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Dramatic Effects of *p*-Dealkylation on the Binding Abilities of *p-tert*-butylcalix[6]arenes: New Cs^+ and Sr^{2+} Selective Receptors

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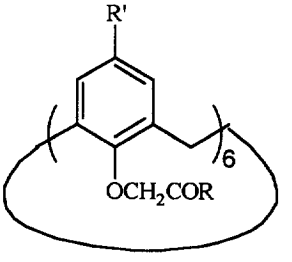
Abstract : Removal of the *p-tert*-butyl substituent from *p-tert*-butylcalix[6]arene hexadiethylamide **3** produces cation receptor **4** with enhanced extraction and complexation selectivities for Cs^+ and Sr^{2+}.

It is now well established that the cation binding selectivity of chemically modified calix[n]arenes (n = 4 - 8) depends on various factors such as the degree of condensation (n), the conformation, and the nature of the functional groups attached to the phenolic oxygen atoms.[1] Surprisingly, very little work has been done on the influence of substituents at the upper rim. In a recent study, we found that the removal of the *tert*-butyl groups of the *p-tert*-butylcalix[6]arene ester **1** (to give *p*-Hcalix[6]arene ester **2**), results in an amazing increase in the extraction (from water into CH_2Cl_2) and complexation (in methanol) Cs^+/Na^+ selectivities,[2] the values of which are among the highest ever found for a neutral ligand. In order to investigate this interesting result in more detail, we have now : i) extended the extraction studies of **2** towards all alkali and alkaline-earth cations; ii) synthesised the new *p*-Hcalix[6]arene hexadiethylamide **4**; iii) assessed the binding abilities of **4** and of the known *p-tert*-butylcalix[6]amide **3**[3] toward alkalis and alkaline-earths; iv) compared the performances of ester **1** and amide **3** with those of their respective "de-alkylated" counterparts **2** and **4**.

Hexamer amide **4** was prepared from the known hexamer ester **2**[4] via hydrolysis with sodium hydroxide to hexaacid **5**. Treatment of **5** with thionyl chloride furnished acid chloride **6** which, on exposure to diethylamine in tetrahydrofuran, produced **4**.



1. R = OEt, R' = Bu^t
2. R = OEt, R' = H
3. R = NEt_2, R' = Bu^t
4. R = NEt_2, R' = H
5. R = OH, R' = H
6. R = Cl, R' = H

Percentage extraction (%E) of alkali picrates from water into dichloromethane, measured according to Pedersen's procedure,[5] are reported in Table 1. Ester derivatives **1** and **2** show more or less the same trend, the values of %E increasing with the ionic radius. The higher Cs^+/Na^+ selectivity shown by the "de-alkylated" ligand **2** is the result of a significant increase in the extraction level for Cs^+. Removal of the *p-tert*-butyl groups has a more dramatic effect on the extraction abilities of the amide derivatives. "Alkylated" ligand **3** extracts all the alkali cations more or less to the same extent and appears to be completely unselective within the alkali series. Going from ligand **3** to the "de-alkylated" ligand **4**, a drop of the extraction levels is observed for all cations but Cs^+, for which, on the contrary, a remarkable increase is found. This ligand is therefore able to discriminate in extraction among alkali cations with a marked preference for Cs^+.

Table 1. Percentage extraction (%E)[a] of Alkali and Alkaline Earth Picrates from Water into Dichloromethane at 20°C ($C_{picrate} = C_{calixarene} = 2.5.10^{-4}M$).

Ligands	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
1	0.9	2.7	17.6	16.4	33.0	c	c	c	c
2	0.5	0.8[b]	3.1	16.6	46.4[b]	c	c	c	c
3	23.4	27.0	23.6	22.4	26.4	8.7	84.2	83.8	85.5
4	5.2	4.8	7.5	17.2	45.4	2.6	25.7	45.0	58.0

a) standard deviation on the mean of several experiments : $\sigma_{n-1} < 1$; b) ref.2, c) not detected

A similar trend is observed when comparing stability constant (log β) values found for the two amides **3** and **4** in methanol (Table 2). The low solubility of ligand **3** in methanol and the weak spectral changes observed on complexation prevented an assessment of the stoichiometry of the complexes involved. Thus two sets of data are given for the assumption of mononuclear ML and dinuclear M_2L complexes. Casnati *et al.*[3] have found that **3** forms dinuclear complexes with either K^+ or Na^+ in $CHCl_3$ whilst it forms mononuclear complexes in NPOE (o-nitrophenyl-octylether). These contrasting results have been explained by the higher permittivity ε of NPOE and the resulting higher dissociation of ion pairs in this solvent, which make unlikely a complex presenting two charges in close proximity without any screening from the counter anions. In view of the high ε value of methanol, one might think that the complexes formed in this solvent should be mononuclear, but it is clear that this argument is too weak to remove the uncertainty from our data.

Table 2. Stability Constants (log β)[a] of Alkali Complexes of Calix[6]arenes in Methanol at 25°C, I = 0.01M (Et_4NCl)

Ligands	Li^+	Na^+	K^+	Rb^+	Cs^+
2[b]		≤1.5			≥6
3 c	2.6±0.1	2.8±0.1	3.3±0.1	2.6±0.1	2.8±0.1
d	5.1±0.1	5.9±0.1	6.9±0.1	6.0±0.2	6.0±0.1
4	≤1.5	≤ 1.5	2.1±0.1	2.8±0.2	4.1±0.1

a) standard deviation σ_{n-1} on the mean of at least two experiments; b) ref. 2; c) mononuclear and d) dinuclear assumptions

However, whatever the assumption taken into account, the "alkylated" ligand **3** does not show any selectivity of complexation within the alkali series. It is thus unable to discriminate among alkali cations both in complexation and extraction. Fortunately, there was no ambiguity in analysis of the spectrophotometric data for the "de-alkylated" ligand **4**, which clearly pointed to the formation of 1:1 complexes. Log β values increase in the series with the ionic radius and reach a maximum of 4.1 for Cs^+. Ligand **4** is therefore, within the alkali series, a selective extracting and complexing agent for this cation. A comparative analysis of complexation data for the ester derivatives in methanol was not possible, because of the insolubility of **1** in this solvent.

It must be clear, at this point, that what we would like to emphasize is not the selectivity shown by ligand **4**, which is *per se* not specially interesting,[6] but the fact that it has been achieved simply by removal of the *tert*-butyl groups from the upper rim. However, a very interesting selectivity emerged when the effect of the removal of *p-tert*-butyl groups was examined for the binding of alkaline-earth cations. As already observed for other calixarene amides,[5] ligand **3** shows high %E for Ca^{2+}, Sr^{2+} and Ba^{2+}, although it does not extract Mg^{2+} to a significant extent (Table 1). Dealkylation does lead to an overall decrease of the extraction levels in the series, but since the decrease is less pronounced for Sr^{2+} than for Na^+, it results in a Sr^{2+}/Na^+ extraction selectivity $S = \%E(Sr^{2+})/\%E(Na^+) = 10$ for "de-alkylated" ligand **4**, which is three times higher than for the "alkylated" analogue **3**. For comparison, we found that under our conditions S = 9 for dicyclohexyl-18C6, a ligand which is often considered to be one of the best Sr^{2+} selective extractants. This result is very interesting since the selective extraction of Sr^{2+} over Na^+ is a very important goal for the decontamination of nuclear waste.[7]

On the other hand, both esters **1** and **2** do not extract alkaline earths to any significant extent, a fact that confirms the low affinity of calixarene esters towards these cations. The stability of the Ca^{2+}, Sr^{2+} and Ba^{2+} complexes with **3** and **4** was too high to allow direct spectrophotometric determination. An attempt to use the potentiometric method[8] failed because of the poor solubility of ligand **3** and the low stability constant of the silver complex with **4** ($\log \beta = 3.6$). Therefore, only a lower limit ($\log \beta \geq 6$), can be given for Ca^{2+}, Sr^{2+} and Ba^{2+} complexes of ligands **3** and **4** in methanol. Nevertheless, these results show that the "de-alkylated" compound **4** has an exceptional Sr^{2+}/Na^+ complexation selectivity. With lower and upper limits of 6 and 1.5 log units, this selectivity can be estimated to be higher than 3.2×10^4. It is, to the best of our knowledge, the highest value ever recorded for a neutral macrocycle in methanol. For instance, values of 1.8×10^3 to 3.0×10^4 can be found for diazatetraoxa[18]ane in methanol and 5.2×10^3 for cryptand 222.[9,10] It should be pointed out, however, that complexation with these aza ligands is pH dependent, a property which could severely limit their potential applications in acidic media. The same selectivity has been reported to be S = 17 for dicyclohexyl-18C6,[11] a value 1.8×10^3 lower than for compound **4**. There does not appear to be a simple explanation for the results obtained so far. In view of the small difference between the Hammett coefficients σ_p for H and *tert*-butyl, electronic effects should not play an important role.

The ^1H NMR spectrum of ligand **4** at room temperature is quite simple with well defined signals for all the protons. No appreciable changes are seen on the spectra recorded at 50°C, while a broadening of all the signals is observed at -50°C. This result indicates that amide **4** is undergoing rapid conformational interconversion and that, even at -50°C, it is not "frozen" into well defined conformation(s). In contrast, Casnati *et al.*[3] have reported that the "alkylated" analogue **3** has a complex ^1H NMR spectrum in $CDCl_3$ at

25°C, and that signals become sharper and more clearly defined at -25°C. As pointed out by the authors, these results indicate that, at -25°C, the ligand is "frozen", on the NMR scale time, into a mixture of conformers. Since a similar situation has been observed for the ester derivatives **1** and **2**,[12] the "de-alkylated" ligands **2** and **4** appear to be, not surprisingly, conformationally more mobile than their "alkylated" counterparts. However, whether this conformational freedom is responsible for the different behaviour observed is, at the moment, hard to say. We are now making calorimetric measurements and plan to extend our studies to other solvents (DMF, Acetonitrile, THF). The results arising from these studies will allow us to assess the relative significance of the enthalpic and entropic contributions to the difference (if any) in complexation behaviours of the two ester derivatives **1** and **2**, and might lead to a better understanding of the results obtained so far.

In conclusion, our preliminary studies have shown that : i) the removal of *tert*-butyl from the *para* position does have a significant effect on the binding abilities of calix[6]arene esters and amides; ii) the "de-alkylated" amide **4** shows, to the best of our knowledge, the highest Sr^{2+}/Na^{+} selectivity ever found for a neutral ligand in methanol.

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