Selective Binding of Trivalent Metals by Hexahomotrioxacalix[3]arene Macrocycles: Determination of Metal-Binding Constants and Metal Transport Studies

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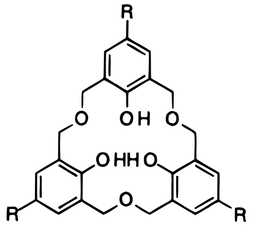
The hexahomotrioxacalix[3]arene macrocycles **1a**,**b** are observed to bind Sc^{3+}, Lu^{3+}, Y^{3+}, and La^{3+} more strongly than alkali or alkaline earth metal ions. Binding constants have been determined for the trivalent metal ions using an NMR titration method and are observed to increase with increasing charge-to-radius ratio for the metal ion (Na^+, Li^+, $Ca^{2+} < Mg^{2+} < La^{3+} \ll Y^{3+} < Lu^{3+} \ll Sc^{3+}$) and increasing macrocycle acidity [*p*-*tert*-butyloxacalix[3]arene (**1a**) < *p*-chlorooxacalix[3]arene (**1b**)]. Macrocycle **1b** is observed to transport Sc^{3+} across a liquid membrane without any detectable transport of Li^+ or Mg^{2+}.

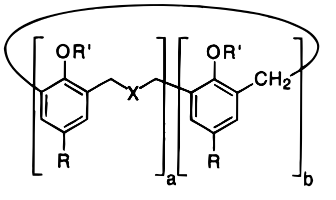
Introduction

The design of ligands for the selective binding of metal ions is an important area of research, since metal-ion specificity is essential to the separation of mixtures of metals, the detection of metal ions, and the binding of metal ions that are used in radiopharmaceuticals and MRI contrast agents (i.e. the lanthanides).[2,3] The crown ethers[4,5] and the calixarenes[6,7] are two families of macrocycles that have been examined extensively for their metal-binding behavior, and many examples of selective metal-ion-binding have been reported for these macrocycles. For the calixarenes, metal-complexation studies have been performed on the lower-rim unsubstituted[6] (R′ = H) and *O*-alkylated[7] (R′= alkyl) macrocycles.

Although there has been considerable research into the binding properties of crown ethers and calixarenes, hybrid structures have not received a great deal of attention. To our knowledge, the only heterocalixarenes to be examined extensively for their metal-binding properties are the hexahomotrioxacalix[3]arene[2c,8−10] macrocycles (**1**), abbreviated as "oxacalix[3]arenes" in this paper. There have only been limited studies of the metal-binding properties of bishomooxacalix[4]arene[11] (**2**), tetrahomodioxacalix[4]arene[2c] (**3**), and octahomotetraazacalix[4]arene[12] (**4**) macrocycles. We have previously reported the synthesis[8a] of oxacalix[3]arene macrocycles **1a**,**b** and an examination of their metal-binding[9] properties. Scandium(III), titanium(IV), oxovanadium(V), yttrium(III), and



1a: R= *t*-Bu
1b: R= Cl



Calix[*n*]arenes: a= 0, b= 4 - 8
2: X= O, a= 1, b=3
3: X= O, a= 2, b=2
4: X= NH, a= 4, b= 0

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Table 1. Apparent Binding Constants between $M(OTf)_3$ and Macrocycles **1a,b** under Nonaqueous Conditions

$M(OTf)_3$	H_3L	buffer[a]	[BHX] (M)/[B] (M)	log K_{app}
$Sc(OTf)_3$	**1a**	Im	0.2/0.2	−15.87
			1.0/1.0	−15.87
$Lu(OTf)_3$	**1a**	DABCO	0.2/0.2	−22.62
$Y(OTf)_3$	**1a**	DABCO	0.2/0.2	−23.20
			1.0/1.0	−23.22
$La(OTf)_3$	**1a**	Et_3N	0.2/0.2	−25.64
$Sc(OTf)_3$	**1b**	Im	0.2/0.2	−15.12
$Lu(OTf)_3$	**1b**	Im	0.2/0.2	−17.06
$Y(OTf)_3$	**1b**	Im	0.3/0.1	−17.57
$La(OTf)_3$	**1b**	Et_3N	0.2/0.2	−23.56
		DABCO	0.3/0.1	−23.94

[a] Im = imidazole; DABCO = 1,4-diazabicyclo[2.2.2]octane, and Et_3N = triethylamine.

lanthanide [La(III), Eu(III), Gd(III), Lu(III)] complexes of the oxacalix[3]arenes have been synthesized. X-ray crystal structures of $[M(L)(DMSO)]_2$ complexes [M = Sc(III) (**5**), Lu(III) (**6**), Y(III) (**7**), La(III) (**8**); L = the trianion of macrocycle **1a**] have been determined and exhibit a bis(μ-aryloxo)-bridged dimeric structure.[9b,c] The only other reports of metal binding by the oxacalix[3]arenes have involved *O*-alkylated derivatives of the macrocycles.[2c,10]

In this paper, we report the determination of relative binding constants for Sc(III), Lu(III), Y(III), and La(III) with the oxacalix[3]arenes **1a**,**b** using a ^1H NMR titration method. The use of the oxacalix[3]arenes for the selective transport of trivalent metal ions across a liquid membrane is also examined. In this paper, macrocycles **1a**,**b** will be abbreviated as H_3L and the macrocycle monoanion, dianion, and trianion will be abbreviated as H_2L, HL, and L, respectively.

Experimental Section

General Procedures. All solvents and bases were purchased from commercial sources, dried using either calcium hydride or sodium−benzophenone ketyl, and degassed. Lithium, sodium, magnesium, and lutetium trifluoromethanesulfonates (triflates), *p*-chlorophenol, and triflic acid were purchased from commercial sources and used without purification. Oxacalix[3]arenes[8a] **1a**,**b** and scandium, yttrium, and lanthanum triflates[13] were prepared by literature procedures. NMR spectra were recorded on a Bruker AC-250 at resonant frequencies of 250 and 62.9 MHz for ^1H and ^{13}C, respectively. Chemical shifts were referenced to either tetramethylsilane or protio solvent impurity. Atomic absorption measurements were performed on a Perkin-Elmer Model 303 spectrometer.

Metal-Binding Studies. ^1H NMR spectra were recorded while a DMSO-d_6 solution of **1a** or **1b** (5 mM) in a nonaqueous buffer (0.2 M) was titrated with a DMSO-d_6 solution (0.2−0.8 M) of $M(OTf)_n$ [M = Sc, Lu, Y, La, Mg, Ca, Li, Na]. The buffers were prepared by reacting an organic base (imidazole, 1,4-diazabicyclo[2.2.2]octane, triethylamine) with sufficient triflic acid to generate the desired ratio of base and conjugate acid ($[B]/[BH^+]$); the buffer systems used in the titrations are listed in Table 1. After each addition of metal triflate, a ^1H NMR spectrum was obtained and the ratio of complexed to uncomplexed macrocycle ($[M(L)]_e/[H_3L]_e$) was determined by integrating the macrocycle methylene or aromatic signals. Binding constants (K_{app}) were determined as discussed in the Results section. The reported K_{app} values in Table 1 are the average of at least two individual experiments, and the standard deviations were less than 6% of the average K_{app} values.

Metal-Transport Studies. Metal-transport experiments were conducted via a liquid membrane cell as previously reported by Izatt and co-workers.[6a,b] The cell consists of a 30 mL capped vial with a glass tube (i.d. = 1 cm) inserted through the center of the lid 1 cm from the bottom of the vial. The organic phase consisted of 12 mL of 1% DMSO in $CHCl_3$ containing **1a** or **1b** (1.0 mM). The receiving phase (10 mL of 0.1 M HNO_3) was layered on top of the organic phase, outside of the glass tube. The source phase was layered on top of the organic phase inside of the glass tube and consisted of 1 mL of 4 mM $Sc(NO_3)_3$, 0.09 M $Mg(NO_3)_2$, or 0.5 M $LiNO_3$ held at constant pH with TRIS buffer (1 M). For experiments with cation mixtures, the source phase contained 9 mM of $Sc(NO_3)_3$, 0.09 M $Mg(NO_3)_2$, and 0.5 M $LiNO_3$. After being stirred for 24 h, the receiving phase was analyzed for metal cation concentration using atomic absorption spectrophotometry. The experiments were reported as the mean of three identical runs; the standard deviation was less than 2% of the measured value. Controls were performed with no macrocycle present to detect membrane leakage and yielded fluxes for all salt solutions less than each metal's detection limit.

Results

Metal Binding by the Oxacalix[3]arenes. We have previously reported[9b,c] that the addition of an organic base to an equimolar mixture of macrocycle **1a** or **1b** and $M(OTf)_3$ (M = Sc, Lu, Y, La; OTf = OSO_2CF_3) in DMSO-d_6 results in the gradual disappearance of the singlet for the macrocycle methylene protons[8a] and the appearance of a pair of doublets in the same region of the ^1H NMR spectrum. Identical spectral changes occur when a solution of macrocycle **1a** or **1b** is titrated with $M(OTf)_3$ (M = Sc, Lu, Y, La) in DMSO-d_6 in the presence or absence of a nonaqueous buffer consisting of an organic base [B = imidazole (Im), 1,4-diazabicyclo[2.2.2]octane (DABCO), or triethylamine (Et_3N)] and its conjugate acid (BH^+OTf^-).[14] For titrations with macrocycle **1a**, the chemical shifts of the doublets are identical to those of spectra of the isolated complexes **5**−**8** in DMSO-d_6.[9b,c] We have previously proposed that complexes **5**−**8** dissociate in DMSO to form monomeric $[M(L)(DMSO)_2]$ complexes, abbreviated as M(L) in this paper.

Only one set of doublets was observed during these titrations, and the chemical shifts of the doublets and the macrocycle singlet remained constant throughout the titration regardless of whether the titrations were performed at constant MX_3 concentration and variable pH, constant pH (nonaqueous buffer systems) and variable MX_3 concentration, and variable pH and variable MX_3 concentration. These observations indicate that the macrocycle (H_3L) and the M(L) complex are the only species present at appreciable concentration during the titrations. The complexes of the macrocycle monoanion $[M(H_2L)X_2]$ and dianion [M(HL)X] must be formed in very low concentrations, since there is no evidence of additional signals in the ^1H NMR spectra. Although rapid proton/X exchange between $M(H_2L)X_2$, M(HL)X, and M(L) species on the NMR time scale could result in the appearance of a single pair of doublets for these metal complexes, the chemical shifts of the doublets should change during the titration due to the different NMR spectra for these species. The possibility that the $M(H_2L)X_2$, M(HL)X, and M(L) complexes have identical NMR spectra is unlikely.

Determination of Metal-Binding Constants. The water-insolubility of macrocycles **1a**,**b** and the reported difficulties associated with nonaqueous titrations[15] (*i.e.* slow electrode response) have caused us to utilize NMR titrations at constant pH (nonaqueous buffer systems) to determine relative metal binding constants for macrocycles **1a**,**b** with metal ions.

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Although constant pH titrations suffer from the limitation that pH-dependent speciation of metal complexes cannot be observed, there is no speciation in this system since only the M(L) complex is observed during variable pH titrations (*i.e.* $M(H_2L)X_2$ and M(HL)X complexes are not formed).

The equilibria in eqs 1 and 2 can be used to describe the titrations in these nonaqueous buffer systems. Equation 3 can be derived from the expressions for the equilibria in eqs 1 and 2, where $[H_3L]_e$, $[M(L)]_e$, and $[MX_3]_e$ are the concentrations of free macrocycle (**1a** or **1b**), M(L) complex, and free metal ion at equilibrium, respectively. The ratio (R) of the concentrations of the M(L) complex and the free macrocycle (H_3L) at equilibrium can be determined from the ratio of the ^{1}H NMR integrals for the doublets (M(L) complex) and the singlet (H_3L). Ratios obtained during the titrations were constant over several weeks. The equilibrium concentration of the metal salt ($[MX_3]_e$) can be calculated by material balance ($[MX_3]_e = [MX_3]_i - [M(L)]_e$) using eq 4, where $[H_3L]_i$ is the initial concentration of macrocycle **1a** or **1b** and $[MX_3]_i$ is the concentration of metal triflate added at each point in the titration. Plots of R vs $[MX_3]_e$ were linear and had negligible *y*-intercepts as predicted by eq 3. The apparent binding constant K_{app} between the macrocycle and metal triflate (eq 1) can be calculated from the slope of the line using the known buffer ratio ([B]/[BHX]) and the K_a of the buffer conjugate acid.[14] Table 1 lists log K_{app} values for each of the metal triflates ($MOTf_3$: M = Sc, Lu, Y, and La) and macrocycles **1a**,**b**.

$$H_3L + MX_3 \overset{K_{app}}{\rightleftharpoons} M(L) + 3H^+ + 3X^- \qquad (1)$$

$$BH^+X^- \overset{K_a}{\rightleftharpoons} B + H^+ + X^- \qquad (2)$$

$$R = \frac{[M(L)]_e}{[H_3L]_e} = \frac{K_{app}}{K_a^{\,3}}\left(\frac{[B]}{[BHX]}\right)^3 [MX_3]_e \qquad (3)$$

$$[MX_3]_e = [MX_3]_i - \frac{R[H_3L]_i}{R + 1} \qquad (4)$$

Several observations indicate that the role of the buffer in these systems is simply to control the pH during the titration. First, the K_{app} values for $M(OTf)_3$ (M = Sc, Y) binding to macrocycle **1a** (Table 1) are observed to be independent of the buffer concentration (0.2−1 M) at constant pH. This indicates that the base (B) component of the buffer does not facilitate metal binding through the formation of $M(L)(B)_n$ complexes, since larger binding constants would be anticipated at the higher buffer concentrations. Second, the binding constant for $La(OTf)_3$ with macrocycle **1b** was nearly identical in two different buffer systems (DABCO and Et_3N) consistent with the equilibria in eqs 1−3.

The binding constants (K_{app}) are observed to be larger for the electron-deficient *p*-chlorooxacalix[3]arene **1b** compared to the more electron-rich *p-tert*-butyloxacalix[3]arene **1a**, and they increase with the following trend: La(III) ≪ Y(III) < Lu(III) ≪ Sc(III). The observation that the binding constants for Sc(III) and La(III) differ by almost 10 orders of magnitude is evidence for the dramatic selectivity of the oxacalix[3]arenes between trivalent metals. Although macrocycle **1b** exhibits larger apparent binding constants than macrocycle **1a**, the relative selectivities between Sc^{3+} and the other metal ions are poorer for macrocycle **1b** compared to macrocycle **1a**.[16]

When macrocycles **1a**,**b** are titrated with LiOTf, NaOTf, and $Ca(OTf)_2$ in a triethylamine buffer system (0.2 M Et_3N, 0.2 M $Et_3NH^+OTf^-$), no new peaks are observed, and the chemical shift of the macrocycle methylene singlet remains constant. New baseline peaks are observed in the methylene region when a large excess of $Mg(OTf)_2$ is added to the macrocycles under the same buffer conditions. Thus, the observed trend in the apparent binding constants (K_{app}) of macrocycles **1a**,**b** with metal ions is the following: $Sc^{3+} \gg Lu^{3+} > Y^{3+} \gg La^{3+} > Mg^{2+} > Ca^{2+}, Na^+, Li^+$.

Liquid−Liquid Membrane Metal-Transport Studies. The ability of macrocycles **1a**,**b** to transport Li^+, Mg^{2+}, and Sc^{3+} across an organic/aqueous liquid membrane was investigated using the apparatus described in the Experimental Section.[6a,b] Macrocycle **1b** was observed to transport 44% of the Sc^{3+} from the source phase to the receiving phase over 24 h when the source phase was buffered to pH 8.8. There was no transport of Li^+ (<0.5%) and Mg^{2+} (<0.2%) under these conditions. When a mixture of the three metals (Sc^{3+}, Mg^{2+}, Li^+) was used as the source phase, only Sc^{3+} was transported by macrocycle **1b**. No transport of Sc^{3+} was observed when the pH of the source phase was lowered to pH 8.4. Control experiments indicated no metal-ion transport in the absence of macrocycle. Macrocycle **1a** displayed no transport of Sc^{3+} at pH 8.8. Transport experiments at higher pH were not possible, since scandium hydroxides precipitated. No transport of any of the metals was observed when *p*-chlorophenol was added to the organic phase instead of macrocycle **1a** or **1b**.

Discussion

The apparent binding constants (Table 1) are observed to increase with increasing charge-to-radius ratio[17,18] for the metal ions ($Ca^{2+}, Na^+, Li^+ < Mg^{2+} < La^{3+} \ll Y^{3+} < Lu^{3+} \ll Sc^{3+}$), and the binding constants are larger for the *p*-chlorooxacalix[3]arene **1b** compared to the *p-tert*-butyloxacalix[3]arene **1a**. The trend in the metal-binding constants resembles the reported hydrolysis equilibrium constants[19,20] for these metal ions (eq 5). For this reason, we propose that the successive ionization equilibria in eqs 6−8 describe the process by which trivalent metal ions bind to the oxacalix[3]arene macrocycles. On the basis of this proposed mechanism, the apparent binding constants

$$MX_3 + H_2O \overset{K_h}{\rightleftharpoons} M(OH)X_2 + H^+ + X^- \qquad (5)$$

$$MX_3 + H_3L \overset{K_1}{\rightleftharpoons} M(H_2L)X_2 + H^+ + X^- \qquad (6)$$

$$M(H_2L)X_2 \overset{K_2}{\rightleftharpoons} M(HL)X + H^+ \qquad (7)$$

$$M(HL)X \overset{K_3}{\rightleftharpoons} M(L) + H^+ \qquad (8)$$

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[16] Selectivities (in parentheses) are defined as log $K_{app}(Sc^{3+})$ − log $K_{app}(M^{3+})$: **1a**, M = Lu (6.8), Y (7.3), La (9.8); **1b**, M = Lu (1.9), Y (2.5), La (8.6).

[17] Charge-to-radius ratios were calculated using crystal radii[18] for the six-coordinate (Sc^{3+}, Lu^{3+}, Y^{3+}, Mg^{2+}, Ca^{2+}, Li^+, Na^+) and eight-coordinate (La^{3+}) metal ions: Sc^{3+}, 3.39; Lu^{3+}, 3.00; Y^{3+}, 2.88; La^{3+}, 2.31; Mg^{2+}, 2.33; Ca^{2+}, 1.75; Li^+, 1.11; Na^+, 0.78. The coordination numbers for Sc^{3+}, Lu^{3+}, Y^{3+}, and La^{3+} were selected on the basis of the observed structures for complexes **5**−**8**.[9c]

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[19] Aqueous hydrolysis log equilibrium constants (log K_h) for alkaline earth and alkali metal ions[20] are the following: Sc^{3+}, −4.3; Lu^{3+}, −7.7; Y^{3+}, −8.0; La^{3+}, −9.1; Mg^{2+}, −11.42; Ca^{2+}, −12.70; Li^+, −13.82; Na^+, −14.48.

[20] (a) Baes, C. F., Jr.; Mesmer, R. F. *Hydrolysis of Cations*; John Wiley and Sons: New York, 1976. (b) Huheey, J. E. *Inorganic Chemistry: Principles of Structure and Reactivity*, 3rd ed.; Harper and Row: New York, 1983; p 295.

(K_{app}) determined in this study (eq 1) are the product of the three equilibrium constants in eqs 6−8 ($K_{app} = K_1K_2K_3$).

Binding of a metal ion is proposed to occur initially via an alcoholysis reaction between the macrocycle and metal ion resulting in the formation of a $M(H_2L)X_2$ complex. Once the $M(H_2L)X_2$ complex is formed, the second and third macrocycle protons can be removed more easily than the first due to favorable electrostatic interactions with the metal center, *i.e.* $K_1[MX_3] < K_2 < K_3$. The larger binding constants for macrocycle **1b** compared with macrocycle **1a** is consistent with the anticipated relative acidity of the macrocycles, since the more acidic macrocycle **1b** will exhibit a more favorable alcoholysis equilibrium (eq 6) and a more facile ionization of the $M(H_2L)X_2$ and M(HL)X complexes (eqs 7 and 8). Prior ionization of the macrocycle to form H_2L^-, HL^{2-}, or L^{3-} species followed by metal-ion binding to the deprotonated macrocycles is unlikely due to the predicted high pK_a's for the macrocycles. Although it has not been possible to determine pK_a's for macrocycles **1a**,**b**, simple phenols[21] are reported to have pK_a's of 18−20 in DMSO. The observation that the spectrum of macrocycle **1b** in DMSO-d_6 is identical in the presence or absence of the most basic buffer system (1:1 $Et_3NH^+OTf^-/Et_3N$, pH 9.0) indicates that there is no significant ionization of the macrocycle under these conditions. In a previous study, we reported that the ^{1}H NMR spectra of alkali metal complexes of the monoanions of macrocycles **1a**,**b** [$M(H_2L)$, M = Li, Na, K] were significantly different than the neutral macrocycles **1a**,**b** (H_3L).[8a]

The selective transport of Sc^{3+} by macrocycle **1b** is consistent with the significantly larger binding constant for Sc^{3+} compared to Li^+ or Mg^{2+}. The observation that macrocycle **1a** exhibited no transport of Sc^{3+} is also consistent with the weaker binding of Sc^{3+} by macrocycle **1a** compared to **1b**. During metal ion transport, the equilibrium in eq 1 occurs at both the source phase/organic phase and the receiving phase/organic phase interfaces. The result is a net flux of Sc^{3+} from the source phase to the receiving phase and the transport of protons from the receiving phase to the source phase. It appears that the cooperative interaction of the three phenolic groups in macrocycle **1b** is important in metal-ion transport, since *p*-chlorophenol was not observed to transport Sc^{3+}, Mg^{2+}, or Li^+ under conditions where **1b** was observed to transport Sc^{3+}. It was not possible to examine the transport of yttrium(III), lutetium(III), or lanthanum(III) ions by the oxacalix[3]arenes due to their precipitation at high pH.

Conclusion

The oxacalix[3]arene macrocycles **1a**,**b** bind trivalent metals more strongly than monovalent and divalent metals and exhibit good selectivity between trivalent metals. The metal-binding constants are observed to increase with increasing Lewis acidity of the metal ions ($Sc^{3+} \gg Lu^{3+} > Y^{3+} \gg La^{3+} \gg Mg^{2+} > Ca^{2+}, Na^+, Li^+$) and increasing macrocycle acidity (**1a** < **1b**). The observation that the oxacalix[3]arene macrocycles appear to bind metals on the basis of their electrostatic properties suggests that other metals that have large hydrolysis equilibrium constants may also bind strongly to the oxacalix[3]arene macrocycles, *i.e.* Al(III), Ga(III), In(III), Cr(III), and Fe(III).

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[21] The pK_a's of *p*-chlorophenol, phenol, and *p*-cresol in DMSO are 16.7, 18.0, and 18.9.[15]