

## Cation Complexation by Chemically Modified Calixarenes. 5. Protonation Constants for Calixarene Carboxylates and Stability Constants of Their Alkali and Alkaline-Earth Complexes

Françoise Arnaud-Neu,<sup>\*,†</sup> Geraldine Barrett,<sup>‡</sup> Steven J. Harris,<sup>§</sup> Michael Owens,<sup>‡</sup> M. Anthony McKervey,<sup>‡</sup> Marie-José Schwing-Weill,<sup>†</sup> and Pascale Schwinté<sup>†</sup>

Laboratoire de Chimie-Physique, URA 405 au CNRS, EHICS, 1, rue Blaise Pascal, 67000 Strasbourg, France, School of Chemistry, The Queen's University, Belfast 9BT 5AG, Northern Ireland, Research and Development, Loctite (Ireland) Ltd., Whitestown Industrial Estate, Tallaght, Dublin, Ireland

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The complexing properties of some calix[4]arenes in which carboxylic acid ligating groups have been progressively attached to the lower rim through the phenolic hydrogen atoms have been measured with alkali and alkaline-earth metal cations in methanol by means of potentiometric titrations. The acid–base characteristics of these compounds were first determined. The weak acidities generally observed may be explained by the formation of intramolecular hydrogen bonding. The formation of mononuclear 1:1 complexes and their corresponding protonated forms was established in most cases. The latter species were predominant in the acidic range of pH. Additionally, dinuclear complexes were also found with the diacid derivatives. The results show that, in appropriate acidity conditions, calixarene acids, which are very efficient complexing agents for alkalis and especially alkaline-earth metals, are much stronger binders than calixarene esters, ketones, or amides. In the tetraphenol or the tetraester, the stepwise substitution of the phenolic hydrogens or ester functions by a carboxylic acid leads to an enhancement of the stability of the resulting complexes but a decrease of the Na<sup>+</sup>/K<sup>+</sup> selectivity. With respect to the alkaline-earth metals, a huge Ca<sup>2+</sup>/Mg<sup>2+</sup> selectivity is exhibited by all the compounds.

The ability of calixarene derivatives of the general formula shown in Figure 1a to bind metal cations is now well established.<sup>1–7</sup> In the tetramer series the macrocycle in the cone conformation (Figure 1b) acts as platform or substructure holding the ligating podands (functional groups) in an arrangement well disposed toward binding a guest cation within the electron-donating ethereal and carbonyl groups. The phenolic hydroxyl groups offer convenient points for attaching binding groups. The most useful thus far developed are esters,<sup>2,3,5–7</sup> ketones,<sup>2,3</sup> amides,<sup>4,7</sup> calixcrown ethers,<sup>8</sup> calixspherands,<sup>8</sup> and thioamides.<sup>7</sup> We have now extended this series to include the binding power of carboxylic acid functions.

The phenolic groups of the parent calixarenes can of course function as ionizable ligands, a property exploited originally by

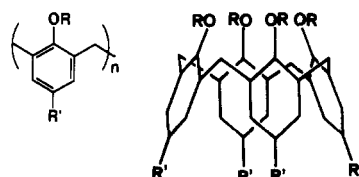


Figure 1. Left: (a) Calixarene derivatives: R = functional group; R' = H or alkyl; n = 4–8. Right: (b) Calix[4]arene derivative in the cone conformation.

Izatt and his co-workers<sup>9,10</sup> for cation transport from basic solution through a haloformic membrane and later used for the same purpose by Ungaro's group<sup>8</sup> in the form of a crown ether-capped calix[4]arene. *tert*-Butylcalix[8]arene is partly deprotonated in forming a binuclear complex with Eu(III)<sup>11</sup> and Gutsche<sup>12</sup> has suggested that complex formation between *tert*-butylcalix[4]arene and *tert*-butylamine involves deprotonation with formation of a hydrogen-bonded ammonium cation within the cavity. A 1:1 complex between cesium ion and a monodeprotonated tetramer was recently shown to have the guest deeply embedded in the host cavity.<sup>13</sup> Alternatively, ionizable ligands can be attached to the calixarene substructure. Ungaro<sup>14</sup> has prepared a tetraacetic acid of *p-tert*-butylcalix[4]arene (I) whose alkali metal salts display solubilities in water indicative of selective complexation. These workers also showed that extraction of divalent metal acetates by this ligand and its homologous diacid–diphenol

<sup>†</sup> EHICS.

<sup>‡</sup> The Queen's University.

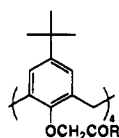
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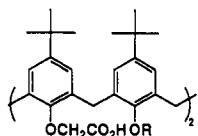
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occurred at neutral pH<sup>14</sup> and that these ligands were also effective carriers at low pH.<sup>15</sup>

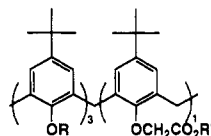
Because of the potential for carboxylic acids in macrocyclic arrays to act as ionophores, we have conducted a systematic quantitative study of the acid-base properties of some calixareneacetic acids LH<sub>n</sub> and their alkali and alkaline-earth metal complexation characteristics. In addition to *p*-*tert*-butylcalix[4]arenetetracarboxylic acid (I),<sup>14,15</sup> we studied some derivatives with mixed functionality such as *p*-*tert*-butylcalix[4]arene-dicarboxylic acid (II<sub>a</sub>),<sup>14</sup> *p*-*tert*-butylcalix[4]arene-dicarboxylic acid di-*tert*-butyl ester (II<sub>b</sub>), the *p*-*tert*-butylcalix[4]arene-monocarboxylic acid (III<sub>a</sub>), the *p*-*tert*-butylcalix[4]arene-monocarboxylic acid tri-*tert*-butyl ester (III<sub>b</sub>),<sup>16</sup> and the *p*-*tert*-butylcalix[4]arene-monocarboxylic acid triethyl ester (III<sub>c</sub>).<sup>16</sup> The *p*-*tert*-butyltetrahomodioxacalix[4]arenetetracarboxylic acid (IV) has also been studied. Protonation constants and stability constants have been determined in methanol, a solvent which solubilizes all these ligands.



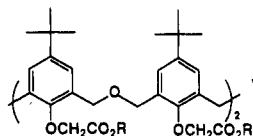
I : R = OH  
V : R = OEt  
VI : R = OBU<sup>t</sup>  
IX : R = C<sub>4</sub>H<sub>9</sub>N



II<sub>a</sub> : R = H  
II<sub>b</sub> : R = CH<sub>2</sub>CO<sub>2</sub>BU<sup>t</sup>



III<sub>a</sub> : R = H, R' = H  
III<sub>b</sub> : R = CH<sub>2</sub>CO<sub>2</sub>BU<sup>t</sup>, R' = H  
III<sub>c</sub> : R = CH<sub>2</sub>CO<sub>2</sub>Et, R' = H  
VII : R = H, R' = Et



IV : R = H  
VIII : R = Et

## Experimental Section

**Materials.** The solvent, methanol (Carlo Erba with low water content, maximum 0.01% in weight), was used without further purification. The ligands were used as the free acids. The ligand solutions were made from dissolution of a weighted quantity of ligand in methanol. The ionic strength was held constant at 10<sup>-2</sup> M by addition of tetraethylammonium perchlorate, recrystallized twice from methanol. The titrant base used was tetraethylammonium hydroxide made from a dilution of the commercial solution (25% in MeOH, Fluka) and standardized against potassium acid phthalate.

The metallic salts were the alkali metal perchlorates LiClO<sub>4</sub> (Fluka), NaClO<sub>4</sub> (Merck, p.a.), and KClO<sub>4</sub> (Prolabo, Normapur) and the salts CsNO<sub>3</sub>, RbNO<sub>3</sub>, CsCl, and RbCl (Merck, p.a.). The alkaline-earth metal salts were the following perchlorates: Mg(ClO<sub>4</sub>)<sub>2</sub>·xH<sub>2</sub>O (Merck), Ca(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (Fluka, purum), Ba(ClO<sub>4</sub>)<sub>2</sub> (Prolabo, Normapur), and Sr(NO<sub>3</sub>)<sub>2</sub> (Merck). All the salts were dried at room temperature under vacuum before use. The stock solutions of Mg<sup>2+</sup> and Ca<sup>2+</sup> salts were titrated by complexometry with EDTA using calmagite as indicator.

**Preparation of Acids.** Tetraacid I,<sup>14</sup> diacid diphenol II<sub>a</sub>,<sup>14</sup> monoacid tri-*tert*-butyl ester III<sub>b</sub>,<sup>16</sup> and monoacid triethyl ester III<sub>c</sub><sup>16</sup> were prepared according to the literature procedures.

**Diacid Di-*tert*-butyl Ester II<sub>b</sub>.** Tetra-*tert*-butyl ester VI (310 mg) was dissolved in chloroform (5 mL) containing trifluoroacetic acid (0.04 mL). The solution was stirred at room temperature without exclusion of moisture for 24 h and then was washed with water (3 × 5 mL), dried over MgSO<sub>4</sub>, and concentrated to a crystalline mass (278 mg). Recrystallization from aqueous ethanol furnished diacid II<sub>b</sub> (214 mg, 77%) as needles: mp 136–138 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.767 (s, Bu<sup>t</sup>, 18H), 1.266 (s, Bu<sup>t</sup>, 18H), 1.422 (s, OBU<sup>t</sup>, 18H), 3.217 (d, H<sub>B</sub>ArCH<sub>2</sub>Ar, 4H), 6.722 (s, 4H, ArH), and 7.189 (s, 4H, ArH). Anal. Calcd for C<sub>60</sub>H<sub>80</sub>O<sub>12</sub>: C, 72.55; H, 8.12. Found: C, 72.29; H, 8.14.

**Monoacid Triphenol III<sub>a</sub>.** Monoethyl ester VII<sup>17</sup> (3.0 g) was dissolved in water (50 mL) and ethanol (200 mL) containing sodium hydroxide, and the solution was heated under reflux for 24 h. The cooled solution was diluted with water (20 mL) and filtered. The precipitated sodium salt was suspended in 50% sulfuric acid and thoroughly mixed for 12 h. The precipitate was again isolated, washed with water, and crystallized from aqueous ethanol to furnish monoacid III<sub>a</sub> (2.88 g, 83%): mp >300 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.185 (s, Bu<sup>t</sup>, 9H), 1.218 (s, Bu<sup>t</sup>, 18H), 1.227 (s, Bu<sup>t</sup>, 9H), 3.514 (dd, H<sub>B</sub>H<sub>B</sub>, ArCH<sub>2</sub>Ar, J = 13.7 Hz, J' = 14.0 Hz, 4H), 4.119 (d, ArCH<sub>2</sub>Ar, H<sub>A</sub>, 2H), 4.255 (d, ArCH<sub>2</sub>Ar, H<sub>A</sub>, 2H), 4.783 (s, OCH<sub>2</sub>, 2H), 7.039 (s, ArH, 2H), 7.076 (s, ArH, 2H), 7.103 (s, ArH, 2H), 9.476 (s, OH, 2H), and 10.104 (s, OH, H). Anal. Calcd for C<sub>46</sub>H<sub>58</sub>O<sub>6</sub>·H<sub>2</sub>O: C, 76.27; H, 8.34. Found: C, 76.72; H, 8.15.

**Tetrahomodioxo Tetraacid IV.** Tetrahomodioxo tetraethyl ester<sup>5</sup> VIII was hydrolyzed with sodium hydroxide in aqueous ethanol exactly as described above for monoacid III<sub>a</sub> to yield tetraacid IV: mp 251–253 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.230 (s, Bu<sup>t</sup>, 36H), 3.612 (d, ArCH<sub>2</sub>Ar, H<sub>B</sub>, 2H), 4.224–4.873 (m, OCH<sub>2</sub>; H<sub>C</sub>H<sub>C</sub>, H<sub>D</sub>H<sub>D</sub>, ArCH<sub>2</sub>Ar, H<sub>A</sub>, ArCH<sub>2</sub>Ar, 36H), 7.152 (s, ArH, 4H), and 7.617 (s, ArH, 4H).

**Stability Constants Determination.** The stability constants of the complexes were determined potentiometrically using a competitive method with the proton. The concentrations of free hydrogen ions, [H<sup>+</sup>], were measured by a combined glass electrode (Ingold) connected to an automatic titrator (Titroprocessor Metrohm 636), at 25 °C. The standard filling solution (saturated aqueous KCl) of the external reference of the combined glass electrode was replaced by a 0.01M Et<sub>4</sub>NCl solution in MeOH saturated with AgCl. The electrode was calibrated at pH = -log [H<sup>+</sup>] = 2 with a solution of 10<sup>-2</sup>M HClO<sub>4</sub> in MeOH obtained by dilution of the commercial concentrated ca. 11.6 M perchloric acid. As the junction potentials vary exponentially with -log [H<sup>+</sup>],<sup>18</sup> the following correction relationship was used:

$$-\log[H^+]_{\text{real}} = -\log[H^+]_{\text{meas}} + a + b[H^+]_{\text{meas}}$$

The constants *a* and *b* were determined by measuring the pH of a methanolic solution of 10<sup>-3</sup> M HClO<sub>4</sub> in the presence of 9.10<sup>-3</sup> M Et<sub>4</sub>NClO<sub>4</sub>. Mean values for *a* and *b* were respectively +0.25 and -25. The working solutions were made up as follows: 20 mL of a stock solution of ligand in methanol was added to an accurately weighted amount of metallic salt or to a precise volume of a stock solution of the metallic salt, in 25-mL flasks. The final ligand concentrations C<sub>L</sub> vary from 10<sup>-3</sup> M for compound III<sub>c</sub>, to ca. 5 × 10<sup>-4</sup> M for compounds I, II<sub>a</sub>, and III<sub>a</sub>, ca. 3 × 10<sup>-4</sup> M for IV, and 10<sup>-4</sup> M for III<sub>b</sub> and II<sub>b</sub>. The 10-mL aliquots of these solutions were titrated with Et<sub>4</sub>NOH in a thermostated cell (25 ± 0.05 °C) under an atmosphere of argon. For each determination at least four experiments were performed with different *R* values defined as the metal/ligand concentration ratio. The data were treated by the program Miniquad<sup>19</sup> which refines the overall stability constants β<sub>xy</sub> (see later). The protonation constants of the carboxylate forms of the ligands, obtained from titration of the ligand in the absence of metal, were settled as constant during the refinement procedure. The autoprotolysis constant of methanol used for the calculations was pK<sub>MeOH</sub> = -16.7.<sup>20</sup>

## Results and Discussion

The acid-base properties of these calixareneacetic acids and their complexation characteristics will undoubtedly be influenced by the nature of the conformations they adopt in solution. In some conformations intramolecular hydrogen bond formation will be more accessible than in others. The magnitude of electrostatic interactions will also be influenced by the confor-

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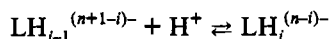
**Table I.** Logarithms of the Protonation Constants ( $\log K_i$ ) of the Ligands Studied in MeOH, at 25 °C ( $I = 0.01$  M in Et<sub>4</sub>NClO<sub>4</sub>)

ligands	$\log K_i$			
	$i = 1$	$i = 2$	$i = 3$	$i = 4$
I	13.39 ± 0.03	10.89 ± 0.05	9.19 ± 0.02	8.25 ± 0.09
II <sub>a</sub>	9.3 ± 0.1	8.0 ± 0.1		
II <sub>b</sub>	11.41 ± 0.06	9.52 ± 0.08		
III <sub>a</sub>	13.4 ± 0.1	13.02 ± 0.09	12.14 ± 0.07	7.52 ± 0.03
III <sub>b</sub>	10.55 ± 0.09			
III <sub>c</sub>	10.25 ± 0.06			
IV	13.2 ± 0.1	12.22 ± 0.09	9.9 ± 0.1	7.82 ± 0.03

mations adopted, which may of course differ from protonated to unprotonated forms. All the available evidence<sup>14</sup> suggests that tetraacid I possesses the cone conformation: the <sup>1</sup>H NMR spectrum exhibits the AB system for the protons of the bridging methylenes characteristic of the cone conformation. Furthermore, the sample of the tetraethyl ester V from which I was obtained by hydrolysis is known from X-ray diffraction and NMR evidence to possess a stable cone conformation in solution.<sup>2</sup> The tetrahomodioxo tetraacid IV was prepared by hydrolysis of a tetraester whose conformation has been determined by X-ray diffraction to have a 1, 2 alternate arrangement, i.e. two adjacent ester groups are cis and anti to the two remaining ester groups on the opposite face of the macroring.<sup>5</sup> We presume that it is also the conformation of its hydrolysis product IV.

Of the four remaining compounds, monoacid triethyl ester III<sub>c</sub> possesses a distorted cone conformation in the solid state structure obtained from X-ray diffraction, and there is strong NMR evidence that it is also the solution conformation.<sup>16</sup> We believe that the same conclusion may be drawn concerning its tri-*tert*-butyl counterpart III<sub>b</sub>: this monoacid was prepared by partial hydrolysis of the tetra-*tert*-butyl ester VI, which is known to have the cone conformation.<sup>14</sup> Furthermore, apart from differences due to the different ester alkyl residues in III<sub>b</sub> and III<sub>c</sub>, the two compounds have virtually identical <sup>1</sup>H NMR spectra. Partial hydrolysis of VI was also used to prepare the diacid di-*tert*-butyl ester II<sub>b</sub> which is therefore presumed to possess the cone conformation. Alkylation of *p*-*tert*-butylcalix[4]arene with a deficiency of ethyl bromoacetate furnished the monoester VII. Hydrolysis of this ester yielded the monoacid III<sub>a</sub> whose <sup>1</sup>H NMR spectrum is fully consistent with the presence of the cone conformation. Finally, there is substantial evidence for the presence of the cone conformation in the diacid diphenol II<sub>a</sub>.<sup>14</sup> Further evidence for this conclusion is provided by the fact that partial hydrolysis of the diethyl ester diphenol produces a monoacid monoester diphenol in the cone conformation.<sup>21</sup>

**Acid-Base Properties.** Protonation of the carboxylate forms of the ligands is described by



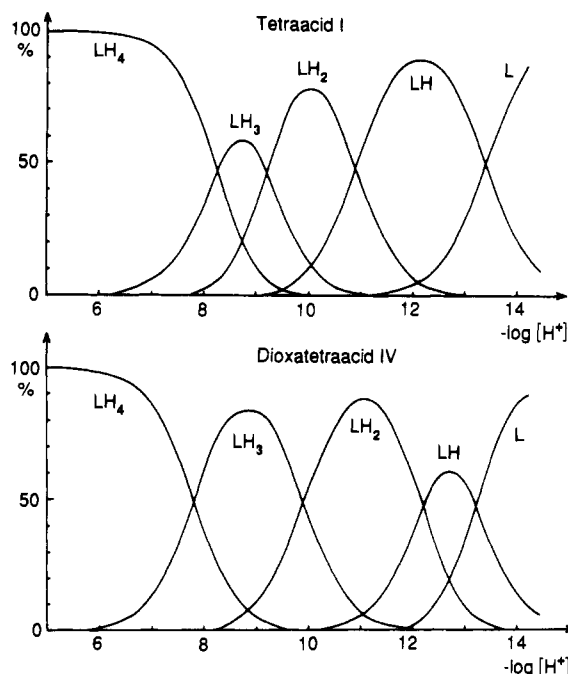
and characterized, under particular conditions of temperature and ionic strength, by the stepwise apparent protonation constants, defined in terms of concentrations

$$K_i = [\text{LH}_i^{(n-i)-}] / [\text{LH}_{i-1}^{(n+1-i)-}][\text{H}^+]$$

with  $1 \leq i \leq n$ . The notation  $\log K_i$ , instead of the acidity  $\text{p}K_a$ 's, is preferred in this paper for the sake of consistency because they are formation constants similar to the complexation stability constants given below. The values of  $\log K_i$ , given in Table I, are the arithmetic means of  $N$  experiments ( $N \geq 4$ ) and the precisions indicated correspond to  $\pm \sigma_{N-1}$ ,  $\sigma_{N-1}$  being the standard deviation of these means.

In general the protonation constants are rather high, an indication of weak acid functions. However it should be specified,

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**Figure 2.** Distribution curves of the protonated species of compounds I and IV versus  $-\log [\text{H}^+]$ .  $C_L = 3 \times 10^{-4}$  M.

for comparison, that we found  $\log K_1$  for acetic acid and phenoxyacetic acid in methanol to be respectively 9.3 and 7.7 instead of 4.7 and 3.0 in water,<sup>22</sup> i.e.  $\Delta(\log K_1)$  of ca. 4.7 on going from water to methanol.

All four protonation constants of the tetracarboxylates I and IV could be determined. The first acidity ( $\log K_4 = \text{p}K_a^1$ ) of IV is stronger (7.8 log units) than that of I (8.3 log units) and is of the same order of magnitude as that of their constitutive subunit, *p*-*tert*-butylphenoxyacetic acid ( $\log K_1 = 7.9$ ). A similar result has been found by Arena et al.<sup>23</sup> in water for the *p*-tetrasulfonate of calix[4]arenetetra-carboxylic acid. Clearly tetraacid I in the cone conformation possesses more possibilities for intramolecular hydrogen bonding than does tetraacid (IV) where two acid functions are on the opposite side of the macroring. However the second and the third acidities of IV ( $\log K_3 = \text{p}K_a^2 = 9.9$  and  $\log K_2 = \text{p}K_a^3 = 12.2$ ) are slightly weaker than those of I ( $\log K_3 = 9.2$  and  $\log K_2 = 10.9$ ). In other words removal of the second and the third proton of LH<sub>4</sub> is more difficult for IV than for I. This result could be explained in terms of stabilization of the LH<sub>2</sub><sup>2-</sup> and LH<sub>3</sub><sup>-</sup> protonated species through hydrogen bonding with the two additional oxygen atoms present in the macrocyclic array. The high values of  $\log K_1$  (or  $\text{p}K_a^4$ ) observed with both ligands show the difficulty in achieving full deprotonation. The results are visualized in Figure 2 which shows the distribution curves of the protonated species plotted against  $-\log [\text{H}^+]$  for both tetramers. The percentage of ligand in each species was calculated with the program Haltfall.<sup>24</sup> The values of pH at which there is maximum formation of the different protonated species confirm the relative acidities of the two ligands discussed above. The main difference between these ligands is that the monoprotated species of IV is formed at a maximum of 60% only (instead of 90% for I), as L<sup>-</sup>, LH<sub>3</sub><sup>-</sup>, and LH<sub>2</sub><sup>2-</sup> are present simultaneously in a very small range of pH (between 12 and 13.5).

The monoacid derivatives III<sub>b</sub> and III<sub>c</sub> have a very low acidity ( $\log K_1 = 10.5$  and 10.2, respectively) as compared with

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**Table II.** Logarithms of the Overall Stability Constants of Alkali metal Complexes of the Ligands Studied, in MeOH at 25 °C, ( $I = 0.01 \text{ M Et}_4\text{NClO}_4$ )

ligands	xyz	$\log \beta_{xyz}$				
		Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
I	110	7.89 ± 0.08	9.94 ± 0.02	9.05 ± 0.01	7.72 ± 0.04	6.2 ± 0.1
	111	18.93 ± 0.03	20.61 ± 0.02	19.77 ± 0.01	18.38 ± 0.02	17.2 ± 0.1
	112	27.98 ± 0.06	30.67 ± 0.01	29.35 ± 0.01	27.76 ± 0.01	27.3 ± 0.1
	113	35.68 ± 0.13	38.52 ± 0.01	37.35 ± 0.02	35.93 ± 0.06	35.9 ± 0.1
II <sub>a</sub>	110	4.5	4.6 ± 0.1	4.7 ± 0.3	5.2 ± 0.1	4.21 ± 0.03
	210	7.6 ± 0.1	8.3 ± 0.3	8.3 ± 0.5	8.98 ± 0.06	8.05 ± 0.01
	111	12.4 ± 0.3	12.32	12.4	12.85 ± 0.06	
II <sub>b</sub>	110	4.6 ± 0.2	6.6 ± 0.2	6.6 ± 0.3	4.6 ± 0.1	4.3 ± 0.3
	210	9.5 ± 0.4	11.5 ± 1.2	10.8 ± 0.6	9.2 ± 0.4	
	111	15.0 ± 0.2	16.54 ± 0.09	15.92 ± 0.04	15.1 ± 0.1	15.0 ± 0.1
III <sub>b</sub>	110	3.54 ± 0.02	5.6 ± 0.2	5.0 ± 0.1	4.00 ± 0.05	3.9 ± 0.1
III <sub>c</sub>	110	3.47 ± 0.04	5.71 ± 0.02	4.91 ± 0.01	3.15 ± 0.01	2.56 ± 0.02

phenoxyacetic acid. The weak acidity of both compounds, i.e. the reluctance to lose the proton, can be explained by a stabilization of the proton within the cavity defined by the three ester functions. Indeed this is in agreement with the observation of Boehmer et al.<sup>25</sup> who suggested that the hydrolysis of the tetraethylester into compound III<sub>c</sub> was initiated by reversible hydronium ion complexation within the hydrophilic cavity of the tetraester. The X-ray crystal structure of III<sub>c</sub> reveals that the carboxylic acid function points into the cavity where it is hydrogen bonded to the phenolic oxygen atom of an adjacent ester moiety.<sup>16</sup> Furthermore, steric inhibition to solvation of the carboxylate ion within the cavity immediately surrounded by three ester functions may contribute to low acidity. This effect should be more pronounced with the tri-*tert*-butyl ester on steric grounds as is indeed observed ( $\log K_1 = 10.55$ ). This situation is not encountered in compound III<sub>a</sub> and explains its higher acidity.

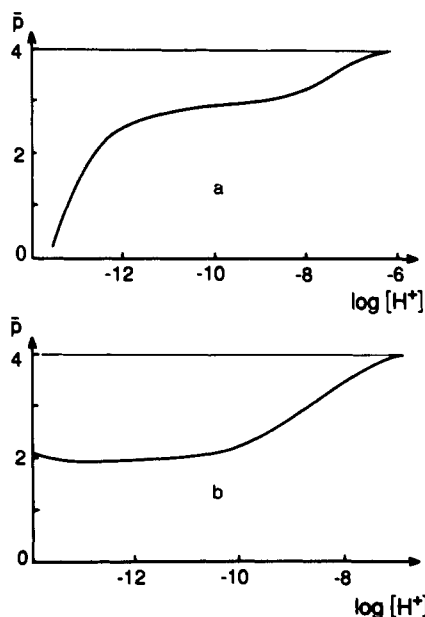
The triphenol monoacid III<sub>a</sub> displays four acidity constants. The lowest,  $\log K_1 = 7.5$ , which is 3 units more acidic than monoacid III<sub>c</sub>, should correspond to the protonation of the carboxylate; the other three, which are much higher (12.1, 13.0 and 13.4), to the acidity of the three phenols.<sup>26</sup> Here the carboxylate can receive stabilization from the surrounding phenolic hydroxyl groups via intramolecular hydrogen bonding as has been shown for salicylic acid.<sup>27</sup> The presence of the cone conformation should facilitate such stabilization. The fact that all the phenolic functions could be ionized is clearly evidenced by the plot of  $\bar{p}$ , the average number of H<sup>+</sup> ions bound per mole of ligand versus  $-\log [H^+]$ :

$$\bar{p} = (C_H - [H^+] + K_{MeOH}/[H^+])/C_L$$

$C_H$  is the total hydrogen concentration including the three phenolic hydrogens (Figure 3a). In this case one can remove up to four protons from LH<sub>4</sub> so that  $4 < \bar{p} < 0$ .

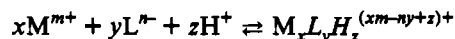
Only two constants have been determined for the diacid diphenol derivative II<sub>a</sub>. They are comparable to  $\log K_4$  and  $\log K_3$  of the dioxa tetraacid within experimental errors. Unlike the monoacid triphenol III<sub>a</sub>, all the phenolic functions of compound II<sub>a</sub> were too weakly acidic to be ionized during the titrations, as indicated by the deprotonation plot (Figure 3b) for which  $4 > \bar{p} > 2$ .

In conclusion, the decreasing acidity sequence of the more acidic functions ( $\log K_n$ ) falls into the following order: monoacid triphenol III<sub>a</sub> > dioxa tetraacid IV ≈ diacid diphenol II<sub>a</sub> > tetraacid I > diacid di-*tert*-butyl ester II<sub>b</sub> > monoacid triethyl ester III<sub>c</sub> > monoacid tri-*tert*-butyl ester III<sub>b</sub>. The fact that all

**Figure 3.** Plots of  $\bar{p}$ , versus  $\log [H^+]$  for compounds III<sub>a</sub> (a) and II<sub>a</sub> (b).

the ligands studied except the monoacid triphenol III<sub>a</sub> are less acidic than phenoxyacetic acid can be interpreted in terms of stabilization of the protonated forms by intramolecular hydrogen bonding. This assumption is confirmed by FTIR measurements in CHCl<sub>3</sub>. For the tetraacid I and the monoacid triethyl ester III<sub>c</sub>, in contrast to the monoacid triphenol III<sub>a</sub>, the frequencies of the carbonyl and OH bands are shifted towards lower wavenumbers in the free ligands as compared to the deprotonated forms and phenoxy acetic acid.

**Complexation Studies.** The logarithms of the overall apparent stability constants  $\beta_{xyz}$  characterizing the following general complexation equilibria



are given in Tables II and III respectively for alkali and alkaline-earth metals and Table IV for ligand IV and both types of cations. As for protonation, the numbers tabulated correspond to the arithmetic means of at least four experiments.

In the case of the monoacid III<sub>c</sub> the complexation has been also studied by UV absorption spectrophotometry, adding the K<sup>+</sup> salt to the neutral methanolic solution of III<sub>c</sub>. Only small spectral changes were noticed upon addition of the increasing amounts of K<sup>+</sup>. But when the ligand solutions were made up in the presence of a slight excess of base ( $C_{Et_4NOH}/C_L \approx 1.2$ ), significant variations of the spectrum were observed. The interpretation of the different spectra by the program Letagrop-Spefo<sup>28</sup> led to a stability constant

(25) Boehmer, V.; Vogt, W.; Harris, S. J.; Leonard, R. G.; Collins, E. M.; Deasy, M.; McKervey, M. A.; Owens, M. J. *Chem. Soc., Perkin Trans. I* 1990, 431–432/

(26) The corresponding monoethylester of triphenol monoacid III<sub>a</sub> displays three constants (11.9, 12.5, 12.6) corresponding to the acidity of the three phenols. This derivative shows no complexation of alkali or alkaline-earth metal cations.

(27) Baker, W. *Nature* 1936, 137, 236. Musso, H. *Chem. Ber.* 1955, 88, 1915.

(28) Sillen, L. G.; Warnqvist, B. *Ark. Kemi* 1968, 31, 377–390.

**Table III.** Logarithms of the overall stability constants of alkaline-earth complexes of the ligands studied, in MeOH at 25 °C, ( $I = 0.01 \text{ M Et}_4\text{NClO}_4$ )

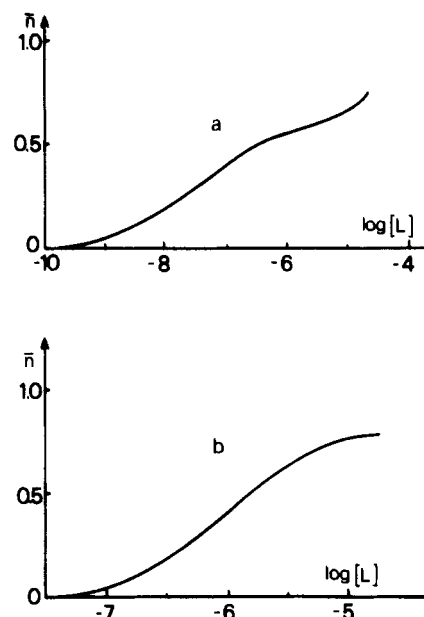
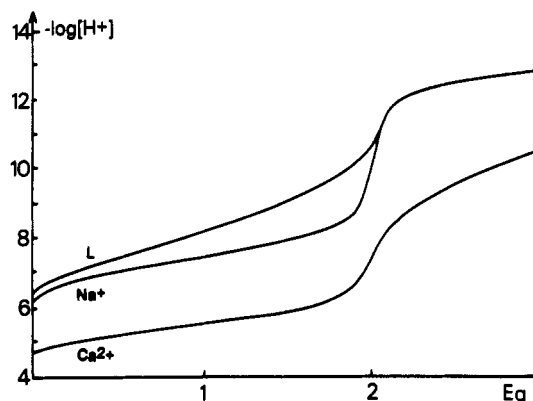
ligands	xyz	$\log \beta_{xyz}$			
		Mg <sup>2+</sup>	Ca <sup>2+</sup>	Sr <sup>2+</sup>	Ba <sup>2+</sup>
I	110	11.02 ± 0.01	22.44 ± 0.01	20.92 ± 0.04	17.96 ± 0.03
	111	21.43 ± 0.01	30.24 ± 0.01	28.69 ± 0.01	26.26 ± 0.03
	112	30.52 ± 0.02	36.39 ± 0.01	34.89 ± 0.01	33.53 ± 0.01
	113	37.96 ± 0.01	40.25 ± 0.02		
II <sub>a</sub>	110	7.3 ± 0.3	9.0 ± 0.2	8.3 ± 0.3	8.3 ± 0.1
	210	11.0 ± 0.3	11.8 ± 0.2	11.2 ± 0.3	11.58 ± 0.02
II <sub>b</sub>	110	5.0 ± 0.2			
	210	9.5 ± 0.2	16.2 ± 0.4	14.72 ± 0.05	13.1 ± 0.4
	111	15.99 ± 0.04	18.6 ± 0.4	17.79 ± 0.02	16.8 ± 0.2
III <sub>a</sub>	110	6.4 ± 0.1	7.9 ± 0.2	6.71 ± 0.08	7.0 ± 0.2
	111	18.4 ± 0.2	20.3 ± 0.3	19.0 ± 0.6	19.6 ± 0.2
	112	30.8 ± 0.3	32.42 ± 0.08	31.34 ± 0.03	31.8 ± 0.1
	113	41.8 ± 0.2	42.3 ± 0.3	41.4 ± 0.3	41.4 ± 0.3
III <sub>b</sub>	110	4.48 ± 0.07	6.25 ± 0.04	5.02 ± 0.06	4.58 ± 0.06
III <sub>c</sub>	110	3.88 ± 0.03	5.85 ± 0.01	4.5 ± 0.1	3.87 ± 0.01

of 4.6 log unit, which is in agreement with the value 4.9 obtained by pH-metry.

**Nature of the Complexes.** The carboxylic calixarenes generally form a number of protonated complexes in addition to the 1:1 complexes ( $x = y = 1$ ). In the case of the tetraacid I, there is formation of the 1:1 complexes and the corresponding mono-, di-, and triprotonated forms ( $z = 1, 2, 3$ ) with the alkalis and alkaline-earth metals except with Sr<sup>2+</sup> and Ba<sup>2+</sup> where MLH<sub>3</sub> was rejected during the refinement. It must also be noticed that with Li<sup>+</sup>, Rb<sup>+</sup>, and Cs<sup>+</sup>, the percentages of formation of these species do not exceed 10% (4, 7, and 10%, respectively).

With alkali metal cations and the mixed ligands diacid diphenol II<sub>a</sub> and diacid di-*tert*-butyl ester II<sub>b</sub>, there is formation of 1:1 complexes and their corresponding protonated species. The fit of the experimental data, estimated mainly on the basis of the values of the residuals on all the mass balance equations and of the reliability factor  $r$ ,<sup>19</sup> is always improved if additional 2:1 species ( $x = 2, y = 1$ ) are also considered. The existence of binuclear complexes could be predicted from the shape of the curve  $\bar{n} = f(\log [L])$ ,  $\bar{n}$  being the average number of mole of ligand bound per mole of metal ion, tending to 0.5 for a metal-to-ligand ratio of 1 (Figure 4a). To our knowledge, it is the first example of the formation of binuclear complexes with calix[4]-arene derivatives.

The behavior of compound II<sub>a</sub>, which includes two phenolic and two carboxylic functions, is different with alkali and alkaline-earth metals, as shown on the titration curves in the presence of Na<sup>+</sup> and Ca<sup>2+</sup> (Figure 5). In the case of Na<sup>+</sup>, the titration curve

**Figure 4.** Formation curves  $\bar{n} = f(\log [L])$  for (a) II<sub>b</sub> and K<sup>+</sup> ( $C_L = C_M = 1.4 \times 10^{-4} \text{ M}$ ) and (b) III<sub>c</sub> and Ca<sup>2+</sup> ( $C_L = C_M = 10^{-3} \text{ M}$ ).**Figure 5.** Titration curves for ligand II<sub>a</sub> ( $C_L = 7.1 \times 10^{-4} \text{ M}$ ), alone and in the presence of Na<sup>+</sup> and Ca<sup>2+</sup> ( $C_L = 7.1 \times 10^{-4} \text{ M}$ ,  $C_{Na} = 8.1 \times 10^{-4} \text{ M}$  and  $C_{Ca} = 8.7 \times 10^{-4} \text{ M}$ , respectively).

with an inflection point at two equivalents of ligand clearly shows that only the two carboxylates participate in the complexation. With Ca<sup>2+</sup> there is also a drop in the pH values after two equivalents of ligand. The buffer region observed from this point may correspond to solvolysis and formation of methoxy species

**Table IV.** Possible Models and Corresponding Overall Stability Constants for the Systems IV/Alkali and IV/Alkaline-Earth Metals

ligand	xyz	$\log \beta_{xyz}$				
		Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
IV	110	5.2 ± 0.2	5.84 ± 0.06	5.95 ± 0.08	5.89 ± 0.04	6.0 ± 0.1
	111	18.17 ± 0.07	18.86 ± 0.02	19.04 ± 0.04	18.95 ± 0.01	19.08 ± 0.06
	112	28.83 ± 0.08	29.34 ± 0.01	29.45 ± 0.03	29.41 ± 0.01	29.77 ± 0.03
R = 2	210	8.75 ± 0.08	9.89 ± 0.05	9.85 ± 0.05	9.55 ± 0.09	9.91 ± 0.05
	211	21.84 ± 0.03	23.00 ± 0.01	22.99 ± 0.03	22.69 ± 0.05	22.99 ± 0.01
	112	28.82 ± 0.01	29.51 ± 0.01	29.60 ± 0.01	29.42 ± 0.01	29.74 ± 0.02

ligand	xyz	$\log \beta_{xyz}$			
		Mg <sup>2+</sup>	Ca <sup>2+</sup>	Sr <sup>2+</sup>	Ba <sup>2+</sup>
IV	111	25.7 ± 0.5	30.41 ± 0.02 <sup>a</sup>	29.90 ± 0.01 <sup>a</sup>	30.01 ± 0.04
	112	33.6 ± 0.2	37.05 ± 0.03 <sup>a</sup>	36.21 ± 0.01 <sup>a</sup>	36.30 ± 0.02
R = 1, 2	113			40.61 ± 0.02 <sup>a</sup>	
R = 1, 2	210	23.0 ± 0.5	26.7 ± 0.2	26.2 ± 0.3	24.61 ± 0.08
	211	30.5 ± 0.2	34.1 ± 0.6	33.28 ± 0.03	33.0 ± 0.7
	112		37.05 ± 0.03	36.20 ± 0.01	36.24 ± 0.01
	112			40.8 ± 0.3	
	113				40.98 ± 0.02

<sup>a</sup> Only when R = 2.

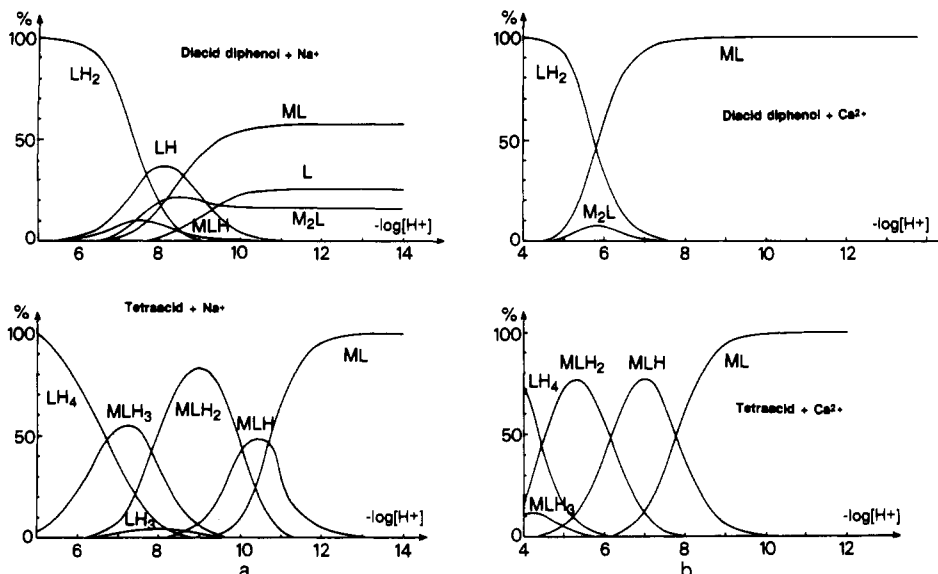


Figure 6. Distribution curves of the complexes versus  $-\log [H^+]$ : (a)  $II_a/Na^+$  and  $I/Na^+$  and (b)  $II_a/Ca^{2+}$  and  $I/Ca^{2+}$ .  $C_L = C_M = 6 \times 10^{-4}$  M.

or to the participation of one or two phenolic functions in the complexation. As the protonation constants of the phenoxy groups could not be determined (see above), and interpretation involving methoxy species not possible, only the first buffer region was considered in the calculations. In this case, both the 1:1 and 2:1 complexes were found. For compound  $II_b$  and alkaline-earths, the best refinements were found by assuming the existence of mainly the 1:1 protonated species ( $x = y = z = 1$ ) and the binuclear complex ( $x = 2, y = 1, z = 0$ ). Only in the case of  $Mg^{2+}$  was the formation of the additional 1:1 complex observed. However it must be stated here that the difficulty in choosing the best model is mainly due to the low concentrations used for this ligand.

As expected, only 1:1 complexes were found with the monoacids  $III_b$  and  $III_c$ . At higher pH values the formation curves  $\bar{n} = f(\log[L])$  show deviation from the theoretical curve which could be ascribed to solvolysis phenomena (Figure 4b). Again, interpretation of the data including methoxy species was not possible.

With regards to triphenol monoacid  $III_a$ , the titration curves showed little or no complexation of the alkalis, and the data could not be satisfactorily interpreted. However, there is complexation of alkaline-earth ions with the formation of ML, MLH,  $MLH_2$  and  $MLH_3$  species, involving partial and total ionization of the three phenolic moieties.

In the case of the dioxa tetraacid IV, the interpretation of the data was subject to the cumulative difficulties inherent in a complex system where several types of species could form and to the low working concentrations. However with alkali metal cations, the best model involved ML, MLH, and  $MLH_2$  species when  $R = 1$  and  $M_2L$ ,  $M_2LH$ , and  $MLH_2$  when  $R = 2$ . The common species  $MLH_2$  has the same stability constant in both models (Table IV). With the alkaline-earth metals it was not possible to decide between the following models, MLH,  $MLH_2$  with or without  $MLH_3$ , or  $M_2L$ ,  $M_2LH$ ,  $MLH_2$ , and  $MLH_3$  which worked equally well. There was no ambiguity about the rejection of the simple 1:1 species, a result which could have been foreseen from the titration curves showing an inflection point at 3 equiv of ligand.

**Stability of the Complexes.** The high values of the stability constants show that *calixarene carboxylic acids are effective complexing agents for alkali and alkaline-earth metal cations*. The divalent alkaline-earth metals are more strongly bound than the monovalent alkali metals. This result is consistent with the electrostatic effect governing the complexation of metal cations with anionic ligands.

The comparison with other known ligands containing several carboxylic functions is not obvious for several reasons: many of

these ligands have very different structures, some of them containing amino acid functions, e.g. the macromonocyclic ligand 1,4,8,11-tetraaza-cyclotetradecane-*N,N',N'',N'''*-tetraacetic acid, TETA,<sup>29</sup> and some are carboxylated crown ethers.<sup>30</sup> Moreover all the data available in the literature were obtained from aqueous solutions. For example, the stability constants in water of the  $Na^+$  complexes with TETA and 18C6A<sub>4</sub> are 1.6 and 4.5, respectively. The stabilities of the corresponding  $Ca^{2+}$  complexes are higher: 4.5 and 8.6 log units, respectively. Notwithstanding the increase of ca. 4.6 log units observed for the protonation constants of some carboxylic acids from water to methanol (see the section above on the protonation constants), it is clear that the calixarene acid I is a much stronger binder than these modified coronands. This difference may be ascribed to the relatively high flexibility of the latter. The tetraacid binds the alkaline-earth metals more strongly than does the bicyclic cryptand 222, which forms the most stable complex with  $Ba^{2+}$  ( $\log \beta_{110} = 12.9$  in MeOH).<sup>31</sup>

All the calixarene acids studied, including the monoacids, are stronger binders for alkali metals than the nonionizable calix-[4]arene tetra-alkyl esters and ketones.<sup>2,6</sup> The tetraacid is also better than tetraamides<sup>4</sup> when consideration is made for appropriate pH-control. With the alkaline-earth metals, the diacids and monoacids have a binding power comparable to that of calixareneamides but the tetraacid again is a much better complexing agent. The binding ability of the monoacid triester derivatives  $III_b$  and  $III_c$  is high ( $\log K = 6.25$  and 5.85, respectively, for  $Ca^{2+}$ ) and this result is remarkable as we know from previous studies that calixarene esters do not complex alkaline-earth metals.<sup>4</sup> This complexation is thus entirely due to the electrostatic interaction between one carboxylate and the  $Ca^{2+}$  ion.

**Speciation.** Some of the results are illustrated on the speciation plots for compounds  $II_a$  and I, each with 1 equiv of  $Na^+$  and  $Ca^{2+}$ , respectively (Figure 6a,b). In the case of the diacid diphenol  $II_a$  with  $Na^+$ , the formation of both the neutral species MLH and  $M_2L$  does not exceed 10% and 20%, respectively, of the total ligand with formation of ML at a maximum of 60% from pH 10. With  $Ca^{2+}$ , the neutral ML species is always predominant and is totally formed at pH 8.

In the case of the tetraacid I, it is clearly visible that  $Ca^{2+}$  is complexed at lower pH values than  $Na^+$ . The protonated species are formed until rather high pH values, and among them the

(29) Delgado, R.; Frauto da Silva, J. J. R. *Talanta* 1982, 29, 815-822.

(30) Dutton, P. J.; Fyles, T. M.; McDermid, S. J. *Can. J. Chem.* 1988, 66, 1097-1107.

(31) Arnaud-Neu, F.; Yahya, R.; Schwing-Weill, M. J. *J. Chim. Phys.* 1986, 83, 403-408.

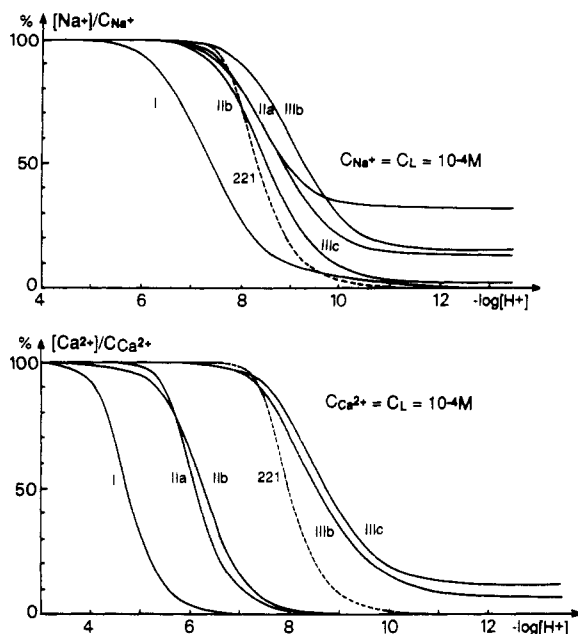


Figure 7. Calculated percentages of free cation as a function of  $-\log[H^+]$  for the ligands studied and 221.<sup>31</sup>

least charged and neutral species are predominant. ML is formed totally at pH 13 and 10 for  $\text{Na}^+$  and  $\text{Ca}^{2+}$ , respectively.

The plots in Figure 7, giving the calculated percentage of free  $\text{Na}^+$  and  $\text{Ca}^{2+}$  versus pH, provide another way of comparing the complexing power of all the ligands, independently of the type of complexes formed. At high pH values, corresponding to the formation of the ML species, the free metal ion concentrations reflect the order of the stability of the complexes:  $\text{I} > \text{II}_b > \text{III}_c > \text{III}_b > \text{II}_a$  and  $\text{I} > \text{II}_a > \text{II}_b > \text{III}_b > \text{III}_c$  for  $\text{Na}^+$  and  $\text{Ca}^{2+}$ , respectively. This last order is consistent with the increasing electrostatic effect on going from a mono- to a di- to a tetraacid. The deviations observed with  $\text{Na}^+$ —and for alkali metal complexes in general—are an indication that this effect is not predominant in this case. It can be also seen that the tetraacid complexes  $\text{Na}^+$  and especially  $\text{Ca}^{2+}$  in relatively acidic solution (from  $\text{pH} > 6$  and  $\text{pH} > 4$  respectively) while 221 requires a more basic medium.

**Complexation Selectivities.** The results are visualized in Figure 8, which represent the variation of  $\log \beta_{110}$  versus the atomic radii of alkali and alkaline-earth metal cations, respectively. Some particular selectivities for one cation ( $M^+$ ) relative to another ( $M'^+$ ), expressed by the ratio  $S_{M/M'} = \beta_{110}(ML)/\beta_{110}(M'L)$  are given in Table V.

**For the alkali metals** the selectivity patterns are rather flat. The tetraacid I and the monoacid triesters  $\text{III}_b$  and  $\text{III}_c$  are the only derivatives showing the  $\text{Na}^+/\text{K}^+$  selectivity normally encountered with tetramers. But even with the tetraacid it is low ( $S_{\text{Na}/\text{K}} = 7.8$ ) when compared to the tetraethyl ester ( $S_{\text{Na}/\text{K}} = 400$ ) and the tetrapyrrolidiny amide IX ( $S_{\text{Na}/\text{K}} = 57$ ). With carboxylic derivatives, the complexation of  $\text{K}^+$  is always favored over  $\text{Na}^+$ , so the selectivity observed, although low, is the result of a predominant size effect, inherent to calix[4]arene derivatives. The electrostatic effect is more commonly observed with anionic ligands.

The diacid di-*tert*-butyl ester forms the most stable complexes with  $\text{Na}^+$  and  $\text{K}^+$  but is unable to discriminate between these cations as is the parent tetra-*tert*-butyl ester.<sup>6</sup> The diacid diphenol displays a slight selectivity for the larger  $\text{Rb}^+$ . Although these ligands have a cone conformation (see above), they seem to be

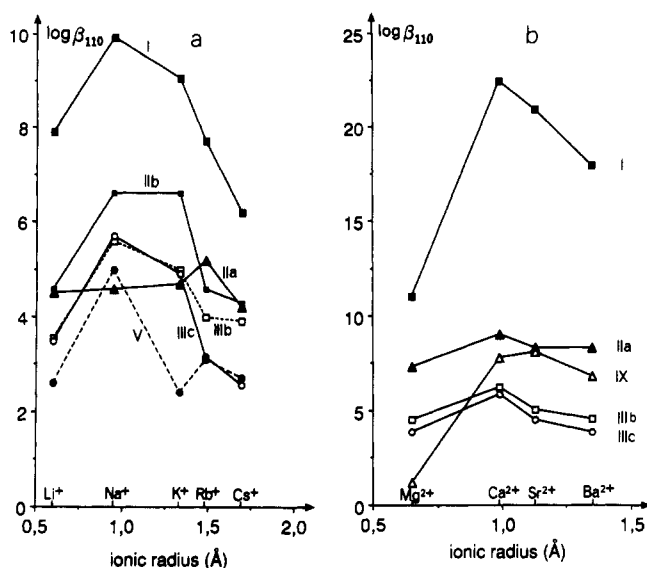


Figure 8. Variation of  $\log \beta_{110}$  with the ionic radius of (a) alkali and (b) alkaline-earth metal cations.

Table V. Selected Selectivities of Complexation with the Ligands Studied:  $S(M/M') = \beta_{110}(ML)/\beta_{110}(M'L)$

ligands	$S(\text{Na}/\text{K})$	$S(\text{Ca}/\text{Mg})$	$S(\text{Ca}/\text{Sr})$	$S(\text{Sr}/\text{Na})$
I	7.8	$2.7 \times 10^{11}$	33	$9.5 \pm 10^{10}$
II <sub>a</sub>	0.8	50	5	5012
II <sub>b</sub>	1			
III <sub>b</sub>	4	59	17	0.3
III <sub>c</sub>	6.3	93	22.4	0.06
IV	1.2			
V	400			
IX	57	$4 \times 10^6$	0.5	8

less effective in holding specifically a cation within the cavity. A consequence is the formation of binuclear complexes.

With the dioxo tetraacid IV, regardless of the model retained, there is a slight plateau selectivity for the larger cations with a poor discriminating power from  $\text{Na}^+$  to  $\text{Cs}^+$ . Such selectivity profiles have already been observed with two dioxo tetraesters and were explained by the 1, 2 alternate conformation of these receptors and consequently their larger cavities.<sup>5,7</sup>

**For the alkaline-earth metals** Figure 8b shows that in all cases the ligands are selective for  $\text{Ca}^{2+}$ ; the diacid diphenol, which was not selective for  $\text{Na}^+$ , and the dioxo tetraacid form the most stable complexes with  $\text{Ca}^{2+}$ . Our results confirm previous studies by Ungaro et al.<sup>14,15</sup> on the extraction and transport properties of ligands  $\text{II}_a$  and I toward alkaline-earth metals, which showed maximum efficiency with  $\text{Ca}^{2+}$ .

The  $\text{Ca}^{2+}/\text{Mg}^{2+}$  selectivity displayed by I is remarkably high with  $S = 2.7 \times 10^{11}$ , much higher than for TETA, which, in anionic form, displays a very high  $\text{Ca}^{2+}/\text{Mg}^{2+}$  selectivity in water ( $S = 2 \times 10^6$ )<sup>29</sup> and the *p-tert*-butylcalix[4]arene tetrapyrrolidinyamide IX ( $S = 10^7$  in MeOH).<sup>4</sup> It seems that in the  $\text{Ca}^{2+}$ /tetraacid I complex, which is the most stable and selectively formed, there is a cooperative effect between the preorganization of the ligand and the charge effect.

The monoacid triesters behave quite in parallel, with  $\text{Ca}^{2+}/\text{Mg}^{2+}$  and  $\text{Ca}^{2+}/\text{Sr}^{2+}$  selectivities of the same order of magnitude. An interesting  $\text{Sr}^{2+}/\text{Na}^{2+}$  selectivity is displayed by the tetraacid ( $S_{\text{Sr}/\text{Na}} = 9.5 \times 10^{10}$ ) and the diacid diphenol  $\text{II}_a$  ( $S_{\text{Sr}/\text{Na}} = 5012$ ).

**Acknowledgment.** We thank the Ciba-Geigy Trust Foundation for a ACE award.