Thermodynamic and electrochemical aspects of the interactions of functionalised calix(4)arenes and metal cations in 'allosteric media'

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Abstract To gain an understanding of the various factors which are likely to contribute to the overall extraction of metal cations by alkyl p–tert–butylcalix(4)arene esters, different approaches are considered. Thus, ligand–solvent interactions are detected from transfer enthalpies of calixarene esters in the appropriate solvents obtained calorimetrically. Conductance measurements are used to determine stability constants of metal cations and these ligands and ion-pair formations for the single and complexed electrolytes with the anion in the non–aqueous medium. Thermodynamic data (free energies, enthalpies and entropies) of complexation involving calixarene esters are for the first time derived from titration microcalorimetry and some representative data are reported. The extraction of metal cations from aqueous solutions by water insoluble calixarene esters is discussed.

INTRODUCTION

The different nature of the two cavities found in p–substituted calix(4)arene derivatives

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(refs. 1–3) such as the esters 1 confers interesting properties to these macrocycles. Thus, the hydrophilic cavity created by suitable functionalisation of the phenolic hydrogens in the lower rim shows selective properties towards metal cations while the hydrophobic cavity situated between the benzene rings is able to interact with organic species. In solution processes, the ligand may interact with the solvent (reaction medium) (refs. 4–6). Interactions of this kind were found to have interesting implications on the binding properties of the hydrophilic cavity towards metal cations. Therefore, our final goal is to make use of the 'allosteric control' exerted by the reaction medium to design new methodology for the selective extraction of cations from water to these media. To gain an understanding on the various factors which are likely to contribute to the overall extraction, different approaches are considered and these are discussed below.
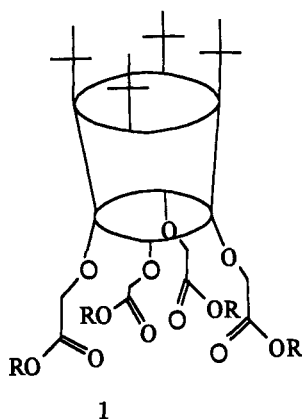
LIGAND–SOLVENT INTERACTIONS

Ligand–solvent interactions are often best reflected in the enthalpies, $\Delta_t H^\circ$ and entropies, $\Delta_t S^\circ$, of transfer of the macrocycle between two solvents. Interpretation solely based on Gibbs energy data, $\Delta_t G^\circ$, can be misleading. A representative example of this statement is found in the $\Delta_t G^\circ$ values for cryptand 222 (6.5 kJ mol⁻) (ref. 7) and that for β–cyclodextrin (4.26 kJ mol⁻¹) (ref. 8) from water to N,Ndimethylformamide at 298.15K.

These values are very similar. However, for the former ligand, the $\Delta_t G°$ value is the result of large and positive values for the transfer enthalpy ($\Delta_t H° = 59.29$ kJmol^{-1}) and entropy ($\Delta_t S° = 177.0$ JK^{-1}mol^{-1}) (ref. 7), while corresponding data for the latter ligand ($\Delta_t H° = -50.04$ kJmol^{-1}); $\Delta_t S° = -153.6$ JK^{-1}mol^{-1}) (ref. 8) are large and negative for transfers from water to N,Ndimethylformamide. On these bases, to detect interactions between alkyl p-$tert$-butylcalix(4)arene ethanoates and solvents, transfer enthalpies are derived from solution enthalpies, $\Delta_s H°$ in different solvents. Table 1 lists $\Delta_s H°$ and derived $\Delta_t H°$ values for the transfer of calix(4)arene esters in the acetonitrile (AN)–benzonitrile (BN) solvent system.The results show that these ligands are enthalpically more stable in benzonitrile than in acetonitrile and suggest that the interaction of calix(4)arene esters is stronger with the former solvent relative to the latter.

Table 1.   Solution enthalpies (kJ mol^{-1}) of alkyl p-$tert$-butylcalix(4)arene tetraethanoate in acetonitrile and in benzonitrile. Derived enthalpies of transfer from acetonitrile at 298.15K

Calix(4)arene esters[a]	$\Delta_s H°$/kJ mol^{-1}		$\Delta_t H°$/kJ mol^{-1}
	⌐AN————————BN⌐		
Me Calix(4)	25.03±0.33	17.51±0.20	−7.52
Et Calix(4)	22.67±0.17[b]	14.03±0.10	−8.64
n–Bu Calix(4)	20.80±3.20	12.20±0.08	−8.60

[a]Me Calix(4), Et Calix(4) and n–Bu Calix(4) denote methyl, ethyl and n–butyl p-$tert$-butylcalix(4)arene tetraethanoate; respectively.   [b]Ref (5).
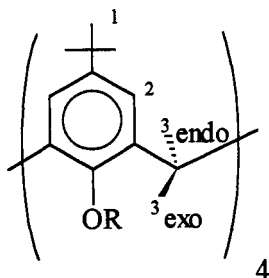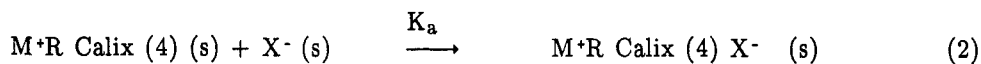

^{1}H NMR spectra show downfield shifts in the H–1 ($\Delta\delta = 0.12$ ppm) and the endo H–3 ($\Delta\delta = 0.23$–0.26 ppm) signals on going from CDCl$_3$ to benzonitrile suggesting that they are affected by the paramagnetic shielding of the aromatic ring of the solvent. This might be taken in favour of the latter interacting with the calixarene cavity. In going from methyl to n-butyl calix(4)arene esters, the endo H–3 show even larger shielding effects ($\Delta\delta = 0.26$–0.28 ppm) relative to those of the exo–protons which seems to be consistent with the above interpretation. Further details on ^{1}H NMR and ^{13}C NMR studies carried out for these systems will be reported shortly.

STABILITY (log K$_s$); ION-PAIR FORMATION (Ka) CONSTANTS AND MOLAR CONDUCTANCES AT INFINITE DILUTION, $\Lambda°$, AT 298.15 K

Stability constants for a number of calix(n)arene derivatives including the esters and metal cations in methanol and in acetonitrile at 298.15K have been reported by Arnaud et. al. (refs.9&10). In methanol, the data have been checked by direct and competitive potentiometry. Although the authors found good agreement between the two methods, log K$_s$ values obtained by the potentiometric method have not been reported. The limitations of the spectrophotometric method for relatively low (log K$_s$ < 2) or relatively high (log K$_s$ > 5) stability constants have been discussed previously (ref. 11). Limitations in the determination of stability constants by titration calorimetry are also found (log K$_s$ < 2 and log K$_s$ > 6 to 6.5). Quite clearly, stability constant measurements are by no means a trivial process; particularly for systems which are characterised by high stability. Therefore, it is necessary to explore other methods. We have chosen the conductimetric method since highly accurate conductimetric

measurements allows the determination of data for the following processes (ref. 12).

$$R \ Calix \ (4) \ (s) \ + \ M^+ \ (s) \quad \xrightarrow{K_s} \quad M^+R \ Calix \ (4) \quad (s) \quad (1)$$

$$M^+R \ Calix \ (4) \ (s) \ + \ X^- \ (s) \quad \xrightarrow{K_a} \quad M^+R \ Calix \ (4) \ X^- \quad (s) \quad (2)$$

$$M^+ \ (s) \ + \ X^- \ (s) \quad \xrightarrow{K_a'} \quad M^+X^- \quad (s) \quad (3)$$

where K_s (eqn 1) is the stability constant of the complex between the metal cation (M^+) and the ligand RCalix(4) in the non–aqueous medium and K_a (eqn. 2) and K_a' (eqn. 3) are the ion–pair formation constants between the complexed and free cation with the anion. Already in a solvent like acetonitrile (ionising medium) some ion–pair formation of electrolytes can be detected as assessed by the K_a' (eqn. 3) values of alkali–metal perchlorates reported in the literature (ref. 13). In a lower dielectric medium than acetonitrile, ion–pair formation is expected to be higher and if so, knowledge of the ion–pair formation constants for processes (2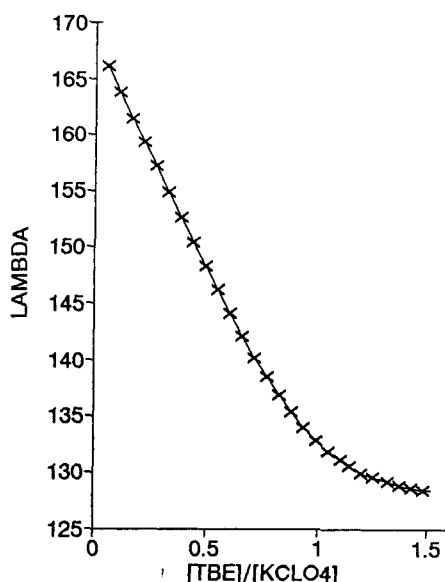) and (3) is required. Undoubtedly, these data must be considered in the derivation of thermodynamic parameters of complexation processes involving macrocyclic ligands and metal cations in order to ensure that the data obtained are referred to a single process (complexation) rather than to an overall process involving side reactions taking place simultaneously. A further advantage of the conductimetric technique is that molar conductances, Λ° at infinite dilution can be derived. These data and K_a values for process (2) are particularly interesting to study the behaviour of the new electrolytes formed by metal calixarenates $(M^+R \ Calix)$ and anions in solution. A typical conductimetric titration curve for $KClO_4$ with n–butyl p–tert–butylcalix(4)arene tetra–ethanoate, n–BuCalix(4); in acetonitrile at 298.15K is shown in Fig. 1. This figure unambiguously demonstrates that a 1:1 complex is formed in solution. Λ°, K_a and log K_s values derived from the conductimetric data shown in the figure are listed in Table 2. For comparison purposes data for $KClO_4$ in acetonitrile at 298.15K are included. For analysis, the Λ° value for the complexed electrolyte is resolved into individual ionic contributions taken the λ° for the perchlorate anion, in acetonitrile reported in the literature (ref.13).

Fig. 1. Conductimetric titration curve for KClO₄ and n–BuCalix(4) in acetonitrile at 298.15 K

Table 2. Limiting electrolyte and ionic conductances, ion–pair formation and stability constants for the $KClO_4$ + n–BuCalix(4) system in acetonitrile at 298.15K.

Λ°/S cm²mol⁻¹	$KClO_4$	187.41±0.01[b]	[K⁺n–BuCalix(4)]ClO₄⁻	133.19±0.04
λ°/S cm²mol⁻¹ [a]	K⁺	83.79	[K⁺n–BuCalix(4)]	29.57
K_a/mol⁻¹ dm³	$KClO_4$	32.80[b]	[K⁺n–BuCalix(4)]ClO₄⁻	0
log K_s	–		K⁺ + n–BuCalix(4)	4.38

[a] Calculated from Λ° values and λ° (ClO₄⁻) = 103.62 S cm² mol⁻¹ in AN at 298.15K (ref. 13). [b] (Ref. 13).

A definite size effect is observed in moving from K^+ to the complexed cation which results in a considerable drop of the ionic conductivity for the latter relative to the former cation. This finding is in line with differences observed in the λ°_+ values for relatively small (Na, K^+, etc) and relatively large (Ph_4As^+) cations. It is of interest to point out that the slight ion–pair formation observed for $KClO_4$ (as reflected in its K_a value) does not take place when the electrolyte contains the complexed cation, which is fully dissociated in this solvent. As far as the stability constant (log K_s) is concerned, the value obtained for K^+ and the calix(4)arene ester in acetonitrile agrees well with the value obtained by us calorimetrically (log K_s = 4.38±0.01) and with the reported value derived from UV spectrophotometric measurements (ref. 9). Generally speaking for systems whose stability constants are lower than 5 and higher than 2, good agreement is found among the data obtained by conductimetry, calorimetry and spectrophotometry. For systems of higher (log K_s > 5) and lower (log K_s < 2) stability constants such agreement is not generally found and these systems are being discussed separately.

Data for $NaClO_4$ and ethyl p–tert–butylcalix(4)arene tetraethanoate, Et Calix(4) in benzonitrile at 298.15 K are listed in table 3.

Table 3.   Limiting electrolyte conductance, ion–pair formation and stability constant for the $NaClO_4$ and Et Calix(4) in benzonitrile at 298.15 K.

Λ°/S cm^2 mol^{-1}	$NaClO_4$	49.28±0.06	$[Na^+EtCalix(4)]ClO_4^-$	42.18±0.01
K_a/mol^{-1}dm^3	$NaClO_4$	207.2±5.4	$[Na^+EtCalix(4)]ClO_4^-$	229.2±0.6
log K_s			Na^+ + EtCalix(4)	6.16

Since the Λ° value obtained for $NaClO_4$ in benzonitrile has not been reported, a comparison cannot be established. However, the data in table 3 is well within the range of Λ° values observed for other electrolytes in this solvent (ref. 14). Again a definitive size effect is found in the Λ° values in moving from $NaClO_4$ to the new electrolyte containing the sodium cation complexed with the calixarene ester. However, the most striking feature of the data shown in table 3 are the ion–pair formation constants for the single and complexed cation with the anion. The data show that the sodium complex in benzonitrile appears to undergo association with the perchlorate anion slightly higher to that of $NaClO_4$. This could be an indication that, in benzonitrile, the sodium cation in the complex may be situated at a site where it still has access to interact with the perchlorate anion. This is also observed in the thermodynamic data (entropies of complexation) of metal cations and the methyl calix(4)arene ester discussed below.

THERMODYNAMIC DATA FOR THE COMPLEXATION PROCESS DERIVED FROM TITRATION MICROCALORIMETRY

The advantages of titration microcalorimetry with respect to classical titration macrocalorimetry with particular reference to calixarene chemistry have been recently discussed in (ref. 15). Thus, table 4 shows thermodynamic data (obtained by titration microcalorimetry) for the complexation of alkali–metal cations (lithium, sodium and potassium) and methyl p–tert–butylcalix(4)arene tetraethanoate in benzonitrile at 298.15 K. These are the first microcalorimetric data ever reported on complexation reactions involving calixarenes.

Table 4.   Thermodynamic data (titration microcalorimetry) for the complexation of methyl p–tert–butylcalix(4)arene tetraethanoate and alkali–metal cations in benzonitrile at 298.15 K.

Cation	log K_s	Δ_cG° kJ mol^{-1}	Δ_cH° kJ mol^{-1}	Δ_cS° JK^{-1}mol^{-1}	$\Delta_{solv}S^{\circ\,a}$ JK^{-1}mol^{-1}
Li^+	5.27±0.03	−30.08	−47.02±0.29	−56.8	−237.6
Na^+	5.51±0.05	−31.45	−41.08±1.23	−32.3	−218.4
K^+	2.70±0.02	−15.41	−21.34±0.68	−19.9	−205.0

aRef. 16

Previous investigations involving alkali–metal cations and butyl *p–tert*–butylcalix(4)arene tetraethanoate in benzonitrile using titration macrocalorimetry (ref. 5) have shown that the butylcalix(4)arene ester in this solvent is unable to complex the larger cations such as rubidium and caesium. The same results were found with the methylcalix(4)arene ester and these two cations in this solvent when attempts were made to derive thermodynamic data for these systems using microcalorimetry. However, the latter technique has a much higher degree of sensitivity than the former and therefore, on the basis of the microcalorimetric data for the various esters available, it can now be concluded that, independently of the alkyl moiety of the ester group of these ligands, calixarene esters are able to discriminate against the large cations (Rb^+ and Cs^+) when the reaction medium is benzonitrile. The data in table 4 show that for these cations and this ligand in this solvent, the process is enthalpically controlled and the loss of entropy results mainly from the combination of two species (ligand and cation) to give the metal–ion complex. Also included in table 4 are the entropies of solvation ($\Delta_{solv}S°$) of these cations in benzonitrile (ref. 16). In fact, entropies of complexation (table 4) follow the same trend of that observed for the entropies of solvation of these cations in this solvent. This is a strong indication that for these metal–ion calixarenates, the cations are quite exposed to the solvent. In fact, in going from lithium to potassium, the following correlations are found.

$$\Delta_cS° \ (Li^+) - \Delta_cS° \ (Na^+) \cong \Delta_{solv}S° \ (Li^+) - \Delta_{solv}S° \ (Na^+) \qquad (4)$$

$$\Delta_cS \ (Na^+) - \Delta_cS° \ (K^+) \cong \Delta_{solv}S° \ (Na^+) - \Delta_{solv}S° \ (K^+)$$

It must be emphasised that all thermodynamic data are now being checked by calculation of the Gibbs energy, enthalpy and entropy for the coordination process in the solid state. Furthermore, enthalpy data so far reported for the complexation of calixarene derivatives and metal cations in methanol, acetonitrile and various other solvents are now being checked by titration microcalorimetry.

Further work in this area involves ¹H and ¹³C NMR of these calixarenes and metal cations in benzonitrile. Due to the ability of calixarene esters to interact with the solvent, structural information for the interpretation of the complexation process is valid if these studies are carried out in the same reaction medium. It must be realised that once the solvent interact with the ligand, the resulting adduct is unlikely to have the same properties of the free ligand. These studies will be reported separately.

## EXTRACTION OF CATIONS BY ALKYL *p-tert*-BUTYLCALIX(4)ARENE TETRAETHANOATE

The individual processes which contribute to the overall extraction of amines by parent calix(n)arenes (n = 6, 8) have been recently discussed in (ref. 6). The ability of calixarene derivatives (esters, ketones and others) to extract alkali–metal cations from aqueous solutions has been demonstrated previously by (refs. 9, 10). However, to date the individual processes which contribute to the overall extraction of metal cations from aqueous solutions into the organic phase by calixarene derivatives have not been thoroughly investigated.

As far as the neutral macrocycles are concerned, **knowledge about the properties and behaviour of the ligand, the free and complexed electrolytes in the solvent system in which the extraction process is to be carried out** is required in order to identify the individual steps likely to contribute to the overall process. This is **particularly important** for ⸱᠌ **calixarene derivatives** such as the esters since, as pointed out above, interactions between the solvent and the ligand may alter <u>selectivity</u>. It must be emphasised that the individual contributions to the overall extraction of metal cations are <u>not</u> the same for a water soluble ligand (18 crown 6 or cryptand 222) than for ligands which are <u>not</u> soluble in water (alkyl *p–tert*–butylcalix(4)arene tetraethanoates). For the latter, the individual steps which mainly contribute to the overall extraction are

i) The partition of the electrolyte from water to the non–aqueous phase (s) used in the extraction process

$$M^+ \ (H_2O) + X^- \ (H_2O) \longrightarrow M^+ \ (s) + X^- \ (s) \qquad (5)$$
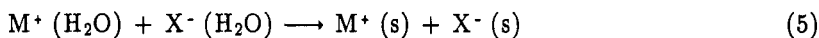
ii) The complexation of the cation and the ligand in the same non–aqueous phase

$$M^+ \ (s) \ + RCalix(4) \ (s) \longrightarrow M^+ \ RCalix(4) \ (s) \qquad (6)$$
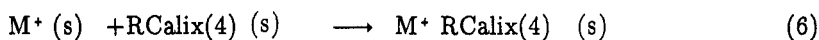
iii) The ion–pair formation constants for the single cation (eqn 3) and the complexed cation (eqn 2) and the anion in the organic phase (s). However, under certain experimental conditions, the contribution given by the process given by eqn 3 may be very small.

Therefore, the overall extraction of metal cations by alkyl *p–tert*-butylcalix(4)arene esters can be represented by

$$M^+(aq) + X^-(aq) + RCalix(4)\ (s) \rightarrow M^+\ RCalix(4)X^-\ (s) \qquad (7)$$
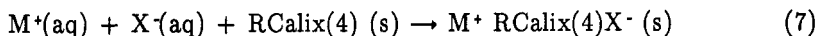
We are now deriving equilibria data for process (7) using alkali–metal picrates in various water–non aqueous systems and several calixarene derivatives. In doing so extraction data calculated from the individual parameters (eqns 2, 5 and 6) are compared with direct partition experiments containing the macrocycle in the organic phase.

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