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MODULATION OF THE CATION COMPLEXING PROPERTIES IN THE 'LOWER RIM' CHEMICALLY MODIFIED CALIXARENE SERIES

M. J. SCHWING-WEILL, F. ARNAUD-NEU

Laboratoire de Chimie-Physique, URA 405 au CNRS, EHICS, 1 rue Blaise Pascal, 67000 Strasbourg, France

AND

M. A. McKERVEY

School of Chemistry, The Queen's University, Belfast, BT7 4AG, Northern Ireland, UK

The effect of chemical modifications on the lower rim of calix[*n*]arenes is analysed with respect to the cation binding ability of the receptor. Extraction data and stability constants of the complexes are discussed. Three main factors are investigated: the size of the calixarene, the conformation of the calixarene and the nature of the ligating group attached to the phenolic oxygen. The work concentrates on esters, ketones, amides, thioamides and carboxylic acids. Some data concern chemically modified tetrahomodioxacalix[4]arene esters.

INTRODUCTION

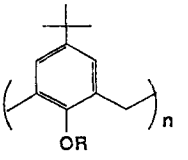
A great number of calixarenes chemically modified on the lower rim by substitution of the phenolic hydrogen have been synthesized (see Figure 1) and their cation complexation abilities have been studied by several groups.[1–4]

In this review commentary, we present an analysis of the different factors which have an influence on the cation binding ability of chemically modified calixarenes synthesized by our group, in which the ligating groups contain carbonyl or thiocarbonyl functions. This is important in order to know how to modify a calixarene to make it efficient for a given purpose, mainly selective extraction or transport and design of selective electrodes.

Three main factors have been investigated: the size of the calixarene, the conformation of the calixarene and the nature of the ligating groups attached to the phenolic oxygen. Our work has concentrated on esters, ketones, amides, thioamides and carboxylic acids (Figure 1). Some work has also been done on the dioxacalixarene series (Figure 1).

Three experimental techniques were used to assess the complexing properties: determination of stability

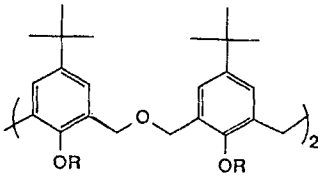
Symmetrical calixarenes



$R = CH_2CO_2R'$: esters
$R = CH_2COR'$: ketones
$R = CH_2CONR'_2$: amides
$R = CH_2CSNR'_2$: thioamides
$R = CH_2CO_2H$: acids

n = 4, 5, 6, 7, 8

Oxacalixarenes



$R = -CH_2COOR'$

$R' = -Et, -(CH_2)OCH_3$

Figure 1. The different chemically modified calixarenes studied

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constants in a homogeneous medium by UV spectrophotometry and/or potentiometry, biphasic picrate extraction experiments from water into dichloromethane and transport experiments from one aqueous solution to another aqueous solution through a thick liquid dichloromethane membrane. Only the stability constants really reflect the true binding ability of the receptors. The extraction results are dependent on additional factors such as the lipophilicity of the constituents of the extraction system, whereas the transport results are dependent on the extraction and the kinetic properties of the system.

Although many of the data presented here have already been published,[1,2,5-9] our intention is to analyse the features of a range of chemical modifications in relation to selective cation binding. We also present new information on pentamer and heptamer ethyl esters, on a tetraacetic acid, on a new dioxacalix-[4]arene and on thioamides.

In the following, β will designate the stability constants of complexes, expressed as concentration ratios $[ML^{m+}]/[M^{m+}][L]$, where M^{m+} = cation and L = calixarene. K_e will designate the thermodynamic extraction constant for the extraction of metallic picrates by a calixarene from an aqueous neutral solution into a dichloromethane organic phase. K_e is equal to the concentration ratio $[\overline{MLA_m}]/[M^{m+}][A^-]^m[\overline{L}]$, where $[A^-]$ is the co-extracted picrate anion; the overlined brackets refer to concentrations in the organic phase. The extraction data can also be expressed as the percentage cation extracted, $\%E = [\overline{MLA_m}]/[\overline{MLA_m}] + [M^{m+}]$.

INFLUENCE OF THE CALIXARENE SIZE IN THE SYMMETRICAL ESTER SERIES

In our first publications on the ester and ketone series,[2,5,6] we presented extraction data for alkali metal picrates from basic aqueous medium into a dichloromethane phase. We have repeated these studies using a neutral aqueous medium in order to avoid extraction saturation and thereby provide a potentially broader range of extraction extent. The new data for *tert*-butylcalix[*n*]arene ethyl esters are given as percentage of cation extracted in Table 1 and are represented as log K_e vs the cation ionic radii in Figure 2.

It is obvious that the size of the calixarene in the series $n = 4$, 5, 6, 7 and 8 has a very significant effect on both the levels of extraction and the cation selectivity. Three effects can be expected with an increase in the degree of condensation: (i) formation of stronger complexes, due to the increase in the number of ligating sites, (ii) an increase in the size of the hydrophilic cavity of the receptor and (iii) conformational changes.

A first observation concerns the tetra- and the pentaethyl esters, which are both in the same cone conformation.[5,11] Nevertheless, Figure 2 shows a great difference in their complexing behaviour towards alkali metal cations: all cations are better extracted by the pentamer, according to effects (i) and (ii), but the extraction profile is different in both cases. The tetramer gives rise to a very sharp peak selectivity in favour of Na^+, whereas the pentamer leads to a

Table 1. Percentage cation extraction from an aqueous neutral alkali metal picrate solution into dichloromethane by *p-tert*-butylcalix[*n*]arene ethyl esters of various degrees of condensation *n*

Degree of condensation	Li^+	Na^+	K^+	Rb^+	Cs^+
$n = 4$[a]	7	29	5	4	6
$n = 5$[b]	8	33	46	51	51
$n = 6$[a]	0·9	2·7	18	16	33
$n = 7$[a]	1·3	1·9	2·7	1·8	1·7
$n = 8$[a]	0	1·0	1·3	1·1	0·8

[a] Ref. 8.
[b] Ref. 11.

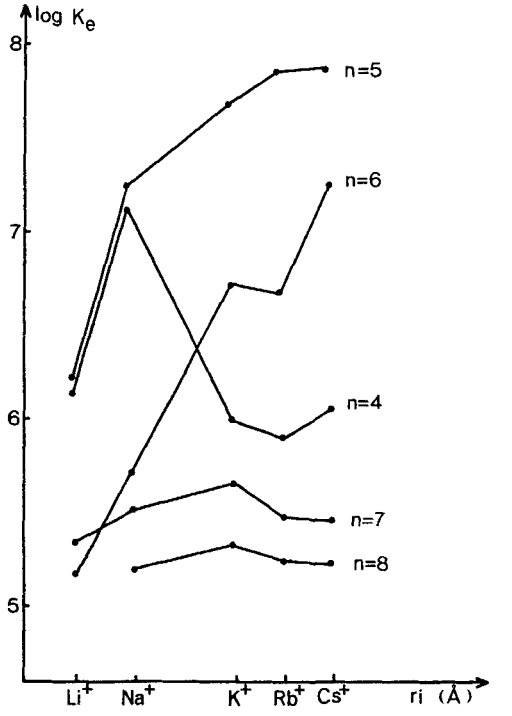

Figure 2. Logarithms of the extraction equilibrium constants K_e for the extraction of alkali metal picrates by *p-tert*-butylcalix[*n*]arene ethyl esters from a neutral aqueous solution (metal concentration = $2·5 \times 10^{-4}$ M) into a dichloromethane solution (ligand concentration = $2·5 \times 10^{-4}$ M) at 20 °C[10,11]

'plateau-like selectivity' for the larger cations, with a lower discrimination between them. This difference can certainly be attributed to factor (ii), i.e. to the more or less good fit between the sizes of the cations and the cavities.

A second observation concerns the larger calixarenes, which have a much weaker extraction power, decreasing from $n = 6$ to 7 and 8. This is in contradiction with factor (i) but results from factors (ii) and (iii). These larger oligomers do not display any sharp selectivity as does the smaller tetramer. The hexamer has a high extraction power for K^+, Rb^+ and Cs^+, intermediate between those of the tetramer and the pentamer. Cs^+ is the alkali metal cation best extracted by the hexamer, in agreement with the structural data, which suggest a better size fit for the larger cations, whereas the heptamer and octamer, which are very weak extractants, do not discriminate much between the five cations, but still exhibit a very slight preference for K^+.

A further example of the influence of the size of the cavity and the conformation may be illustrated by the comparison between the tetraethyl ester and the dioxacalix[4]arene tetraethyl ester.[5,7] In the latter, the aromatic residues adopt the 1,2 alternate conformation (Figure 3), leading to a larger cavity.

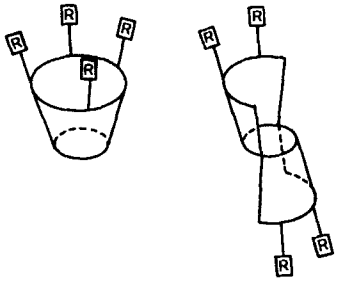

Figure 3. Cone and 1,2 alternate conformations of calix[4]arenes

Table 2. Picrate extraction from water into dichloromethane and stability constants in methanol for the *p-tert*-butyltetrahomodioxacalix[4]arene tetraethylmethoxy ester with alkali metal cations

Parameter	Li^+	Na^+	K^+	Rb^+	Cs^+
Log β	2·2	2·7	4·1	4·0	3.9
%E	2	3	15	15	14

In fact, the dioxatetraethyl ester is conformationally more similar to a hexamer than to a tetramer. We have already reported the stability constants of this dioxa compound, not in methanol where it is insoluble, but in acetonitrile, as well as the %E;[7] it is obvious that it is no longer selective for Na^+, and behaves more like a calix[6]arene ethyl ester in that it prefers the larger cations. The same behaviour is found for another dioxacalix[4]arene tetraester, the tetraethylmethoxy ester, in methanol 10 (Table 2).

INFLUENCE OF THE NATURE OF THE SUBSTITUENT R′ ON THE ESTER GROUP IN THE SYMMETRICAL ESTER SERIES

We have shown previously[1,2] that the calix[4]arene tetramethyl ketone extracts and complexes the alkali metal cations slightly better than the calix[4]arene tetraethyl ester, with, for both, a sharp peak selectivity in favour of Na^+. This behaviour is in agreement with the structural data, which show a better preorganization in the case of the oxygen donor sites in the ketone and greater basicity of the tetraketone donor oxygens. However, another calix[4]arene tetraketone, bearing the bulkier *tert*-butyl substituents, displays a broader peak selectivity, including Na^+ and K^+, and this has been interpreted by an enhancement of the cavity size due to the bulky substituents.[1] This result suggested that the residue on the function attached to the calixarene may also play a role in the complexation selectivity, depending on its electronic and/or steric properties. We therefore studied a number of calix[4]arene tetraesters, all possessing the cone conformation in solution but with different substituents R′ in the CO_2R' group: R′ = methyl, ethyl, *n*-butyl, *tert*-butyl, benzyl, phenyl, phenacyl, methoxyethyl, trifluoroethyl, methylthioethyl and propargyl. The conclusions of the complexation studies in methanol are in the main confirmed by the extraction studies.[9] The Na^+/K^+ selectivity of the receptors, S_{Na}, is expressed as the ratio of the stability constants $\beta(Na^+)/\beta(K^+)$. A substantial substituent effect was observed: in the simple alkyl series, the methyl group decreases S_{Na} (160) with respect to the value for the ethyl group, taken as the reference substituent ($S_{Na} = 400$) and the *n*-butyl group has the reverse effect, leading to $S_{Na} = 800$. The *tert*-butyl group, on the other hand, has the same effect of diminishing S_{Na} (down to 5), as already pointed out for the ketone series. Substituents bearing heteroatoms or multiple bonds induce a large change in selectivity, ranging from 2500 for the phenacyl to 25 for the trifluoroethyl ester. The exceptionally high discriminating power of the phenacyl derivative can be interpreted in terms of a greater rigidity of the molecule, which prevents a good match with K^+.

INFLUENCE OF THE NATURE OF THE FUNCTION ATTACHED TO THE PHENOLIC OXYGEN

In the alkali metal series

Figure 4 shows the log β values in methanol for four types of substituted calix[4]arenes, all known to exist in the cone conformation. It is clear that the stability of the 1 : 1 alkali metal complexes increases in the order tetraethyl ester < tetramethyl ketone < tetradiethyl amide < tetraacetate* (except for Cs^+).

Although the ketonic member of the series is the methyl ketone, not an ethyl ketone, we anticipate that the difference between two such similar structures would be very small. The ester, amide and ketone are all looser binders than the cryptand 221, but the tetraacid derivative is a better complexing agent than 221. In all cases, there is a peak selectivity in favour of Na^+. S_{Na} increases in the reverse order of the stability, from the acid to the amide, ketone and ester derivatives. In this solvent, all calixarenes are more selective than the cryptand 221, which in methanol loses the exceptional selectivity for Na^+ observed in other media.[13] The calix[4]arenes are more selective than the crowns 15C5 and B15C5 and also than the natural antibiotic monensin.[14]

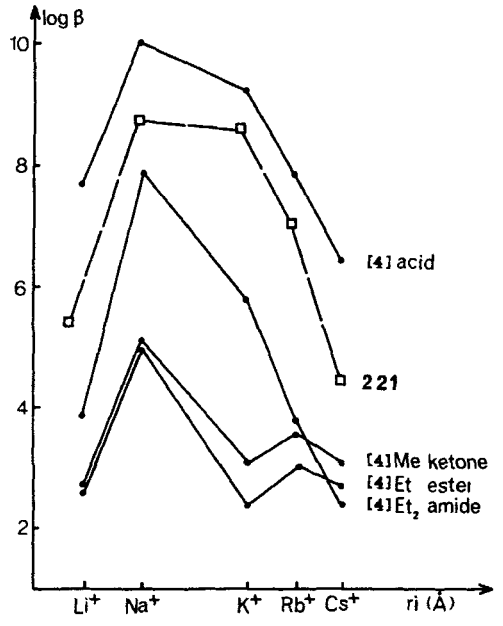

Figure 4. Influence of the nature of the ligating functions attached to the phenolic oxygens of calix[4]arenes on the stability constants β of the 1 : 1 alkali metal complexes in methanol at 25 °C (from Refs 1, 8 and 12). Values for the cryptand 221 are taken from Ref. 13

In the alkaline earth metal series

Whereas esters and ketones do not complex significantly alkaline earth metal ions in methanol, the amide and the tetracarboxylate are excellent complexing agents of these cations, as can be seen from Figure 5.*

The tetraacid displays a very sharp peak selectivity for Ca^{2+}, a cation with about the same ionic radius as Na^+. The tetrapyrrolidinyl amide displays a broader peak selectivity for both Ca^{2+} and Sr^{2+} which, in fact, do not have very different ionic radii (0·99 and 1·13 Å, respectively[15]). A huge Ca^{2+}/Mg^{2+} selectivity is exhibited by these ligands: 10^6 for the amide and 10^{12} for

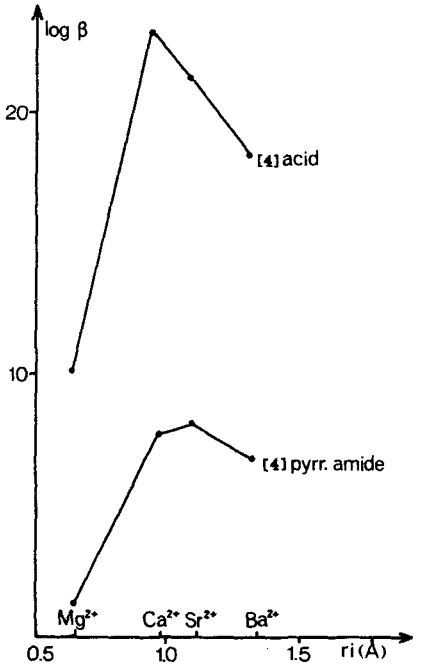

Figure 5. Logarithms of the stability constants of the 1 : 1 complexes of alkaline earths metals with the calix[4]arene *N,N*-diethylamide and the calix[4]arene tetraacetate at 25 °C (from Refs 8 and 12)

* The stability constants of the complexes of the calix[4]arene tetraacetic acid LH_4 are those of the 1 : 1 ML complexes. The four pK_a values of the tetraacid in methanol at 25 °C are $pK_1 = 8·2$, $pK_2 = 9·2$, $pK_3 = 10·9$ and $pK_4 = 13·4$. In addition to the fully deprotonated complex ML, protonated complexes are also formed. For instance, with Na^+, the log β values for the complexation reactions of the protonated forms of the ligand according to $M^{m+} + LH_i^{(n-i)-} \rightleftharpoons MLH_i^{(m-n+i)-}$ are 7·2 for $i = 1$, 6·4 for $i = 2$ and 5·0 for $i = 3$.

the acid. These values are, to our knowledge, the highest ever reported for neutral or ionizable ligands.

Other cations

A great variety of cations have been screened for extraction by thioamides.[16] Results for two tetramers and two hexamers in extraction are shown in Table 3 together with, in parentheses, the data for the corresponding amides.[8,16]

It can be seen that the thioamides hardly extract the alkali metal, alkaline earth metal and lanthanide cations, contrary to the corresponding amides. Whereas Co^{2+} and Cd^{2+} are almost unextracted (except by the hexapyrrolidinyl thioamide in the case of Cd^{2+}), Cu^{2+}, Pb^{2+} and Ag^{+} are well extracted by the four thioamides. The extent of extraction compared with that of the corresponding amides can be inferior (Pb^{2+} and Ag^{+} with the tetradiethyl thioamide), nearly equal (Cu^{2+} with the tetradiethyl thioamide, Pb^{2+} with the tetrapyrrolidinyl thioamide and Ag^{+} with the tetra- and hexapyrrolidinyl thioamides) or superior (Cu^{2+} with the tetrapyrrolidinyl thioamide and Ag^{+} with the hexadiethyl thioamide). This switch from a preference for alkali and alkaline earth metal cations to heavy metals is consistent with the change from a hard oxygen-based binding group to a softer sulphur-based binder, and demonstrates the very wide range of complexing ability that can be achieved with simple chemical modification of the calixarenes.

Table 3. Extraction data for thioamides and, in parentheses, for the corresponding amides[8,16]

	Thioamide			
Cation	Tetradiethyl	Tetrapyrrolidinyl	Hexadiethyl	Hexapyrrolidinyl
Na^{+}	7 (95)	4 (91)	5 (27)	5 (49)
K^{+}	8 (74)	6 (58)	7 (23)	5 (52)
Mg^{2+}	3 (9)	3 (88)	3 (9)	— (20)
Ba^{2+}	3 (74)	2 (67)	7 (86)	3 (94)
Co^{2+}	4	4	3	3
Cu^{2+}	19 (14)	47 (20)	15	42
Pb^{2+}	56 (97)	96 (94)	32	46
Cd^{2+}	8 (97)	9 (81)	8	58
Ag^{+}	80 (99)	98 (97)	95 (81)	94 (97)
Pr^{3+}	2 (14)	3 (11)	2	—

INFLUENCE OF MIXED FUNCTIONALITIES

Combining various functional groups on the same calixarene substructure represents yet another way to modify the complexation selectivities. In previous work,[1,12] S_{Na} in methanol was reported for the mixed

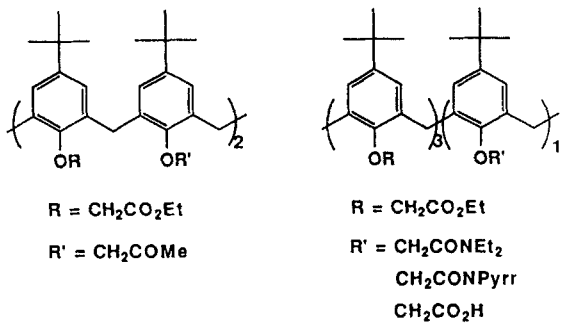

Figure 6. The calixarenes with mixed functionalities[1,12]

2 : 2 and 3 : 1 calix[4]arenes represented in Figure 6. We have shown that the replacement of two ester groups by two ketones in the tetraethyl ester reduces S_{Na} in methanol from 400 to 250, a result which could have been predicted as ketones are less selective than esters. Changing one ester group by a carboxylic acid enhances the complexation level from 5 to 6 log units for sodium and from 2·4 to 4·9 log units for potassium, but S_{Na} is drastically decreased from 400 to 13. This also could be expected as the tetracarboxylic derivative is a stronger binder than the tetraester, but displays a poorer selectivity. The introduction of a tertiary amide among three ethyl ester groups also leads to a decreased selectivity, as expected from the different complexation behaviours of the tetraethyl ester and the tetradiethyl amide (S_{Na} 130 and 400, respectively).

CONCLUSION

This paper has illustrated that one can modulate the complexing properties of a 'lower rim' substituted calixarene by varying the following main factors: (1) the size match between the metallic cation and the ligand hydrophilic cavity, which mainly depends on the degree of condensation and on the conformation; (2) the arrangement of the binding sites and the degree of preorganization of the receptor; and (3) the chemical nature of the binding sites. Another paper in this issue, together with V. Böhmer and W. Vogt, further illustrates the fact that even minor changes in the conformation of the chemically modified calixarene can be associated with drastic changes in the complexation properties.

ACKNOWLEDGEMENTS

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