 0.093 mmol) in 33% acetic acid/ethanol (6 mL), and the mixture was stirred under H_2 at room temperature. After 36 h, the reaction mixture was filtered through Celite, and the Celite was washed with small amounts of $CHCl_3$. The solvent was removed in vacuo, and the residue was washed with diethyl ether to give **1** (0.145 g, 100%) as a rose-colored solid: mp 238 °C (dec); IR (KBr) 1599, 1655, 2954, 3300 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 36 H), 1.58−1.75 (m, 8 H), 1.93−2.08 (m, 8 H), 3.09 (d, J = 12.2 Hz, 4 H), 3.31 (unresolved t, 8 H), 3.80 (unresolved t, 8 H), 4.29 (d, J = 12.2 Hz, 4 H), 4.60 (br s, 8 H), 6.13 (unresolved t, 4 H), 6.7−6.8 (m, 12 H), 6.91 (d, J = 5 Hz, 4 H), 7.67−7.78 (m 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 28.1, 31.0, 31.4, 33.8, 40.4, 52.3, 74.9, 107.3, 115.8, 125.0, 128.5, 133.7, 144.6, 146.6, 153.5, 158.8, 167.2. Anal. Calcd for $C_{88}H_{112}N_8O_{16} \cdot H_2O$: C, 67.93; H, 7.39; N, 7.20. Found: C, 67.91; H, 7.37; N, 7.01.

3-(Benzyloxy)-1-(2-hydroxyethyl)-2(1*H*)-pyridinone (9). To a solution of acid **8**[28] (5.77 g, 22.3 mmol) in freshly distilled THF (20 mL) under N_2 was added $BH_3 \cdot$THF (1 M, 44.5 mmol), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was poured over crushed ice, extracted with dichloromethane, dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo to give **9** (4.59 g, 84%) as a white solid which was used in the next step without purification: mp 75−76 °C; IR (KBr) 1594, 3369 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.94 (t, J = 4.8 Hz, 2 H), 4.13 (t, J = 4.4 Hz, 2 H), 5.09 (s, 2 H), 6.05 (t, J = 7.2 Hz, 1 H), 6.68 (d, J = 6.6 Hz, 1 H), 6.98 (d, J = 6.8 Hz, 1 H) 7.31−7.44 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.46, 61.61, 71.08, 105.31, 116.37, 127.72, 128.46, 128.98, 130.65, 136.08, 148.98, 159.09. Anal. Calcd for $C_{14}H_{15}O_3N$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.36; H, 6.26; N, 5.66.

3-(Benzyloxy)-1-{2-[2-tetrahydro-2*H*-2-pyranyloxy]-ethoxy}ethyl-2(1*H*)-pyridinone (10). To a solution of alcohol **9** (3.0 g, 12.2 mmol) in freshly distilled THF (40 mL) at 0 °C under N_2 was added NaH (60% in oil, 1.49 g, 37.3 mmol), and the suspension was stirred for 5 min at 0 °C and then stirred at room temperature for 20 min. The suspension was then cooled to 0 °C and 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (7.67 g, 36.9 mmol) was slowly added. The reaction was then heated at reflux until disappearance of starting material was indicated by TLC analysis (2.5−3 d). The reaction mixture was then cooled to room temperature, and the reaction was carefully quenched by the addition of water. The solvents were removed in vacuo, and the oily residue was dissolved in ethyl acetate, washed with water, and saturated NaCl. The organic layer was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo to yield a light brown oil (6.21 g). The crude product was purified by column chromatography with ethyl acetate/hexanes gradient elution followed by methanol/ethyl acetate gradient elution to yield **10** as a light yellow oil (3.89, 85%): IR (neat) 1604, 1654 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32−1.97 (br m, 6 H), 3.40−3.54 (m, 2 H), 3.55−3.65 (m, 3 H), 3.75−3.90 (m, 3 H), 4.17 (t, J = 5.1 Hz, 2 H), 4.58 (t, J = 3.3 Hz, 1 H), 5.11 (s, 2 H), 5.97 (t, J = 7.1 Hz, 1 H), 6.65 (dd, J = 7.4 and 1.7 Hz, 1 H), 7.05 (dd, J = 6.9 and 1.7 Hz, 1 H), 7.23−7.49 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.4, 25.5, 30.6, 49.7, 62.2, 66.6, 69.0, 70.8, 98.9, 103.8, 116.1, 127.4, 128.0, 128.6, 130.8, 136.6, 148.8, 158.3. Anal. Calcd for $C_{21}H_{27}O_5N$: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.80; H, 7.26; N, 3.77.

3-(Benzyloxy)-1-[2-(2-hydroxyethoxy)ethyl]-2(1*H*)-pyridinone (11). To a solution of the THP ether **10** (2.90 g, 7.71 mmol) in methanol (10 mL) was added *p*-TsOH (0.146 g, 0.77 mmol), and the solution was stirred at room temperature for 8 h. The methanol was removed in vacuo, and the resulting residue

was dissolved in dichloromethane and washed with saturated $NaHCO_3$ and water. The organic layer was then dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo to yield the crude alcohol **11** (2.33 g, 100%) as a viscous oil which was used in the next step without purification. An analytical sample was prepared by radial chromatography (ethyl acetate/hexanes gradient elution followed by methanol/ethyl acetate gradient elution): IR (neat) 1599, 1651, 3404 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.68 (br s, 1 H), 3.51 (t, J = 4.0 Hz, 2 H), 3.58−3.71 (m, 2 H), 3.78 (t, J = 5.0 Hz, 2 H), 4.15 (t, J = 5.0 Hz, 2 H), 5.08 (s, 2 H), 6.00 (t, J = 7.2 Hz, 1 H), 6.67 (d, J = 7.3 Hz, 1 H), 6.99 (d, J = 6.3 Hz, 1 H), 7.22−7.47 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.7, 61.6, 68.9, 70.8, 72.5, 104.4, 115.9, 127.4, 128.0, 128.6, 130.3, 136.4, 148.8, 158.3. Anal. Calcd for $C_{16}O_4H_{19}N$: C, 66.41; H, 6.62; N, 4.84. Found: C, 66.28; H, 6.55; N, 4.72.

3-(Benzyloxy)-1-[2-(2-methanesulfonyloxyethoxy)ethyl]-2(1*H*)-pyridinone (12). Methanesulfonyl chloride (1.18 g, 10.4 mmol) was added dropwise to a solution of **11** (2.0 g, 6.92 mmol) in dichloromethane (25 mL) and Et_3N (1.40 g, 13.8 mmol) at 0 °C under an atmosphere of N_2. The reaction was stirred at 0 °C for 1 h and then at room temperature for 1.5 h. The reaction mixture was then diluted with dichloromethane and washed with 2 M HCl, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo to yield the crude mesylate **12** (2.38 g, 94%) which was used in the next step without purification. An analytical sample was obtained by radial chromatography (ethyl acetate/hexanes gradient elution): IR (neat) 1606, 1652 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.96 (s, 3 H), 3.67−3.71 (m, 2 H), 3.84 (t, J = 5.0 Hz, 2 H), 4.18 (t, J = 5.0 Hz, 2 H), 4.28−4.33 (m, 2 H), 5.12 (s, 2 H), 6.02 (t, J = 7.1 Hz, 1 H), 6.66 (dd, J = 7.4 and 1.7 Hz, 1 H), 6.98 (dd, J = 6.8 and 1.7 Hz, 1 H), 7.30−7.47 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.6, 49.5, 68.8, 70.8, 104.3, 115.9, 127.4, 128.0, 128.6, 130.5, 136.4, 148.7, 158.1. Anal. Calcd for $C_{17}H_{21}O_6NS$: C, 55.57; H, 5.77; N, 3.81. Found: C, 55.46; H, 5.91; N, 3.65.

3-(Benzyloxy)-1-[2-(2-iodoethoxy)ethyl]-2(1*H*)-pyridinone (13). Sodium iodide (1.40 g, 9.34 mmol) was added to a solution of mesylate **12** (2.27 g, 6.18 mmol) in acetone (20 mL), and the resulting mixture was heated at reflux for 26 h. The solvent was then removed in vacuo, and the oily residue was dissolved in dichloromethane, washed with water, and a Na_2SO_3 solution (10% by weight). The dichloromethane layer was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo to give **13** (2.71 g, 92%) as a light yellow solid which was used in the next step without purification. An analytical sample was obtained by radial chromatography (ethyl acetate/hexanes gradient elution): mp 86−88 °C; IR (KBr) 1604, 1646 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.19 (t, J = 6.4 Hz, 2 H), 3.67 (t, J = 6.4 Hz, 2 H), 3.82 (t, J = 5.0 Hz, 2 H), 4.18 (t, J = 5.0 Hz, 2 H), 5.12 (s, 2 H), 6.01 (t, J = 7.14 Hz, 1 H), 6.67 (dd, J = 7.4 and 1.7 Hz, 1 H), 7.04 (dd, J = 6.9 and 1.7 Hz, 1 H), 7.22−7.47 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.7, 49.7, 68.29, 70.6, 71.0, 104.0, 115.9, 127.3, 127.8, 128.4, 130.6, 136.3, 148.7, 158.2. Anal. Calcd for $C_{16}H_{18}O_3NI$: C, 48.12; H, 4.55; N, 3.51. Found: C, 48.48; H, 4.65; N, 3.32.

25,27-Bis-2-[2-(3-(benzyloxy)-2-oxo-1,2-dihydro-1-pyridyl)-ethoxy]ethoxy-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene (14). The iodide **13** (2.36 g, 5.9 mmol) was added to a suspension of 4-*tert*-butylcalix[4]arene (0.96 g, 1.48 mmol) and K_2CO_3 (0.43 g, 3.11 mmol) in acetonitrile (30 mL), and the reaction mixture was heated at reflux for 26 h. The solvents were then removed in vacuo, and the residue was extracted with dichloromethane. The dichloromethane solution was then washed with water, Na_2SO_3 (10% by weight), dried (Na_2SO_4), and filtered, and the solvents were removed in vacuo. The crude product was purified by column chromatography. The iodide **13** (0.79 g) was recovered by elution with ethyl acetate. Elution with 5% methanol/ethyl acetate gave the desired dialkylated product **14** (1.68 g, 96%) as a crystalline white solid: mp 68−70 °C; IR (KBr) 1606, 1656, 3422 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (3, 18 H), 1.30 (s, 18 H), 3.24 (d, J = 13.2 Hz, 4 H), 3.77−3.89 (m, 4 H), 3.94 (t, J = 4.5 Hz, 4 H), 4.05−4.60 (m, 4 H), 4.24 (t, J = 4.5 Hz, 4 H), 4.30 (d, J = 13.2 Hz, 4 H), 5.07 (s, 4 H), 5.79 (t, J = 7.1 Hz, 2 H), 6.53 (dd, J = 7.5 and 1.6 Hz, 2 H), 6.75 (s, 4 H), 7.03 (s, 4 H), 7.06 (dd, J = 7.5 and 1.6 Hz, 2 H), 7.23−7.46 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.0, 31.4, 31.8, 33.9, 50.4, 69.3, 70.0, 70.8, 75.3, 104.1, 116.0, 125.1, 125.5, 127.4, 128.0, 128.6, 130.2, 131.2, 132.7, 136.6, 141.4, 147.0, 148.5, 149.8, 150.6. Anal. Calcd for $C_{76}H_{90}O_{10}N_2 \cdot H_2O$: C, 75.45; H, 7.67; N, 2.32. Found: C, 75.53; H, 7.39; N, 2.49.

25,26,27,28-Tetrakis-2-[2-(3-benzyloxy-2-oxo-1,2-dihydro-1-pyridyl)ethoxy]ethoxy-*p*-*tert*-butylcalix[4]arene (15). Sodium hydride (60% in oil, 0.06 g, 1.45 mmol) was added to a solution of **14** (0.64 g, 0.54 mmol) in dry DMF (10 mL) at 0 °C under N_2, and the mixture was stirred at 0 °C for 5 min and then at room temperature for 25 min. The reaction was cooled to 0 °C, and iodide **13** (0.86 g, 2.15 mmol) was added. The reaction was allowed to stir under N_2 at 0 °C for 1 h and then at room temperature for 6 d. The reaction was quenched by the addition of water and diluted further with water, and the product was extracted into dichloromethane. The organic layer was then dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo. Purification of the crude product by column chromatography (ethyl acetate/hexanes gradient elution) gave the unreacted iodide **7** (0.39 g) and the all-cone product **15** (0.802 g, 86%): mp 58−60 °C; IR (KBr) 1605, 1656 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 36 H), 3.07 (d, J = 12.5 Hz, 4 H), 3.76 (t, J = 4.7 Hz, 8 H), 3.84 (unresolved t, 8 H), 3.99 (unresolved t, 8 H), 4.10 (t, J = 4.8 Hz, 8 H), 4.33 (d, J = 12.5 Hz, 4 H), 5.05 (s, 8 H), 5.89 (t, J = 7.2 Hz, 4 H), 6.59 (dd, J = 7.4 and 1.6 Hz, 4 H), 6.74 (s, 8 H), 6.92 (dd, J = 6.9 and 1.6 Hz, 4 H), 7.20−7.43 (m, 20 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.0, 31.3, 33.8, 49.8, 68.6, 70.6, 72.8, 104.0, 115.6, 125.0, 127.3, 127.9, 128.4, 130.7, 133.6, 136.3, 144.8, 148.5, 153.2, 158.0. Anal. Calcd for $C_{108}H_{124}O_{16}N_4 \cdot 1.5\ H_2O$: C, 73.64; H, 7.27; N, 3.19. Found: C, 73.67; H, 7.03; N, 3.23.

25,26,27,28-Tetrakis-2-[2-(3-hydroxy-2-oxo-1,2-dihydro-1-pyridyl)ethoxy]ethoxy-*p*-*tert*-butylcalix[4]arene (2). Palladium on carbon (5%, 0.26 g) was added to a solution of **15** (0.60 g, 0.35 mmol) in ethanol (25 mL), and the reaction was stirred under H_2 at room temperature for 22 h. The reaction mixture was then diluted with $CHCl_3$, and the catalyst was filtered off. The solvents were removed in vacuo to provide **2** as a pale rose solid (0.46 g, 96%): mp 218 °C (dec); IR (KBr) 1599, 1651, 3237 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 36 H), 3.03 (d, J = 12.8 Hz, 4 H), 3.78 (unresolved t, 8 H), 3.84 (t, J = 4.7 Hz, 8 H), 3.97 (unresolved t, 8 H), 4.15 (t, J = 4.7 Hz, 8 H), 4.29 (d, J = 12.8 Hz, 4 H), 6.03 (t, J = 7.1 Hz, 4 H), 6.74 (s, 8 H), 6.76 (d, J = 7.0 Hz, 4 H), 6.81 (d, J = 7 Hz, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.4, 33.9, 50.2, 68.7, 70.8, 72.8, 106.2, 114.4, 125.1, 128. 7, 133.7, 144.9, 146.6, 153.4, 158.6. Anal. Calcd for $C_{80}H_{100}O_{16}N_4$: C, 69.93; H, 7.34; N, 4.08. Found: C, 69.54; H, 7.54; N, 3.84.

Solvent Extraction Studies. The protocol for metal ion extraction experiments followed procedures described earlier.[10] A solution of 0.10 M $NaNO_3$/1% HNO_3 was adjusted to pH 1 or 2 with concentrated aqueous NaOH. To a known volume of the aqueous solution, at the desired pH, was then added the appropriate quantity (80−90 μL) of the metal ion stock solution (~0.25 M). Equal volumes (4 mL:4 mL) of the aqueous solution at the specified pH, containing the desired concentration of the metal ion of interest, and chloroform containing a 4−5-fold molar excess of the ligand (1.0 mM) were contacted for 2 h at ambient temperature with gentle shaking. The layers were separated carefully by centrifugation, and the concentrations of the metal ions in the aqueous layers were determined by ICP analysis against NIST traceable standards. The percent metal ion extracted by the ligands could then be determined. All reported extraction values are the average of two or more individual extractions, and the necessary control experiments were also performed to ensure that metal precipitation was not relevant to metal ion removal.

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