

Cation binding properties of alkyl calixaryl derivatives. A new family of molecular receptors

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Abstract - Stability constants of the complexes of alkali cations, Ag^+ and Tl^+ , with tetrameric and hexameric calixarenes functionalized on the phenolic oxygens by ester or ketonic groups are reported, in methanol and/or acetonitrile. Four tetramers were investigated (ethylacetate, methylketone, t-butylketone and phenylketone) and one hexamer (ethylacetate). Their complexation power is comparable with that of DB18C6, but weaker than those of cryptands 221 and 222. The remarkable complexation selectivities are discussed in terms of the structural features of the free receptors and related to the phase-transfer properties. The ionophoric properties are consistent with the magnitude of the stability constants and the complexation selectivities.

INTRODUCTION

Calixarenes are macrocyclic phenol-formaldehyde condensation oligomers (ref. 1). Their name, introduced by Gutsche in 1978, originates from the recognition, in molecular models, of the chalice-like appearance of the tetrameric smallest members of the series (Fig. 1).

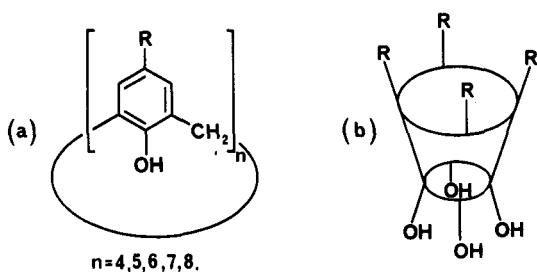


Fig. 1. Parent Calixarenes.
a) General formula of calix[n]arenes.
b) Schematic chalice-like structure of calix[4]arenes.

The continuous search for new synthetic molecular receptors capable of host-guest relationships with ions and neutral molecules has led to many novel structures during the past decades: after the emergence of valinomycin and monensin from natural sources came a succession of synthetic ionophores: cryptands, crown-ethers, podands, spherands and hemispherands, all possessing to varying degrees the ability to sequester and transport alkali metal cations. As will be shown, functionalized calixarenes may prove to be another milestone in receptor chemistry.

Although the parent calixarenes are receptors for small neutral molecules, they display little or no ionophoric activity towards alkali metal cations when the aqueous source phase is neutral. However Izatt and coworkers found that if the source phase is basic enough to allow deprotonation of the phenolic groups, the alkali metal cations can be transported as

neutral complexes through a haloform liquid membrane, with an original selectivity pattern $\text{Cs}^+ > \text{Rb}^+ > \text{K}^+ > \text{Na}^+ > \text{Li}^+$ (ref. 2, 3). No correlation could ever be established between the transport properties and the cation binding ability of the parent calixarenes because of the great insolubility of the latter in all usual dissociating solvents, preventing any stability constants measurement.

Bearing in mind that many natural ionophores possess ethereal and ester carbonyl oxygens as primary donor sites in a macrocyclic array, McKervey and his coworkers recently attached alkylacetate or ketonic carbonyl groups to the phenolic oxygens of the parent calixarenes in order to increase their ionophoric properties (ref. 4-6). The same idea was simultaneously developed, concerning ester groups, by Chang and Cho (ref. 7) as well as by Ungaro and coworkers (ref. 8, 9), but no stability constant of the complexes has ever been determined.

McKervey's preliminary extraction and transport experiments with alkali cations have brought evidence that these new functionalized calixarenes display very efficient and selective phase transfer and ionophoric properties, which may be related to the structures of the receptors (ref. 4-6).

Our goal in the present study has been to situate these new receptors with respect to the widely studied crowns and cryptands, by measuring the stability constants of their complexes with the alkali cations and with "softer" monovalent cations such as Ag^+ and Tl^+ , and to correlate the complexation thermodynamic parameters to the structural, phase transfer and transport properties of the calixarenes.

The compounds studied, represented in Fig. 2, are: the tetrameric and hexameric p-t-butyl calixaryl ethylacetates 1 and 5 (ref. 4), the p-t-butyl calixaryl methylketone 2 (ref. 5), the p-t-butyl calixaryl t-butylketone 3 (ref. 10), and the p-t-butyl calixaryl phenylketone 4.

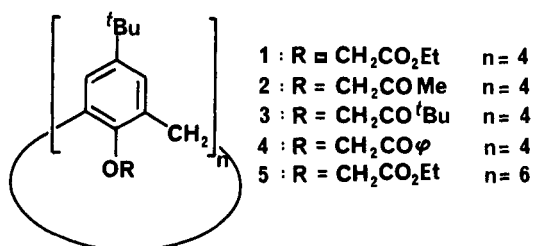


Fig. 2.
Functionalized calixarenes
studied in this work

METHOD AND RESULTS

The stability constants in water of the compounds shown in Fig. 2 could not be determined because of their still too low solubility in this solvent. However, tetramers 1, 2 and 3 are soluble enough in the similar protic solvent MeOH which, moreover, is a reference solvent for further discussion of the ionophoric properties. The hexamer 5 as well as the tetramers 1, 2 and 4 are soluble in acetonitrile AN, a solvent in which it has been possible to compare the binding abilities of the tetramers and hexamer. Both solvents were considered as totally dissociating.

The stepwise addition of an alkali cation, silver or thallium, to a calixarene solution leads to a substantial change of absorbance in the range 250-300 nm, sometimes accompanied by a small hypsochromic shift of the shortest wavelength band, leading to an isobestic point which indicates the presence of at least two absorbing species (Fig. 3). Therefore, the stability constants of the complexes were determined by UV absorption spectrophotometry, coupled to a multiwavelength treatment of the data which provides the stability constants of the complexes as well as their calculated individual electronic spectra (ref. 11).

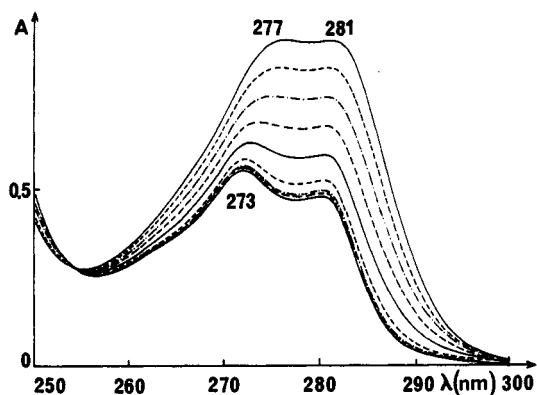


Fig. 3. Change in absorbance A of a $2.5 \cdot 10^{-4} \text{M}$ solution of the tetraketone 2 in AN upon stepwise addition of a 10^{-2}M solution of LiClO_4 in AN ($0 < C_{\text{Li}} < 5 \cdot 10^{-4} \text{M}$). Ionic strength : 0.01M in Et_4NClO_4

All experimental data were consistent with the assumption of the formation of 1:1 complexes, in agreement with the previous X ray (ref. 12) and NMR (ref. 9) studies of similar calixarenes.

The sequence of decreasing intensities of the electronic spectra of the complexes varies with the ligand and with the solvent.

The results are summarized in Table 1, together with some additional data concerning the complexation by dibenzo-18-crown-6 (DB18C6) and by cryptands 221 and 222, respectively the best adapted to Na^+ and K^+ complexation.

TABLE 1. Logarithms of the stability constants β of the metallic complexes of functionalized calixarenes ^{a)} and some other synthetic ionophores. $T = 25^\circ\text{C}$. Ionic strength $\mu = 10^{-2} \text{M}$ (Et_4NCl in MeOH and Et_4NClO_4 in AN). ^{a)} Arithmetic mean of at least two experiments. Standard deviation on the mean : $\sigma_{n-1} = 0.2 \text{ log units}$; ^{b)} ref. 13; ^{c)} ref. 14; ^{d)} ref. 15; ^{e)} ref. 16.

Solvent	Cation	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	221 ^b	222 ^b	DB18C6 ^d
MeOH	Li^+	2.6	2.7	1.8			5.4	2.6	
	Na^+	5.7	5.6	4.3			8.6	7.9	4.4
	K^+	1.9	3.1	5.0			8.5	10.4	5.0
	Rb^+	3.1	3.6	1.6			6.7	8.9	4.2
	Cs^+	2.7	3.1	<1			4.3	4.4	3.5
	Ag^+	4.0	5.8				14.6	12.2	4.0
	Tl^+	1.6	2.4					10.0 ^c	3.9
AN	Li^+	6.4	5.8		6.3	3.7	10.3	6.9	
	Na^+	5.8	5.6		6.1	3.5	>11.3	10.6 ^c	4.8
	K^+	4.5	4.4		5.1	5.1	9.5	10.5 ^c	4.8
	Rb^+	1.9	1.7		4.5	4.8		9.5	3.7 ^e
	Cs^+	2.8	3.7		5.6	4.3		4.5	3.5 ^e
	Ag^+	2.5	2.4			4.2	11.2	8.9	

DISCUSSION

The apparent formation constants β (concentration ratios) of the 1:1 complexes of the calixarenes with alkali cations range between roughly 2 and 6 log units, with a clear maximum, within the alkali series, for Na^+ with the tetramers 1 and 2 in MeOH and for K^+ with the hexamer 5. In AN, the tetramer 4 also complexes Na^+ better than the larger alkali cations : the case of Li^+ will be discussed further. The tetramer 3 complexes K^+ slightly better than

Na^+ . The β values are of the same order of magnitude as with DB18C6, but generally lower than with cryptands. For instance, in MeOH, $\beta(\text{Na}-\underline{1}^+)$ and $\beta(\text{Na}-\underline{2}^+)$ are respectively 3 and 5 log units lower than $\beta(\text{Na}221^+)$ and $\beta(\text{K}222^+)$.

The Na^+/K^+ complexation selectivities in MeOH, calculated as the ratios $\beta(\text{Na}^+)/\beta(\text{K}^+)$, are higher for 1 and 2 (respectively 6300 and 300) than for the cryptand 221, known as the (2)-cryptand best adapted for Na^+ complexation (1.2 according to the data of Table 1). The extent of the selectivity, however, is solvent dependent as for cryptands (ref. 13) : in AN, 221 is more selective (>63) than 1 (20), 2 (16) and 4 (10). The K^+/Na^+ complexation selectivity of 5 in AN, calculated as the ratio $\beta(\text{K}^+)/\beta(\text{Na}^+)$, amounts to 40, and is superior to the value 2.5 which may be calculated for the cryptand 222 from the means of all literature data (respectively 10.4 and 10.8 for $\beta(\text{Na}^+)$ and $\beta(\text{K}^+)$).

In MeOH, Tl^+ forms weaker complexes than any alkali cation, whereas Ag^+ is as strongly complexed as Na^+ by 2 but not by 1.

Stability and structure

The selectivity for Na^+ of the tetramers 1 and 2 is in good agreement with the predictions that could be foreseen from the molecular structures of the free receptors, showing that both tetramers are in a cone conformation in the solid state (ref. 4, 5) as well as in solution (from NMR studies, ref. 24). The substituent groups, mutually *syn*, create a hydrophilic cavity as an extension of the lipophilic calix defined by the aromatic nuclei and the *t*-butyl groups. In this conformation, they may act cooperatively in the binding of metal ions, and favour a high degree of complexation. The high selectivity for Na^+ can be accounted for by the hydrophilic cavity dimensions, defined by the cyclic array of the four phenolic oxygen atoms, mutually separated by 3.10-3.28 Å in 1 and by 3.03-3.26 Å in 2. These dimensions may allow inclusion of a smaller or a larger cation by the more or less flexible side arms, but the contraction or expansion of the receptors cavity will lead to an energetic expense and to a subsequent destabilization of the corresponding complexes. In contrast with previous compounds, the hexameric acetate 5 does not have the cone conformation. It is centrosymmetric and the adjacent O...O intramolecular contacts are much longer (4.04 and 4.70 Å) than in the tetramers, suggesting a better binding ability of the larger cations (ref. 5). The flexible structure of the hexaester leads to a "plateau selectivity" after K^+ , as observed with the larger cryptands 322, and 332.

For all cations studied, the complexes of the tetramethylketone 2 are stronger in MeOH than those of the tetraethylester 1, in agreement again with the structural data which evidence a better preorganization of the ketonic substituent groups, favourable to a stronger complexation power, and also to the more basic character of the ketonic oxygen atoms in MeOH.

No structure of the compounds 3 and 4 is available yet. The fact that the *t*-butylketone 3 does not discriminate clearly between Na^+ and K^+ could be related to an enlargement of the hydrophilic cavity due to the bulky *t*-butyl groups on the substituents. The receptor still keeps a high discrimination ability between these two cations and the smaller Li^+ or larger Rb^+ and Cs^+ ions.

Stability and extraction

The calixaryl acetates and ketones are neutral in basic solution and extract the alkali cations into a non polar phase as ion-pairs. It is well known that the extraction equilibrium constant K_e is proportional to the stability constant $\beta(\text{H}_2\text{O})$ of the 1:1 complex in water and to extractability characteristics of the system. Whether the K_e sequence within a series of homologous cations is governed by one or the other of the two factors depends upon the system under investigation, as demonstrated earlier for the extraction of alkali cations by 18-crown-6 (18C6) and by 15-crown-5 (15C5) (ref. 17).

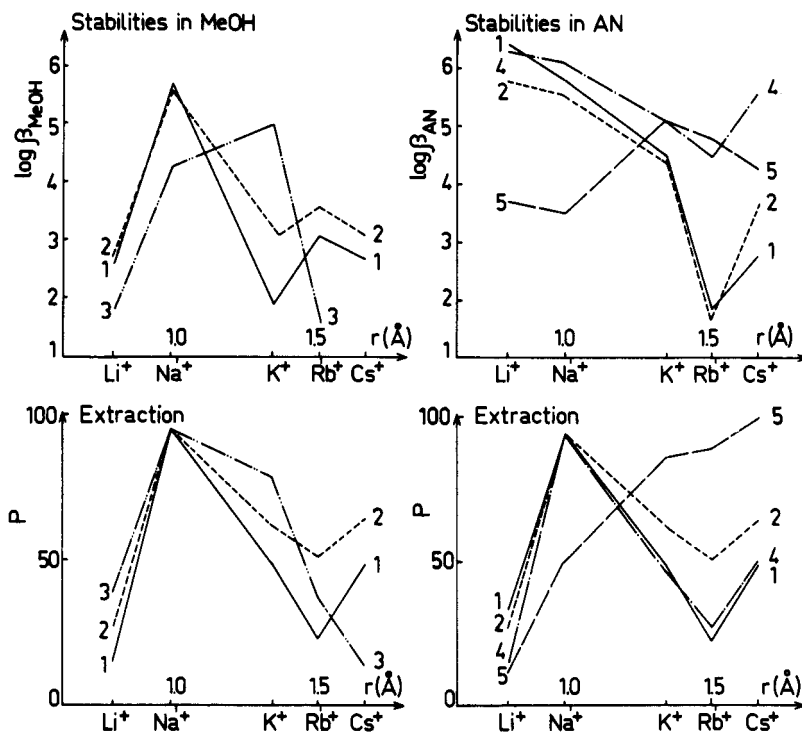


Fig. 4. Comparison of thermodynamic and extraction data : $\log \beta$ and P vs. the cations ionic radii. (Extraction data for compounds 3 and 4 from ref. 18).

McKervey and coworkers have measured the percentage P of cation extracted from an aqueous alkaline picrate solution into a dichloromethane medium (ref. 4, 5, 18). Provided some reasonable assumptions, P may be correlated to K_e when the total concentrations of cation (C_M) and ligand (C_L) are equal. In these conditions, K_e is a monotonous increasing function of P , and it is legitimate to correlate P and $\beta(H_2O)$ in order to check whether the extraction data reflect the sequence of the thermodynamic affinities of the receptors for the cations. In the present work, $\beta(H_2O)$ was inaccessible, but various previous studies have shown that the stability constants of macrocyclic complexes in MeOH are about 2-4 log units higher than in H_2O , without significant changes in complexation selectivities (ref. 19, 20, 13). A correlation between P and $\beta(MeOH)$ therefore also appears to be legitimate.

Figure 4 shows $\log \beta$ and P vs. the alkali cations ionic radii, in methanol and in acetonitrile, and evidences a satisfactory agreement between the extraction and the stability data.

In methanol, the extraction and stability curves of compounds 1 and 2 exhibit the same profiles, with nevertheless one exception : Rb^+ is less extracted than K^+ or Cs^+ but better complexed. 1 and 2 have the same behaviour towards Na^+ , in complexation and in extraction, but for the other alkali cations, the tetraketone is a better complexing and extracting agent than the tetraester, in agreement with the more basic character of the ketonic carbonyl groups. For the *t*-butylketone 3, the extraction and stability profiles show a large peak selectivity for Na^+ and K^+ with, anyhow, a slight difference, as Na^+ is favoured in extraction and K^+ in stability.

The comparison between extraction and stability data is more delicate in the case of acetonitrile, as this solvent is very different from water. A first striking fact observed in AN is the high stability constants of the Li^+ complexes, which do not correspond to high

extraction coefficients P . The increase in stability with respect to the data in MeOH is higher for Li^+ than for the other cations; a similar behaviour is displayed by cryptands (see Table 1) : it may be accounted for, at least partly, by the very large transfer activity coefficients from MeOH to AN of the Li^+ cation (4.5 log units for Li^+ , and between -1 and 1 for the other alkali cations (ref. 21)); consequently, the high stability constants of the Li^+ complexes in AN mainly reflect solvent effects, not encountered in extraction from an aqueous medium. A second striking fact is the different behaviour, both in stability and in extraction, displayed by the hexaester 5, in comparison with the tetramers 1, 2 and 4. With 5, K^+ , Rb^+ and Cs^+ are better complexed and extracted than Na^+ : the rather increasing "plateau", from K^+ to Cs^+ , found in extraction, is replaced in stability by a rather decreasing one. The smaller Li^+ and Na^+ cations are better extracted and complexed by the tetramers 1, 2 and 4 than by the hexamer 5. The three tetramers have the same extraction and stability profiles, but whereas the tetramethylketone 2 extracts better K^+ , Rb^+ and Cs^+ than the tetraphenylketone 4, which behaves very much the same as the tetraethylester 1, the stability constants of the tetraphenylketone 4 are higher than those of 1 and 2 and even higher, in the case of Cs^+ , than that of the hexaester 5.

Stability and transport

Whereas the extraction process only depends upon thermodynamic factors, the ionic transport through a liquid non polar membrane is mostly regulated by the kinetic properties of the system, such as the rates of complex formation, of complex diffusion through the membrane and of release of the cation at the outer liquid-liquid interface. However, Kirch and Lehn (ref. 22) have shown empirically that the efficiency of the transport is maximum when the stability constant in methanol has an optimum value ranging between 5 and 6 log units. Moreover, for this optimum value, the transport and complexation selectivities are identical (ref. 23). Table 1 shows that $\beta(\text{MeOH})$ for the Na^+ complexes of 1 and 2 range between 5 and 6 log units. As far as thermodynamics is concerned the preceding considerations bring an explanation to the good ionophoric properties and transport selectivities reported by Seward (ref. 24), who evidenced a better transport of Na^+ over K^+ and Cs^+ by these two tetramers through a dichloromethane membrane.

CONCLUSION

For the first time, it has been possible to determine the stability constants of the complexes of alkali cations, Ag^+ and Tl^+ , with tetrameric and hexameric calixarenes functionalized by ester or ketonic groups on the phenolic oxygens. It is shown that the complexation power of the compounds studied is comparable with that of DB18C6, but weaker than those of cryptands 221 and 222. The sharp complexation peak selectivity for Na^+ displayed by most tetramers, as well as the plateau selectivity displayed by the hexameric compound for the alkali cations larger than K^+ are in agreement with the structural and phase transfer properties of the free receptors, and evidence the major role of the adequacy between the hydrophilic cavity and the cation sizes. The extent of the Na^+/K^+ selectivity is solvent dependent, as for cryptands : in methanol, the tetramers are more selective for Na^+ than the cryptand 221, but not in acetonitrile. The K^+/Na^+ selectivity of the hexameric compound in acetonitrile is comparable with that of 222 in this solvent.

The excellent ionophoric properties of the compounds are consistent with the magnitude of the stability constants and with the complexation selectivities.

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