

Thermodynamics of Ethyl *p*-*tert*-Butylcalix[5]arene Pentanoate and Its Cation Complexes in Nonaqueous Media

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The solution behavior of ethyl *p*-*tert*-butylcalix[5]arene pentanoate, EtCalix(5), in various protic and aprotic solvents has been assessed from the standard Gibbs energies of transfer of this ligand from acetonitrile to other solvents. These data were derived from solubility measurements of EtCalix(5) in different media. It is concluded that in solvents in which metal cation salts are predominant as ionic species in solution (within a low concentration range), the solvation of the ligand will not contribute significantly to the thermodynamics of cation complexation as a result of the medium effect. Various analytical techniques were used to identify the sites of ligand–cation interaction (^1H NMR) and the composition (conductance and calorimetric measurements) of the metal–ion complexes in the various solvents. Titration calorimetry (direct and competitive) was used to thermodynamically characterize the cation binding ability of EtCalix(5) and gain quantitative information on the complex stability and the factors controlling it. Given the large bulk of data reported in the literature wrongly placed under the thermodynamic umbrella, particular emphasis is made about the need of identifying the process taking place in solution prior to proceeding with its thermodynamic characterization. The results are compared with those for the ethyl ester derivative of the cyclic tetramer, EtCalix(4). It is concluded that in moving from EtCalix(4) to EtCalix(5), (i) the selectivity of the latter for cations is swallowed toward the larger cations and (ii) although the number of binding sites increases, these are not able to exert the efficient control upon the ligand–cation binding ability as that found for the tetramer ester and these cations in these solvents.

Introduction

As compared with crownethers¹ and cryptands,^{2,3} calix[*n*]arenes^{4–6} ($n = 4–8$) are relatively new receptors in the field of macrocyclic chemistry. The interest in these ligands mainly relies on the derivatives obtained by lower and upper rim functionalization of calix[*n*]arenes following the one step procedure introduced by Gutsche and co-workers^{5–6} for the synthesis of the parent compounds.

Most contributions in the field of calixarene chemistry have been centered on derivatives of the cyclic tetramer.^{4–8} As far as the cyclic pentamer and its derivatives are concerned, solubility studies in different media from which transfer Gibbs energies can be derived have not been reported. These investigations are important for solution studies and for assessing the solvation effect due to the receptor in complexation processes involving calix[5]arene and its derivatives with neutral and ionic species. Complexation studies on calix[5]arene derivatives and metal cations are mostly limited to stability constant measurements involving esters and ketones and alkali and silver cations in methanol with a few data in acetonitrile.^{9–11} In the latter solvent, pentaalkyl ester derivatives of *p*-benzylcalix[5]arene and *p*-*tert*-octylcalix[5]arene ligands have been used as complexing agents for these univalent cations. The interaction of calix[5]arene and 1,3 bridged calix[5]crowns and cationic organic guests mainly in chloroform with only a few data in deuterated tetrachloroethane, acetone, and *N,N*-dimethylformamide have been discussed, and stability constant data mostly in apolar solvents have been reported by Arnecke et al.¹² Again, stability constants of lower rim calix[5]arene derivatives and

ammonium salts in chloroform at 298 K have been determined by UV spectrophotometry.¹³ Other investigations are those by Clark and co-workers¹⁴ involving solution and solid state studies on the parent calix[5]arene and isomeric carboranes, Sood et al.¹⁵ on phosphorus-based *p*-*tert*-butylcalix[5]arene ligands, Atwood et al.¹⁶ on the association of C_{70} and the cyclic pentamer, Iwamoto et al.¹⁷ on the synthesis and complexation properties of a Zn(II)–porphyrin containing a calix[5]arene cup, and Garozzo et al.¹⁸ on the molecular recognition properties of a calix[5]arene based receptor for long chain ion paired α,ω -alkanedioldiammonium salts. A calix[5]arene ion selective electrode for *n*-butylammonium ions has been designed by Giannetto et al.¹⁹ Water soluble calix[5]arenes and their thermodynamic parameters of complexation with pyridine derivatives, dipyrindines, and phenantroline in water at 298.15 K have also been reported by Liu and co-workers.^{20,21}

As far as stability constants involving ionic species are concerned, data in low dielectric constant media such as chloroform, tetrachloroethane, and to a certain extent acetone cannot be regarded as “true” stability constants. Indeed these are referred to as an undefined process in which ions and ion pairs are most likely to be involved.^{7,8} Consequently, these data are concentration dependent.

Given that selectivity is one of the main features of supramolecular chemistry, the relevant role of thermodynamics in quantitatively assessing the selective behavior of a receptor in a given solvent for one species relative to another cannot be overemphasized. This is reflected in the selectivity factor, S , obtained from the ratio of the thermodynamic stability constants

of a receptor and two species (ionic or neutral) in a given solvent and at a given temperature. Therefore this paper aims to (i) establish quantitatively the selective behavior of a calix[5]arene ester, namely, pentaethyl calix[5]arene pentaethanoate, EtCalix(5), and metal cations in two solvents, acetonitrile, MeCN, and methanol, MeOH, and (ii) assess how the enthalpy and entropy associated with these processes control the stability of these complexes in these solvents.

Several techniques are explored to identify the process taking place in solution in order to ensure that the thermodynamics reported in this paper are referring to a well-defined process.

Experimental Section

Chemicals. The following chemicals, *p*-tert-butylphenol (98%), paraformaldehyde (95%), and potassium-*tert*-butoxide (95%), purchased from Aldrich were dried over P₄O₁₀ under vacuum for several days before use.

Ethyl bromoacetate and potassium carbonate (K₂CO₃), both from Aldrich, and 18-crown-6 (18-C-6) from Fluka were used without further purification. Potassium chloride, Aldrich (99.9%), was recrystallized from double deionized water and dried at 120 °C.

Metal cation salts as perchlorates, LiClO₄·H₂O, NaClO₄·H₂O, KClO₄·H₂O, RbClO₄·H₂O, CsClO₄·H₂O, Mg(ClO₄)₂·H₂O, Ca(ClO₄)₂·4H₂O, Sr(ClO₄)₂·2H₂O, Ba(ClO₄)₂·H₂O, AgClO₄·H₂O, Cd(ClO₄)₂·H₂O, Pb(ClO₄)₂·H₂O, and Hg(ClO₄)₂·H₂O, were dried over P₄O₁₀ under vacuum for several days before use.

Acetonitrile (HPLC grade) was placed over CaH₂ and refluxed under a nitrogen atmosphere. The middle fraction of the distilled solvent was used.²²

Toluene, methanol (99%), and tetrahydronaphthalene (all from Aldrich) and dichloromethane (Fisher) were used without further purification.

Synthesis of 5,11,17,23,29-Penta-*tert*-butyl-31,32,33,34,35-calix[5]arene Pentaethanoate, EtCalix(5). The parent compound, 5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-hydroxycalix[5]arene, Calix(5), was synthesized in accordance with the procedure reported in the literature^{23–25}.

The procedure used for the synthesis of 5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-calix[5]arene pentaethanoate, EtCalix(5), is the one reported previously by Danil de Namor and co-workers²⁶ for the preparation of the calix[4]arene ester derivatives.

In a dry three-necked round bottomed flask (250 mL), *p*-tert-butylcalix[5]arene (1.0 g, 1.29 mmol), potassium carbonate (1.5 g, 10.32 mmol), and 18-crown-6 (0.075 g, 0.3 mmol) were suspended in dry acetonitrile (150 mL). The mixture was left under continuous stirring for half an hour. This was followed by the addition of ethyl bromoacetate (0.87 mL, 7.81 mmol). The reaction mixture was left overnight at 65 °C under a nitrogen atmosphere. The reaction was monitored by TLC using a hexane–ethyl acetate (4:1) mixture as the developing solvent system. After completion of the reaction, the mixture was cooled to room temperature. Then the solvent was removed under reduced pressure. The oil afforded was dissolved in dichloromethane and extracted with an aqueous solution of 0.2 M HCl and then with distilled water. The organic phase was separated and dried with magnesium sulfate, then filtered. The dichloromethane was removed by rotary evaporation, and the solid obtained was recrystallized from a methanol–chloroform (2:1) mixture. The white crystals were dried at 60 °C over CaCl₂. The product (75–78% yield) was characterized by microanalysis, ¹H and ¹³C NMR, and mass spectroscopy. Microanalysis carried out at the University of Surrey, calculated %: C, 72.55; H, 8.12. Found %: C, 72.27; H, 8.27. MS (FAB) *m/z* 1241.7

[M⁺]. ¹H NMR (300 MHz, in CDCl₃) δ (ppm), *J* (Hz): 6.88 (s, 2H, Ar–H), 4.81 (d, 2H, *J* = 14.41, Ar–CH₂**ax**–Ar), 4.62 (s, 2H, O–CH₂–CO), 4.23 (q, 2H, O–CH₂–CH₃), 3.35 (d, 2H, *J* = 14.71, Ar–CH₂**eq**–Ar), 1.29 (t, 3H, CH₂–CH₃), 1.07 (s, 9H, C(CH₃)₃). ¹³C NMR (300 MHz) (CDCl₃) δ (ppm): 170.16 (CH₂–CO), 152.13, 145.71, 133.39, 125.88 (Ar), 70.89 (O–CH₂–CO), 60.83 (O–CH₂–CH₃), 34.0 (C–(CH₃)₃) 31.34 ((C(CH₃)₃), 30.30 (Ar–CH₂Ar), and 14.21 (CH₂–CH₃).

Solubility Measurements. Saturated solutions of *p*-tert-butylcalix[5]arene and its derivative were prepared by adding an excess amount of the solid to the solvent. The mixtures were left in a thermostat bath at 298.15 K for several days until thermal equilibrium was reached. Aliquots of the saturated solution were taken and analyzed gravimetrically in triplicate. Blank experiments were carried out. Solvate formation was checked by exposing the solid to a saturated atmosphere of the appropriate solvent for several days, following the procedure described in the literature.²⁷ Solvate formation was observed in chloroform, Cl₃CH; benzonitrile, PhCN; dichloromethane, DCM; dimethyl sulfoxide, DMSO; and tetrahydrofuran, THF.

¹H NMR Studies. ¹H NMR measurements were recorded at 298 K using a Bruker AC-300E pulse Fourier transform NMR spectrometer. Typical operating conditions for routine proton measurements involved a “pulse” or flip angle of 30°, spectral frequency (SF) of 300 MHz, delay time of 1.60 s, acquisition time (AQ) of 1.819 s, and line broadening of 0.55 Hz. Samples of the ligand (~0.5 mL, 6.0 × 10^{−3} mol dm^{−3}) in deuterated acetonitrile, CD₃CN, were placed in 5 mm NMR tubes using TMS (tetramethylsilane) as the internal reference.

Stepwise additions of the metal cation salt in CD₃CN (~1.0 × 10^{−2} mol dm^{−3}) were made until no further chemical shift changes were observed. Similar experiments were carried out in deuterated methanol, CD₃OD.

Conductance Measurements. For these measurements, a Wayne Kerr B642 autobalance universal bridge type B642 was used.

The conductivity cell constant was determined by adding, in steps, an aqueous solution of KCl (0.1 mol dm^{−3}) to the cell containing deionized water. The conductance of the deionized water was measured in advance and subtracted from each conductance reading. The corresponding molar conductances, Λ_m (S cm² mol^{−1}), were calculated using the Lind, Zwolenik, and Fuoss equation.²⁸ The molar conductance was used to calculate the corresponding value for the specific conductance and the cell constant.

Conductometric titrations were carried out to determine the composition of the metal–ion complex. Thus, solutions of the metal–ion salt and the ligand in the appropriate solvent (CH₃CN and MeOH) were prepared for each run. The cell was cleaned and dried, and an accurately weighed amount of the metal–ion salt solution (~25 cm³, 9.0 × 10^{−5} mol dm^{−3}) was added. The conductivity of the solution was measured once thermal equilibrium was attained. The appropriate metal–ion salt was titrated with a solution of the ligand in the same solvent (9.0 × 10^{−4} mol dm^{−3}) until no significant changes in conductance were observed. All measurements were taken at 298.15 K.

Calorimetric Measurements. Calorimetric titrations (direct and competitive) were carried out with the aim of determining the stability constant (log *K*_s) and the enthalpy of complexation, Δ*c**H*. In doing so, the Tronac 450 isoperibol titration calorimeter was used. The reliability of the instrument was checked by carrying out the standard reaction of the protonation of an aqueous solution of tris(hydroxymethyl)amino methane (THAM)

with hydrochloric acid (HCl 0.1 mol dm⁻³) at 298.15 K.²⁹ The value determined, -47.4 ± 0.2 kJ mol⁻¹, is in agreement with the one reported by Hill, Öjelund, and Wadsö³⁰ using the LKB calorimeter.

For complexes of moderate stability ($\log K_s < 6$), direct calorimetric titrations were performed. Thus, a solution of the ligand (50 cm^3 , 6.0×10^{-4} to 5.0×10^{-5} mol dm⁻³) placed in the reaction vessel was titrated with a solution of the appropriate metal-ion salt (2.0×10^{-2} to 5.0×10^{-2} mol dm⁻³) in the appropriate solvent.

For complexes with high stability constants ($\log K_s > 6$), competitive calorimetric titrations were performed. A solution of the metal-ion salt (1.8×10^{-3} to 1.5×10^{-2} mol dm⁻³) was prepared in the appropriate solvent, placed in the buret, and titrated into a vessel containing a solution of the metal cation-EtCalix(5) complex (50 cm^3 , 6.0×10^{-4} to 8×10^{-5} mol dm⁻³) for which the stability constant and enthalpy are well established. The stability constant of the complex in the vessel was lower than that expected between the ligand and the metal cation under investigation placed in the buret, enabling the latter to compete and replace the metal cation from the complex in the vessel.

Corrections for the heat of dilution of the metal-ion salt were applied in all cases. An electrical calibration was carried out after each titration experiment.

Stability constants and enthalpy values in acetonitrile were also derived from titration microcalorimetry. For this purpose, the four channel heat conduction microcalorimeter (Thermometric 2277) was used. Electrical (static and dynamic) and chemical calibrations were carried out to check the reliability of the equipment.³¹ For these measurements, a solution of the metal-ion salt (6.0×10^{-3} to 1.0×10^{-2} mol dm⁻³) was prepared in acetonitrile, placed in the syringe, and titrated into the vessel containing a solution of EtCalix(5) (2.8 cm^3 , concentration range 5×10^{-4} to 1.0×10^{-3} mol dm⁻³) prepared in the same solvent. About 24 injections were made at time intervals of 30 min. Corrections for the enthalpy of dilution of the titrant in the solvent were carried out in all cases. A computer program for TAM (Digitam 4.1 for Windows from Thermometric AB and select software AB Sweden) for 1:1 (metal cation-ligand) processes was used to calculate $\log K_s$ and $\Delta_c H$ values.

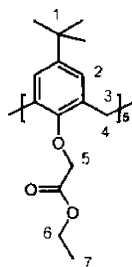
Results and Discussion

Solubility and Derived Standard Gibbs Energies of Solution of the Parent Calix[5]arene. Transfer Gibbs Energies. The solubilities for the parent compound, Calix(5), in protic (methanol, MeOH; ethanol, EtOH), dipolar aprotic (*N,N*-dimethylformamide, DMF; propylene carbonate, PC; acetonitrile, MeCN; dimethylsulfoxide, DMSO; benzonitrile, PhCN), and apolar solvents (hexane, Hex; toluene, C₆H₅CH₃; dichloromethane, DCM; chloroform, Cl₃CH; tetrahydrofuran, THF) were measured at 298.15 K. Data reported in Table 1 are the result of at least three analytical measurements carried out on the same saturated solution when equilibrated with the solid at 298.15 K. In solvents like DCM, Cl₃CH, DMSO, PhCN, and THF, this macrocycle is very soluble due to solvate formation. This was checked by exposing the solid to a saturated atmosphere of these solvents. Therefore, the standard Gibbs energy of solution, $\Delta_s G^\circ$, of this ligand in these solvents could not be calculated. $\Delta_s G^\circ$ values were evaluated in DMF, PC, Hex, MeCN, C₆H₅CH₃, EtOH, and MeOH and are referred to the standard state of 1 mol dm⁻³. Taking MeCN as the reference solvent, the standard transfer Gibbs energies were calculated,

TABLE 1: Solubility and Standard Gibbs Energies of Solution of *p*-*tert*-Butylcalix[*n*]arenes (*n* = 4, 5, 6, 8) in Various Solvents at 298.15 K and Transfer Gibbs Energies from Acetonitrile at 298.15 K

solvent ^a	Calix(5)			Calix(4)			Calix(6)			Calix(8)		
	solubility ^b (mol dm ⁻³)	$\Delta_s G^\circ$ ^b (kJ mol ⁻¹)	$\Delta_c G^\circ$ ^b (MeCN \rightarrow s) (kJ mol ⁻¹)	solubility ^c (mol dm ⁻³)	$\Delta_s G^\circ$ ^c (kJ mol ⁻¹)	$\Delta_c G^\circ$ ^c (MeCN \rightarrow s) (mol dm ⁻³)	solubility ^c (mol dm ⁻³)	$\Delta_s G^\circ$ ^c (kJ mol ⁻¹)	$\Delta_c G^\circ$ ^c (MeCN \rightarrow s) (kJ mol ⁻¹)	solubility ^c (mol dm ⁻³)	$\Delta_s G^\circ$ ^c (kJ mol ⁻¹)	$\Delta_c G^\circ$ ^c (MeCN \rightarrow s) (kJ mol ⁻¹)
MeCN	$(1.59 \pm 0.07) \times 10^{-3}$	16 ± 0.2	0	4.73×10^{-5}	24.69	0	<i>d</i>	<i>d</i>	27.26	1.68×10^{-5}	<i>d</i>	0
MeOH	$(8.0 \pm 0.3) \times 10^{-4}$	17.7 ± 0.3	1.7	5.90×10^{-4}	18.43	-6.26	<i>d</i>	<i>d</i>	<i>d</i>	$<10^{-5}$	<i>d</i>	<i>d</i>
EtOH	$(8.5 \pm 0.3) \times 10^{-4}$	17.5 ± 0.3	1.5	3.30×10^{-4}	19.87	-4.82	<i>d</i>	<i>d</i>	<i>d</i>	$<10^{-5}$	<i>d</i>	<i>d</i>
DMF	$(8.4 \pm 0.2) \times 10^{-3}$	11.9 ± 0.2	-4.1	1.10×10^{-3}	16.89	-7.8	<i>d</i>	<i>d</i>	<i>d</i>	2.20×10^{-3}	15.17	-12.09
<i>n</i> -Hex	$(6.7 \pm 0.2) \times 10^{-3}$	12.4 ± 0.2	-3.6	2.12×10^{-4}	20.97	-3.72	<i>d</i>	<i>d</i>	<i>d</i>	2.51×10^{-3}	26.26	-1.00
PC	$(3.2 \pm 0.2) \times 10^{-3}$	14.2 ± 0.2	-1.8	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>
CH ₂ C ₆ H ₅	$(1.4 \pm 0.1) \times 10^{-3}$	16.3 ± 0.2	0.3	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>
CHCl ₃	very soluble	solvate formation	solvate formation	4.34×10^{-3}	13.48	-11.21	<i>d</i>	<i>d</i>	<i>d</i>	6.23×10^{-3}	12.59	-14.67
PhCN	very soluble	solvate formation	solvate formation	9.47×10^{-4}	17.26	-7.43	5.45×10^{-3}	12.88	<i>d</i>	1.14×10^{-2}	11.09	-16.17
PhNO ₂	very soluble	solvate formation	solvate formation	1.83×10^{-2}	9.92	-14.77	2.26×10^{-2}	9.4	<i>d</i>	2.57×10^{-3}	14.78	-12.48
DCM	very soluble	solvate formation	solvate formation	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>
DMSO	very soluble	solvate formation	solvate formation	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>
THF	very soluble	solvate formation	solvate formation	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>

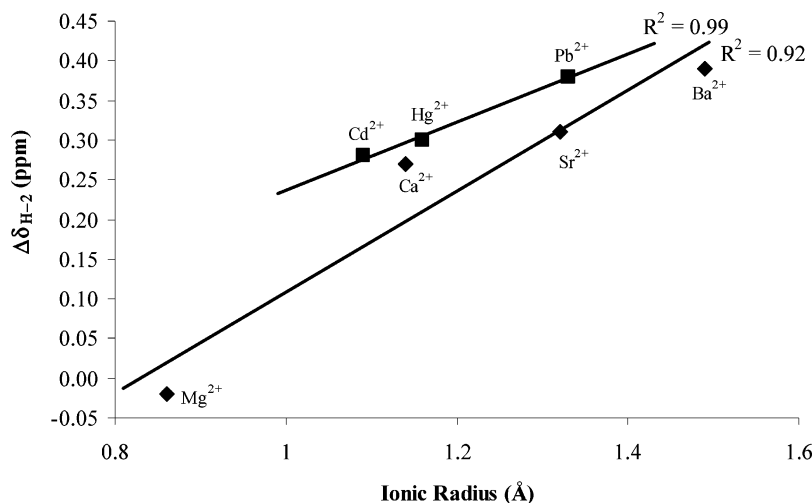
^a Abbreviations for solvents: acetonitrile, MeCN; methanol, MeOH; ethanol, EtOH; *N,N*-dimethylformamide, DMF; *n*-hexane, *n*-Hex; propylene carbonate, PC; toluene, CH₃C₆H₅; chloroform, CHCl₃; benzonitrile, PhCN; nitromethane, PhNO₂; dichloromethane, DCM; dimethylsulfoxide, DMSO; tetrahydrofuran, THF. ^b This work. ^c Reference 7. ^d No data available.

TABLE 2: ^1H NMR Chemical Shift Changes ($\Delta\delta$, ppm) for EtCalix(5) upon Addition of Bivalent Metal Cations (as Perchlorates) in CD_3CN and CD_3OD at 298 K

proton	$\Delta\delta$ (CD_3CN) ^a								$\Delta\delta$ (CD_3OD) ^b Ba^{2+}
	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Cd^{2+}	Hg^{2+}	Pb^{2+}	Zn^{2+}	
H-1	0.00	0.07	0.08	0.10	0.08	0.07	0.12	0.00	0.14
H-2	-0.02	0.27	0.31	0.39	0.28	0.30	0.38	0.01	0.20
H-3 _{eq}	0.04	0.18	0.18	0.17	0.19	0.18	0.21	0.04	0.38
H-4 _{ax}	-0.03	-0.51	-0.53	-0.57	-0.51	-0.53	-0.52	overlap	-0.17
H-5	0.01	-0.11	-0.12	-0.12	0.06	0.13	0.17	0.00	0.10
H-6	0.01	0.23	0.23	0.23	0.22	0.23	0.24	0.05	0.17
H-7	-0.07	0.11	0.12	0.13	0.11	0.12	0.20	0.08	0.13
$\Delta\delta_{\text{ax-eq}}$	1.34	0.72	0.70	0.67	0.71	0.70	0.68		0.91

^a Proton chemical shifts (ppm) of EtCalix(5) in CD_3CN at 298 K: H-1, 1.08; H-2, 7.07; H-3, 3.33; H-4, 4.74; H-5, 4.67; H-6, 4.20; H-7, 1.27.

^b Proton chemical shifts (ppm) of EtCalix(5) in CD_3OD at 298 K: H-1, 1.03; H-2, 6.95; H-3, 3.36; H-4, 4.82; H-5, 4.65; H-6, 4.24; H-7, 1.31.

**Figure 1.** Relationship between ionic radius (Å) of alkaline-earth metal cations and chemical shift changes (ppm) of aromatic protons for EtCalix(5) at 298 K.

and these are also reported in Table 1. It is evident from these values that the difference in solvation of this ligand among these solvents is not substantial. Comparison of these data with those previously reported⁷ for other parent calixarenes such as the cyclic tetramer, Calix(4), hexamer, Calix(6), and the octamer, Calix(8) (also included in Table 1) shows that among all solvents considered the solubility of parent calixarenes reaches a maximum value for Calix(5) and decreases as the number of phenol units increases. Interesting features of these data are that (i) while Calix(4) undergoes “selective solvation” among the various solvents, this decreases significantly in the cyclic pentamer as reflected in the $\Delta_r G^\circ$ values shown in Table 1 and (ii) unlike Calix(4) and Calix(8), Calix(5) undergoes solvate formation in some dipolar aprotic and apolar solvents.

Complexation with Metal Cations. ^1H NMR Measurements. ^1H NMR measurements of EtCalix(5) in different solvents (CDCl_3 , CD_3CN , and CD_3OD) were carried out in an attempt to assess the solvent effect on this macrocycle. No

significant chemical shift changes were observed in moving from one solvent to another. Taking Gutsche’s suggestion^{4,5} in that the difference in chemical shifts of the axial and equatorial protons of the methylene bridge, $\Delta\delta_{\text{ax-eq}}$, provides an indication regarding the conformation adopted by the ligand in solution, these values were calculated. Thus, $\Delta\delta_{\text{ax-eq}}$ values of 1.46, 1.41, and 1.50 ppm were found in CDCl_3 , CD_3CN , and CD_3OD , respectively, indicating that in these solvents EtCalix(5) adopts a distorted “cone” conformation which does not appear to be altered significantly with the solvent.

Upon addition of alkali and silver metal cations (as perchlorates) in CD_3CN and CD_3OD at 298 K, $\Delta\delta_{\text{ax-eq}}$ values decrease to 1.21, 1.13, 1.19, 1.11, and 1.16 ppm for lithium, sodium, potassium, rubidium, and cesium, respectively, in CD_3CN , and similar changes were observed in CD_3OD . These data suggest that the ligand adopts a more “conelike” conformation upon complexation with these metal cations in these solvents which does not seem to be altered by a change in the medium. No

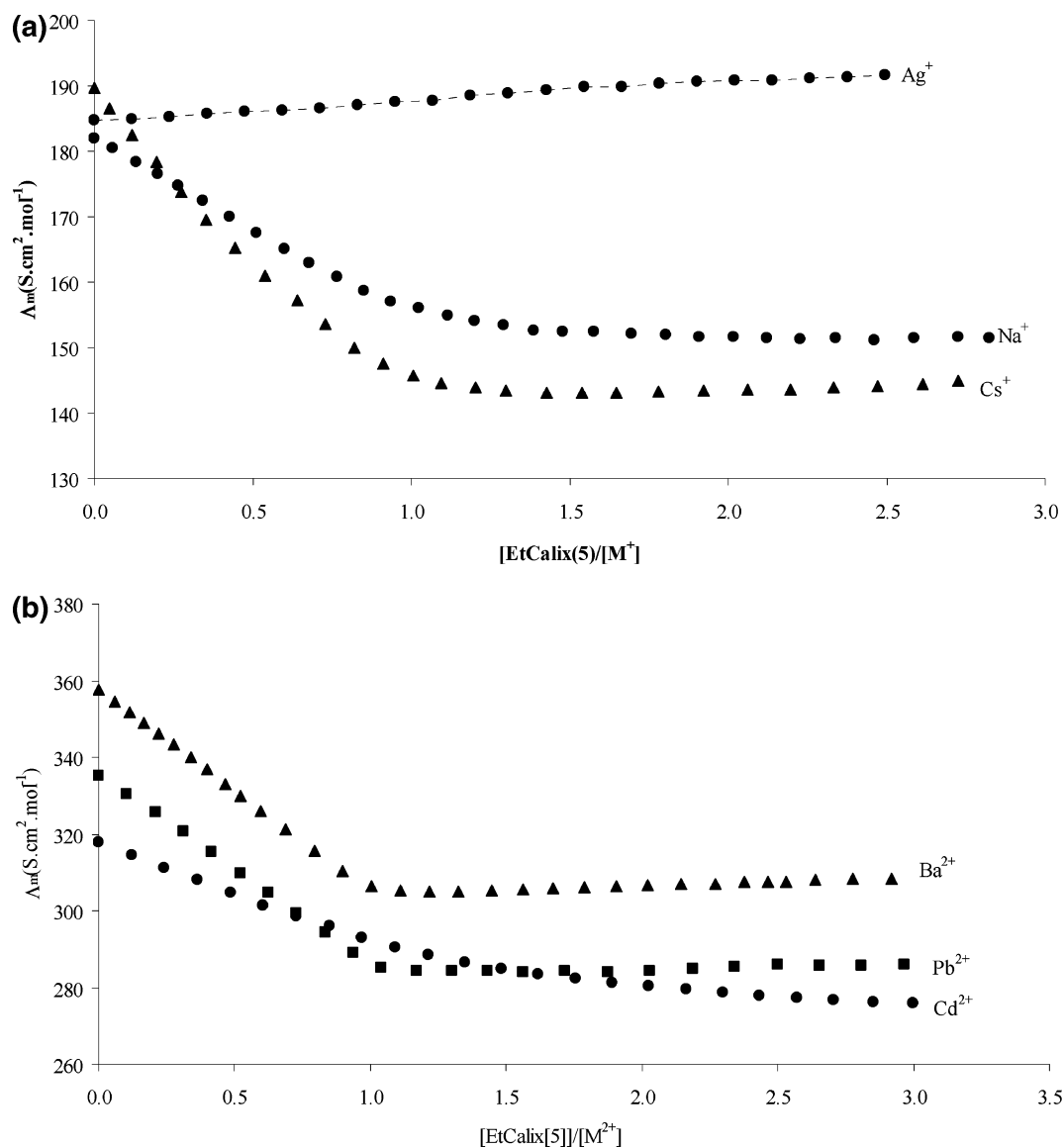


Figure 2. Conductometric curves for the titration of (a) univalent metal cations and (b) bivalent metal cations with EtCalix(5) in acetonitrile at 298.15 K.

other significant chemical shift changes for the remaining protons of the ligand when complexed with the alkali and silver metal cations in acetonitrile are observed. A similar behavior is observed in CD₃OD, except for H-6. Thus, the complexation of EtCalix(5) and univalent cations is only reflected through the $\Delta\delta_{\text{ax-eq}}$ values. Therefore, it is not possible to identify the active sites of complexation of EtCalix(5) in its interaction with alkali metal cations in this solvent.

A different picture emerges by the addition of bivalent cations (alkaline-earth, heavy metal, and Zn²⁺ cations) to this ligand in CD₃CN. Thus, ¹H NMR data in CD₃CN at 298 K are shown in Table 2. $\Delta\delta_{\text{ax-eq}}$ values resulting from the addition of each metal cation to EtCalix(5) in CD₃CN are also included in this Table. The results show that upon complexation of this ligand with these metal cations in CD₃CN, the axial proton (H-4) is shielded while the equatorial proton (H-3) becomes deshielded. Thus, $\Delta\delta_{\text{ax-eq}}$ values decrease significantly from the free ligand (1.41 ppm) to the complex ligand for most of the alkaline-earth and heavy metal cations except Zn²⁺. Among the former cations, the most significant change is that for Ba²⁺ while for the heavy metal cations, complexation with Pb²⁺ leads to a large decrease in the $\Delta\delta_{\text{ax-eq}}$. There is a definite size effect among the alkaline-earth metal cations, with the smallest $\Delta\delta_{\text{ax-eq}}$ value for Mg²⁺

(0.86 Å) and the largest for Ba²⁺ (1.49 Å).^{32,33} The same trend is found among the heavy metal cations where the $\Delta\delta_{\text{ax-eq}}$ is the smallest for Cd²⁺ (1.09 Å) and the largest for Pb²⁺ (1.33 Å).

Significant chemical shift changes upon complexation of EtCalix(5) with bivalent cations are those for the aromatic protons. In fact, there is a linear correlation between the chemical shift changes of this proton upon complexation with the alkaline-earth metal cations in CD₃CN and the size of the alkaline-earth metal cations as observed in Figure 1 with the highest change for the largest Ba²⁺ cation. This is also observed for the heavy metal cations and Zn²⁺, although these do not fall within the same line of the alkaline-earth metal cations. As previously discussed³² this is expected. It is known that while solvation energies for alkaline-earth metal cations are correlated with electrostatic energy (z^2/r ; where z is the cation charge and r is the ionic radius), there are some additional factors for the first transition and soft metal cations such as Hg²⁺ and Cd²⁺ (highly polarizable).³³ These additional changes are not reflected in the ionic radius. The fact that in moving from CD₃CN to CD₃OD no significant chemical shift changes are observed (except for Ba²⁺) may be an indication that the chemical shift changes observed for the aromatic protons and these cations in

TABLE 3: Thermodynamic Parameters of Complexation of EtCalix(5) and Metal Cations in Acetonitrile and Methanol at 298.15 K

cation	log K_s	$\Delta_c G^\circ$ (kJ mol ⁻¹)	$\Delta_c H^\circ$ (kJ mol ⁻¹)	$\Delta_c S^\circ$ (J K ⁻¹ mol ⁻¹)
Acetonitrile				
Li ⁺	4.47 ± 0.04 ^a	-25.5 ± 0.1	-40.0 ± 0.4	-49
Na ⁺	5.19 ± 0.05 ^a	-29.6 ± 0.3	-46.1 ± 0.1	-55
K ⁺	5.56 ± 0.03 ^a	-31.7 ± 0.2	-52.6 ± 0.3	-70
Rb ⁺	5.68 ± 0.02 ^a	-32.4 ± 0.1	-50.6 ± 0.5	-61
Cs ⁺	5.22 ± 0.03 ^a	-29.7 ± 0.2	-43.9 ± 0.6	-48
Mg ²⁺	4.57 ± 0.04 ^a	-26.1 ± 0.2	6.7 ± 0.1	110
Ca ²⁺	5.64 ± 0.03 ^a	-32.2 ± 0.2	-48.4 ± 0.2	-54
Sr ²⁺	8.26 ± 0.02 ^a	-47.2 ± 0.1	-49.8 ± 0.5	-9
Ba ²⁺	8.75 ± 0.05 ^a	-49.9 ± 0.3	-90.1 ± 0.1	-135
Hg ²⁺	5.25 ± 0.03 ^a	-30.0 ± 0.1	-23.7 ± 0.1	-21
Cd ²⁺	5.06 ± 0.06 ^a	-28.9 ± 0.1	0	0
Pb ²⁺	7.83 ± 0.04 ^a	-44.7 ± 0.1	-66.4 ± 0.4	-73
Methanol				
Li ⁺	1.0 ^b	no evidence of complexation		
Na ⁺	4.60 ± 0.03 ^a 4.4 ^b	-26.2 ± 0.2	-28.9 ± 0.5	-9
K ⁺	5.33 ± 0.02 5.3 ^b	-30.4 ± 0.1	-43.3 ± 0.2	-43
Rb ⁺	5.65 ± 0.02 ^a 5.6 ^b	-32.2 ± 0.1	-45.8 ± 0.5	-45
Cs ⁺	5.32 ± 0.04 5.5 ^b	-30.4 ± 0.2	-43.5 ± 0.4	-44
Ag ⁺	4.34 ± 0.04 ^a 4.0 ^b	-24.8 ± 0.2	-22.1 ± 0.3	9
Ba ²⁺	4.42 ± 0.04 ^a	-25.2 ± 0.2	-33.5 ± 0.4	-28

^a This work. ^b Reference 11.

acetonitrile may be attributed to a similar interaction to that observed for the calix[4]arene ester complexes in this solvent where acetonitrile sits in the hydrophobic cavity of the ligand. We visualize Calix(4) and calix[5]arenes as “glove stretchers”, in that as the pendant arms of the ligand gets closer to the cation, the hydrophobic cavity opens. Therefore, when the interaction of the hydrophilic cavity with the cation is greater, the penetration of the solvent in the hydrophobic cavity is greater. This is likely to be the case for the downfield shifts observed in the aromatic protons upon complexation with these cations in CD₃CN. Although the presence of acetonitrile has been observed in the hydrophobic cavity of the free ligand in the ethyl ester of the cyclic tetramer,³⁴ there is no evidence that this is the case for the EtCalix(5) as assessed from the ¹H NMR data discussed above in the different solvents, where no significant downfield chemical shift changes for the aromatic protons in moving from one medium to another are observed.

Conductometric Titrations. In order to obtain further information on the complexation of EtCalix(5) and metal cations and mainly on the composition of the metal–ion complexes, conductometric titrations were carried out in methanol and acetonitrile at 298.15 K.

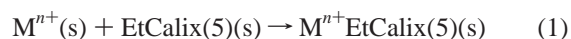
Plots of molar conductance, Λ_m (ohm⁻¹ cm² mol⁻¹), against the ligand–metal cation concentration ratios are shown in Figure 2a for univalent and Figure 2b for bivalent cations in acetonitrile. It is relevant to emphasize that in all conductometric titration curves, the Λ_m values at the ligand–metal cation ratio of zero (which correspond to that for the free metal–ion salt at low concentration) are close to those observed for the Λ_m° of alkali metal perchlorate salts in acetonitrile reported in the literature (Λ_m° values for M⁺ClO₄⁻ (S cm² mol⁻¹) are as follows: NaClO₄, 180.63; KClO₄, 187.41; RbClO₄, 189.49; CsClO₄,

191.08; and AgClO₄, 186.69).³⁵ As far as univalent cations are concerned, conductometric titration curves show the preference of this ligand for the larger cations (K⁺, Rb⁺, and Cs⁺). The complexation with Na⁺ appears to be relatively weak and even weaker for lithium in this solvent. This statement is based on the shape of the conductometric titration curves, where the composition of the metal–ion complex can be obtained at the point of interception of the two linear segments.

For the Ag⁺ cation and this ligand in acetonitrile, a straight line without any sign of curvature is observed, indicating that very weak or no complexation takes place between this cation and this ligand in acetonitrile. For bivalent cations, the selectivity trend can be easily assessed from the shape of the conductometric titration curves. Thus for alkaline-earth metal cations the trend in selectivity follows the sequence Ba²⁺ > Sr²⁺ > Ca²⁺.

The titration curve for Mg²⁺ showed a similar behavior to that for the silver cation and this ligand discussed above. Therefore, EtCalix(5) is unlikely to interact with this cation in this solvent. For the heavy metal cations, the selectivity pattern is Pb²⁺ > Hg²⁺ > Cd²⁺. However, among these cations, the ligand seems to interact strongly with Pb²⁺ and Ba²⁺. In all cases, the composition of the metal–ion complexes is 1:1 (ligand–metal cation) in acetonitrile.

Conductometric titrations involving univalent cations and EtCalix(5) in methanol at 298.15 K show the formation of 1:1 complexes of moderate stability with alkali metal cations. Very weak complexation appears to take place between this ligand and Ag⁺ in this solvent. Among the bivalent cations, a moderate curvature in the titration curve was observed for barium and EtCalix(5) in this solvent. A complex of 1:1 stoichiometry is formed. Given that in the concentration range used in this work, these salts are predominantly in their ionic forms in solution, the process under study is represented as follows,



Having identified the process, we proceeded with the thermodynamics of complexation.

Thermodynamics of Complexation. The thermodynamic characterization of the complexation of EtCalix(5) and metal cations was carried out in acetonitrile and methanol at 298.15 K. Thus log K_s and derived standard Gibbs energies, enthalpies, and entropies of these systems in these solvents are listed in Table 3. Standard deviation of the data is also included in Table 3. These data are derived from direct titration calorimetry for systems in which the stability constants were lower than 10⁶ and by competitive calorimetry when K_s values were found to be greater than 10⁶. Thermodynamic data are referred to the standard state of 1 mol dm⁻³ for the reactants and the product and correspond to the process described in eq 1. For comparison purposes, stability constant data for EtCalix(5) and alkali metal cations in MeOH at 298 K reported in the literature¹¹ are also included in Table 3. These were determined by UV spectrophotometry. There is a reasonable agreement between these two sets of data except for lithium. The reported log K_s value of 1 must be in error for the following reasons: (i) This value is well outside the lowest limit of K_s values that can be accurately determined by UV spectrophotometry. (ii) It is also clear from literature data⁹ that in moving from the pentaalkyl ester derivative of *p*-benzylcalix[5]arene to EtCalix(5) in MeOH, the stability constants of alkali metal cations in MeOH increase up to sodium and then it remains almost constant. The only value which does not follow this pattern is that for Li⁺ and EtCalix(5) in methanol. In fact, neither conductometric nor calorimetric

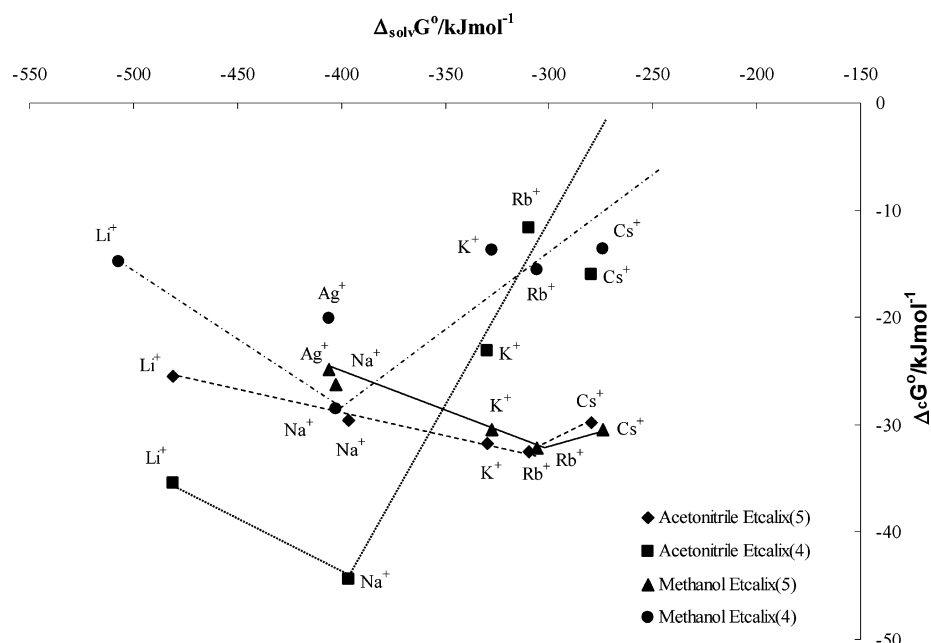


Figure 3. Gibbs energies of complexation of EtCalix(5) and alkali metal cations in acetonitrile and methanol against the standard Gibbs energies of solvation of ions in these solvents. Comparison with corresponding data for EtCalix(4) at 298.15 K.

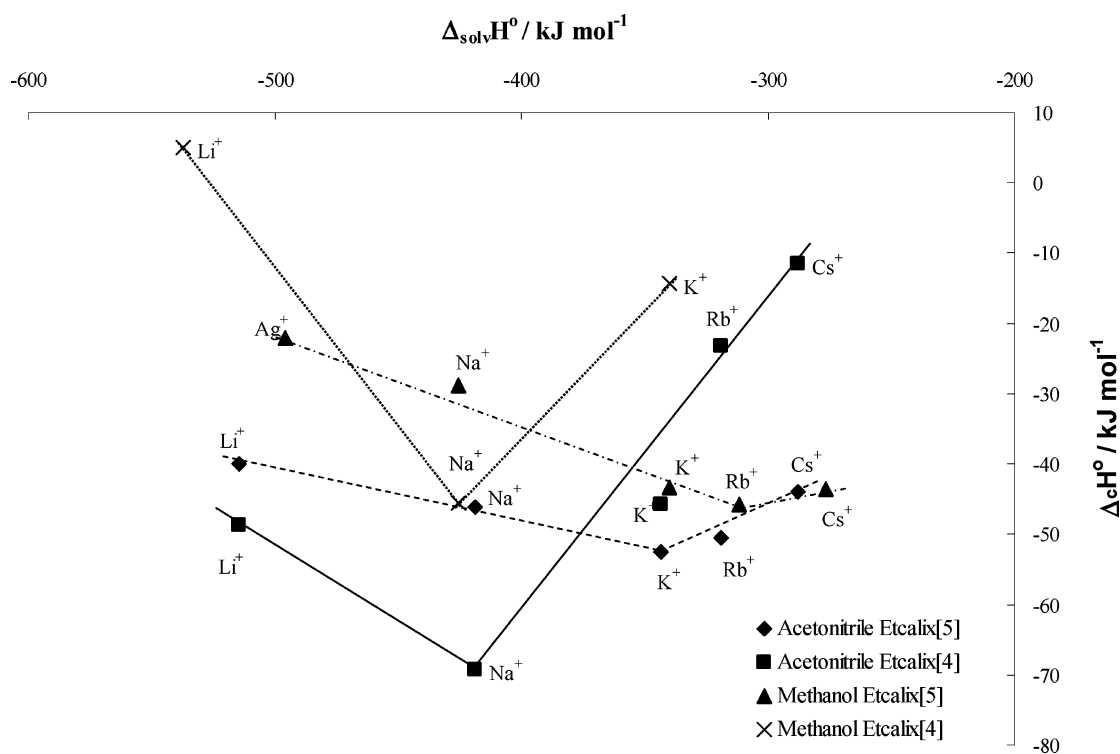


Figure 4. Enthalpies of complexation of EtCalix(5) and univalent cations in acetonitrile and methanol against solvation enthalpies of these cations in these solvents at 298.15 K. Comparison with corresponding data for EtCalix(4).

titrations carried out by us showed any sign of interaction between this ligand and this cation in MeOH.

For most metal cations, the complexation is enthalpically controlled and entropically destabilized, except for Mg^{2+} in MeCN and Ag^+ in methanol. Thus, the complexation of the former cation with EtCalix(5) is entropically controlled and enthalpically disfavored. This is characteristic of systems which undergo strong desolvation upon complexation. On the other hand, the silver complex is favored entropically and enthalpically but controlled by the latter parameter.

There are several factors which contribute to the overall stability of metal–ion complexes. As previously stated,³² cation desolvation and ligand binding energy play a predominant role in the stability of metal–ion complexes. It is the balance of these two processes which contribute significantly to the stability of complex formation. Therefore, we attempt to correlate the $\Delta_c G^\circ$ values for these systems with the Gibbs energies of solvation, $\Delta_{\text{solv}} G^\circ$, of these cations. The latter parameter results from the combination of corresponding data for ionic hydration, $\Delta_{\text{hyd}} G^\circ$, and the single-ion value for the

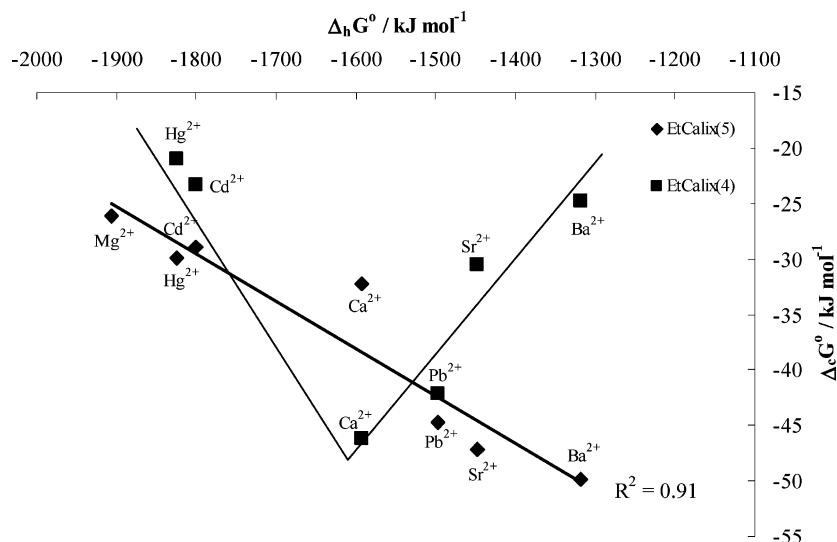


Figure 5. Plot of $\Delta_c G^\circ$ values for EtCalix(5) complexes with bivalent metal cations in acetonitrile against their $\Delta_{\text{hyd}} G^\circ$ at 298.15 K. Comparison with corresponding data for EtCalix(4).

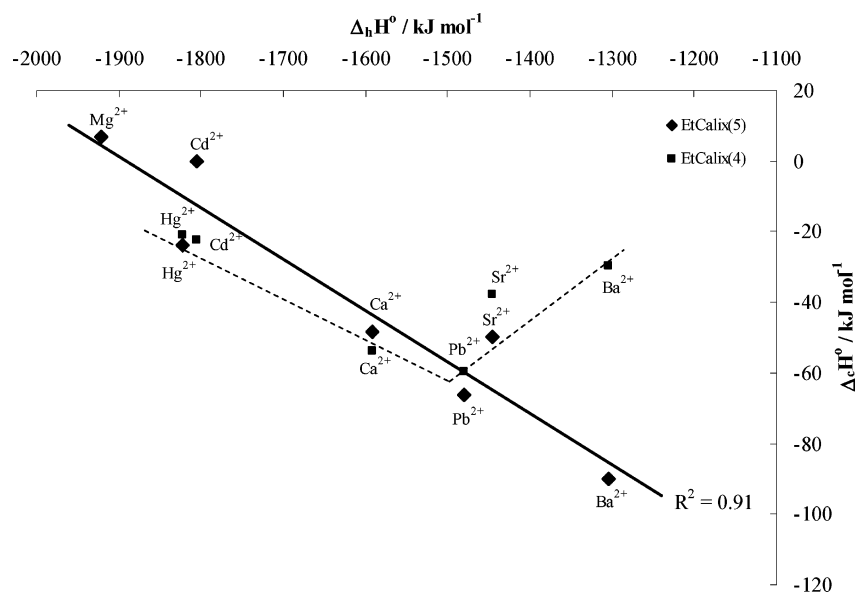


Figure 6. Plot of $\Delta_c H^\circ$ values for EtCalix(5) complexes with bivalent metal cations in acetonitrile against their $\Delta_h H^\circ$ at 298.15 K. Comparison with corresponding data for EtCalix(4).

transfer, $\Delta_t G^\circ$, of the cation from water to the nonaqueous solvent, *s* (data based on the $\text{Ph}_4\text{AsPh}_4\text{B}$ convention)³⁵ as shown in eq 2.

$$\Delta_{\text{solv}} G^\circ(\text{M}^{n+})(\text{s}) = \Delta_{\text{hyd}} G^\circ(\text{M}^{n+}) + \Delta_t G^\circ(\text{M}^{n+})(\text{H}_2\text{O} \rightarrow \text{s}) \quad (2)$$

As far as univalent cations are concerned, $\Delta_{\text{solv}} G^\circ$ values are calculated from $\Delta_{\text{hyd}} G^\circ$ ³⁴ and single-ion $\Delta_t G^\circ$ values from water to acetonitrile and to methanol reported in the literature.^{33,36,37} Thus, $\Delta_c G^\circ$ values for EtCalix(5) and alkali metal cations in acetonitrile and methanol are plotted against the $\Delta_{\text{solv}} G^\circ$ of these cations in these solvents, and these are shown in Figure 3. This figure demonstrates that these forces (binding and desolvation) are partially compensated showing a shallow selectivity peak where the maximum stability in both solvents is observed for rubidium. For comparison purposes, corresponding data for the ester of the cyclic tetramer EtCalix(4) in these solvents are also included in Figure 3. For this ligand a sharp selectivity peak is observed and the maximum stability is found for the sodium complex in both solvents, acetonitrile and methanol. The main

points of interest in these results are the following: (i) There is significant decrease in the selective capacity of the receptor to interact with these metal cations in moving from the cyclic tetramer to the pentamer. (ii) The selectivity sequence is altered as expected, as the size of the cavity increases. Thus, while EtCalix(4) is selective for sodium, EtCalix(5) interacts with the larger cations. (iii) The medium effect leads to drastic changes in stabilities when EtCalix(4) is the host for alkali metal cations in methanol relative to acetonitrile, while these changes are not substantial in moving from acetonitrile to methanol when EtCalix(5) is the receptor.

Therefore, there is enough experimental evidence as to conclude that EtCalix(4) is far better preorganized to interact with alkali metal cations than EtCalix(5).

At this stage, it seems relevant to assess how the variations in the Gibbs energies of complexation and the selectivity maxima are reflected in the enthalpies of complex formation of these systems.

This is illustrated in Figure 4, where $\Delta_c H^\circ$ values in acetonitrile and methanol are plotted against the standard

enthalpies of solvation^{36,37} of these monovalent cations in these solvents. Quite clearly, the enthalpy (and consequently the entropy) seems to be more sensitive to the involvement of the solvent and effects resulting from changes in the solvent structure upon cation complexation.³³ In methanol, the exothermic maximum for complex formation is for rubidium and EtCalix(5) as shown in terms of Gibbs energies. However in acetonitrile, the shallow selectivity peak observed in the $\Delta_c G^\circ$ values is essentially enthalpy controlled. The monotonic increase in entropy as the cation size increases (from K^+ to Cs^+) leads to a displacement of complex stability in favor of Rb^+ despite that the exothermic maximum is observed for potassium. The enthalpic pattern observed for EtCalix(4) and monovalent cations mirrors that observed in Figure 3 when Gibbs energies were considered. The entropy is a destabilizing factor to the extent that as the enthalpic stability increases, the loss of entropy is highest.

The unavailability of transfer data for all the bivalent cations considered in this paper does not allow one to proceed with the detailed analysis shown above for univalent cations and these ligands in these solvents. This statement is based on the fact that the transfer data for these cations from water to acetonitrile will undoubtedly differ from those to methanol. However, these differences are unlikely to be as dramatic as to alter the trend of solvation and therefore the outcome of this discussion. Inspection of Figure 5 where $\Delta_c G^\circ$ values for bivalent cations are plotted against their hydration Gibbs energies, $\Delta_{hyd} G^\circ$, reveals some interesting features particularly when these data are compared with those previously reported³² for these cations and EtCalix(4) in acetonitrile. Thus, the Gibbs energy of the complexation process becomes less favorable (decrease in stability) as the hydration (or solvation) of the cation increases, revealing once again the competition between the ligand and the solvent for the cation³⁸ in these solvents. In fact, the selectivity peak observed in the complexation of EtCalix(4) and bivalent cations in acetonitrile is nonexistent in the complexation of EtCalix(5) and these cations in these solvents. In moving from the cyclic tetramer to the pentamer ester, the number of binding sites in the hydrophilic region of the macrocycle increases. However, the way that the donor atoms and the lower rim functional groups are arranged in the macrocycle undoubtedly depends on the flexibility of the ligand in solution. A considerable increase in flexibility is expected for the pentaester relative to the tetraester due to the reorientation of the additional aryl unit. As a result, a rather shallow selectivity (stability constants are leveled off) is observed for the larger cations. It seems that in the EtCalix(5), *a number of binding sites for complexation are not able to exert the efficient control upon the ligand binding ability as that found for the tetramer ester and these cations in this solvent.* The linear relationship observed in terms of Gibbs energies is also found in the corresponding plots involving enthalpies (Figure 6). Therefore, the trends observed in the $\Delta_c G^\circ$ values are also reflected in the $\Delta_c H^\circ$ values for these systems in acetonitrile.

Conclusions

From the above discussion it is concluded that (i) solubility data for Calix(5) in a variety of solvents are first reported. These were used to derive the standard Gibbs energies of solution in these solvents, and subsequently, the transfer Gibbs energies of this ligand using acetonitrile as the reference solvent. Comparison with data for other calix[n]arenes ($n = 4, 8$) shows that, among these solvents, the solubility of parent calixarenes reaches a maximum value for the cyclic pentamer and decreases

as the number of phenol units increase. Unlike the cyclic pentamer and octamer, Calix(5) undergoes solvate formation in some dipolar aprotic and apolar solvents. (ii) 1H NMR studies with EtCalix(5) and metal cations in CD_3CN and CD_3OD reveal that the interaction of this ligand with univalent cations in these solvents is only reflected in the $\Delta\delta_{ax-eq}$ values. However, significant chemical shift changes are observed by the addition of bivalent cation salts to EtCalix(5) in CD_3CN . The medium effect is noticeable when moving from acetonitrile to methanol in that, except for Ba^{2+} , no significant chemical shift changes in the proton chemical shifts are observed. (iii) Conductometric studies demonstrated that complexes of 1:1 (cation–ligand) stoichiometry are formed in these solvents. (iv) Correlation between the thermodynamics of cation complexation involving EtCalix(4) and EtCalix(5) and ion solvation (for univalent cations) and hydration (for bivalent ions) led to the conclusion that the number of binding sites in EtCalix(5) is not able to exert the efficient control upon the ligand binding ability as that found for the cyclic tetramer and these cations in acetonitrile.

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