Thermodynamics of Calixarene Chemistry

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Contents

1. Introduction

A wide variety of macrocyclic ligands able to interact with cations, anions, and neutral species are known. These have been isolated from natural resources or are the result of the synthetic developments which have taken place in the last 30 years.[1a,b] Among the latter, calixarenes (products of the base-induced condensation of *p*-substituted phenols and formaldehyde) and their derivatives have received considerable attention in recent years. The chemistry of calixarenes has been extensively discussed in several books[2a−c] and review articles.[2d−g] There are several reasons for the current widespread interest in calixarenes. An important one is the remarkably simple way (single-step procedure) used for the synthesis of the parent compounds. In addition, lower and upper rim functionalization of these macrocycles has resulted in a massive expansion in the range of derivatives available.[2e,g] Within this context, calix(4)arenes are of particular interest. Several conformers (cone, partial cone, 1,2 alternate, and 1,3 alternate) have been isolated. A great deal of efforts have been directed toward calix(4)arene derivatives in "cone" conformation. Their particular molecular architecture with well-defined hydrophobic and hydrophilic regions makes these compounds suitable hosts for neutral and ionic species. Calixarenes are potential building blocks for the design of novel supramolecular systems. This is exemplified in the synthesis of calixarenes bridged across the lower and upper rim or indeed coupled between themselves or to other macrocycles.[2g−i] Calixarenes have found a wide range of applications. A good account on the industrial uses of these macrocycles prior to 1992 has been given by Perrin and Harris.[2j] However in the past few years several internationally significant patents have been published.[2k−u] These patents center mostly on the potential use of calixarenes to sequester metal ions and neutral species, although the ultimate use is fairly broad.

The remarkable growth of the field of calixarene chemistry has been greatly motivated by the interest in finding derivatives able to enter into selective complexation with neutral or ionic species. A quantitative measure of the strength of interaction between two chemical species (macrocycle and guest) in a given solvent is provided by the stability constant. Therefore, the role of experimental thermodynamics in understanding the factors contributing to complex stability and selectivity is important and must not be underestimated. It should be explicity stated that the derivation of accurate thermodynamic data requires knowledge of the speciation in the systems under study. A significant point arising from this statement is that a high level of scrutiny and detail regarding the behavior of chemical species in a given medium is required in thermodynamic studies related to solution processes. It is only on the bases of accurate experimental data that the

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validity of the procedures and force fields of molecular dynamics for the simulation of the selective binding of these ligands with guest species can be tested. These underline the reasons for writing this article, the central issue of which is to review the thermodynamics of calixarenes and their derivatives with a focus on the contribution of these data to the understanding of these ligands and their complexes. Most studies and review articles on macrocyclic ligands[3] focus attention on the thermodynamics associated with the complexation process.

However, information regarding solute−solvent interactions involving reactants (macrocycle and guest) and product (complex) is equally important to analyze solvation effects upon host−guest complexation processes. These effects are reflected in the thermodynamic parameters of transfer ($\Delta_t G°$, $\Delta_t H°$, $\Delta_t S°$) of the macrocycle, L, the guest, G, and the resulting complex (LG) between two solvents (s_1, reference solvent, and s_2). The relationship between complexation ($\Delta_c G°$, $\Delta_c H°$, $\Delta_c S°$) and transfer thermodynamics in terms of Gibbs energies is shown in eq 1.

$$\Delta_c G°_{(s_1)} - \Delta_c G°_{(s_2)} = \Delta_t G°(G)_{(s_1 \rightarrow s_2)} + \Delta_t G°(L)_{(s_1 \rightarrow s_2)} - \Delta_t G°(LG)_{(s_1 \rightarrow s_2)} \quad (1)$$

This equation (equally applicable in terms of enthalpy, $\Delta H°$, or entropy, $\Delta S°$) unambiguously demonstrates that the three parameters of transfer determine the medium effect on the complexation process. Therefore, this review article discusses the solution thermodynamics of calixarenes and their metal-ion complexes as well as the complexation of these ligands with various guests (cations, anions, and neutral species) in different reaction media. Its scope is not simply to tabulate data (it covers a great deal but not all the work published until August 1997) or to report only what was done in the field of solution thermodynamics involving calixarenes but to discuss aspects which need to be addressed and to suggest further research when necessary.

The calix(*n*)arenes and derivatives to be discussed in this review are shown in Chart 1 together with their notations. For general purposes, these are denoted by L; otherwise a numerical system is adopted for each series of derivatives (e.g.: parent calixarenes, **1**; esters, **2**; ketones, **3**; amides, **4**; others, **5**; amines, **6**; acids, **7**; calixcrowns, **8**; upper rim

Table 1. Solution Thermodynamics of *p-tert*-Butylcalix(*n*)arenes (*n* = 4, 6, 8) in Various Solvents at 298.15 K

ligand	solvent[a]	solubility, mol dm^{-3}	$\Delta_s G°$, kJ mol^{-1}	$\Delta_t G°_{MeCN\rightarrow S}$, kJ mol^{-1}	$\Delta_s H°$, kJ mol^{-1}	$\Delta_s S°$, J K^{-1} mol^{-1}	T, K	ref
1a	MeCN	$(4.73 \pm 0.23) \times 10^{-5}$	24.69	0			298.15	4a
	MeOH	$(5.90 \pm 0.13) \times 10^{-4}$	18.43	−6.26			298.15	4a
	EtOH	$(3.30 \pm 0.11) \times 10^{-4}$	19.87	−4.82			298.15	4a
	DMF	$(1.10 \pm 0.01) \times 10^{-3}$	16.89	−7.80			298.15	4a
	n-Hex	$(2.12 \pm 0.08) \times 10^{-4}$	20.97	−3.72			298.15	4a
	$CHCl_3$	$(4.34 \pm 0.04) \times 10^{-3}$	13.48	−11.21			298.15	4a
	PhCN	$(9.47 \pm 0.07) \times 10^{-4}$	17.26	−7.43	-14.20 ± 3.70	−105.5	298.15	4a
	$PhNO_2$	$(1.83 \pm 0.04) \times 10^{-2}$	9.92 ± 0.05	−14.77	-14.67 ± 2.88	-82.5 ± 9.7	298.15	4b
1b	PhCN	$(5.55 \pm 0.04) \times 10^{-3}$	12.88		-23.67 ± 1.98	−122.6	298.15	4c
	$PhNO_2$	$(2.26 \pm 0.03) \times 10^{-2}$	9.40 ± 0.03		-34.85 ± 1.96	-148.4 ± 6.6	298.15	4b
1c	MeCN	1.68×10^{-5}	27.26	0			298.15	4a
	MeOH	$<10^{-5}$					298.15	4a
	EtOH	$<10^{-5}$					298.15	4a
	DMF	2.20×10^{-3}	15.17	−12.09			298.15	4a
	n-Hex	2.51×10^{-5}	26.26	−1.00			298.15	4a
	$CHCl_3$	6.23×10^{-3}	12.59	−14.67			298.15	4a
	PhCN	1.14×10^{-2}	11.09	−16.17	-45.90 ± 5.10	−191.1	298.15	4a
	$PhNO_2$	$(2.57 \pm 0.06) \times 10^{-3}$	14.78 ± 0.06	−12.48	-29.09 ± 1.50	-147.1 ± 5.0	298.15	4b

[a] Abbreviations: MeOH, methanol; EtOH, ethanol; DMF, *N*,*N*-dimethylformamide; MeCN, acetonitrile; n-Hex, n-hexane; $CHCl_3$, chloroform; PhCN, benzonitrile; $PhNO_2$, nitrobenzene.

functionalized, **9**; sulfonyl, **10**). When data are available for more than one ligand within a series, a lettering system is used (e.g.: *p-tert*-butylcalix(4)-arene, **1a**; *p-tert*-butylcalix(6)arene, **1b**; *p-tert*-butyl-calix(8)arene, **1c**, etc.).

2. Solution Thermodynamics of p-tert-Butylcalix-(n)arenes (n = 4, 6, 8)

2.1. Solubilities, Enthalpies, and Entropies of Solution

The open and accessible nature of the hydrophobic and hydrophilic regions of calixarenes and their derivatives reflects the fact that the solvent must strongly influence host−guest complexation processes involving these ligands. It has been already shown[4a] that the solution thermodynamics of calixarenes and their derivatives must be characterized in a number of different solvents in order to enhance the understanding of the effect of ligand solvation upon complexation. Solubilities of *p-tert*-butylcalix(4)arenes (*n* = 4, 6, 8) (L_n) referred to the solid (sol.) in equilibrium with its saturated solution (s) (eq 2) in a variety of

$$L_n(\text{sol.}) \rightarrow L_n(\text{s}) \qquad (2)$$

solvents at 298.15 K have been reported[4a−c] and data listed in Table 1. In cases where no solvate formation was detected by exposing the solid for several days to a saturated atmosphere of the solvent, solubility data referred to the standard state of 1 mol dm^{-3} were used to derive the solution Gibbs energies, $\Delta_s G°$, of these macrocycles in these solvents. The changes in solvation of these solutes from a reference solvent (s_1) to another (s_2) were assessed from the standard transfer Gibbs energies, $\Delta_t G°$ [$\Delta_t G° = \Delta_s G°(s_2) - \Delta_s G°(s_1)$] for the process represented in eq 3.

$$L_n(s_1) \rightarrow L_n(s_2) \qquad (3)$$

The most striking feature of the data is the selective solvation that these ligands undergo in the various solvents to the extent that, on the basis of $\Delta_t G°$ values, solvation indexes for **1a**,**c** were for the first time established. Enthalpies of solution, $\Delta_s H°$, derived from calorimetric measurements are much more accurate than those calculated from the temperature coefficient of solubility.[3] However, these data are scarce due to the relatively low solubility of these ligands in most solvents or, in some cases, their slow rate of dissolution. In classical solution calorimetry these pose serious limitations. However, recent advances in solution microcalorimetry are likely to overcome these limitations.[5a,b] Standard entropies of solution, $\Delta_s S°$, were calculated from a combination of Gibbs energies and enthalpies in these solvents. The importance of assessing the enthalpic and entropic contributions to the Gibbs energy of these processes is discussed in section 3.1.2.

2.2. Acid Dissociation Constants

The first attempt to determine the acid dissociation constant ($pK_a = -\log K_a$) of *p-tert*-butylcalix(*n*)arenes in tetrahydrofuran at 298 K was made by Shinkai et al.[6a] These data were derived from the combination of (i) the equilibrium constant for the proton-transfer reaction (K_p) between the calixarene (L_n) and a spectrophotometric indicator in its basic form (Pic^- = picrate) in tetrahydrofuran (THF) (eq 4) and (ii)

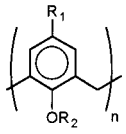
$$L_n(\text{THF}) + Pic^-(\text{THF}) \xrightarrow{K_p} L_n^-(\text{THF}) + \text{HPic(THF)} \qquad (4)$$

$$\text{HPic}(H_2O) \xrightarrow{K_a} H^+(H_2O) + Pic^-(H_2O) \qquad (5)$$

the acid dissociation constant of picric acid (PicH) in water (eq 5). Clearly the outcome of eqs 4 and 5 cannot be equated to the dissociation process in THF. A similar procedure has been used to estimate the pK_a value of *p*-allylcalix(4)arene in CD_3CN[7a] and is subject to the same reservations.

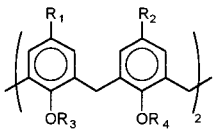
The dissociation of *p-tert*-butylcalix(*n*)arenes (*n* = 4, 6, 8) in benzonitrile (PhCN) at 298.15 K has been investigated by Danil de Namor and co-workers[4b,c] by potentiometry. In the case of the cyclic tetramer,

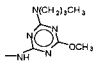
Chart 1

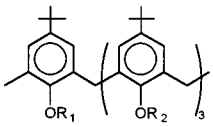


Ligand	n	R_1	R_2
1a	4	tBu	H
1b	6	"	H
1c	8	"	H
2a	4	"	CH_2CO_2Et
2b	"	"	CH_2CO_2Me
2c	"	"	CH_2CO_2nBu
2d	6	"	CH_2CO_2Et
2e	4	"	CH_2CO_2tBu
2f	"	"	CH_2CO_2Ph
2g	"	"	$CH_2CO_2CH_2Ph$
2h	"	"	$CH_2CO_2CH_2COPh$
2i	"	"	$CH_2CO_2CH_2CH_2OMe$
2j	"	"	$CH_2CO_2CH_2CH_2SMe$
2k	"	"	$CH_2CO_2CH_2CF_3$
2l	"	"	$CH_2CO_2CH_2C{\equiv}CH$
3a	"	"	CH_2COMe
3b	"	"	CH_2COPh
3c	"	"	CH_2COtBu
4a	"	"	CH_2CONEt_2
4b	"	"	$CH_2CON(CH_2)_4$
4c	"	"	CH_2CONH_2
4d	"	"	$CH_2CON(iPr)_2$
5t	"	"	
5u	"	"	$CH_2CH(OH)CH_2NH_2$
5v	8	"	$(CH_2CH_2O)_nH$
5x	4	"	$(CH_2)_3SO_3H$
5y	6	"	"
5z	8	"	"
5aa	6	nBu	"
5ab	6	tBu	
5ac	4	H	Me
6a	"	tBu	$(CH_2)_2\ N(CH_3)_2$
6b	"	"	$(CH_2)_2\ N(Et)_2$
6c	"	"	$(CH_2)_2\ N(iPr)_2$
6d	"	"	$(CH_2)_2$cyclohexylamine
6e	"	"	$(CH_2)_2$cyclopentylamine
6f	"	"	$(CH_2)_2$ morpholine
6 l	4	tBu	

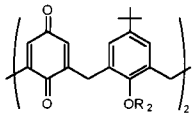
6m	"	"	
6n	"	"	
7a	"	"	CH_2CO_2H
9a	4	$SO_2NHCH_2CH_2OH$	$CH_2CH_2OCH_3$
9b	"	$SO_2N(CH_2CH_2OH)_2$	$CH_2CH_2OCH_3$
9c	"	$SO_2NHC(CH_2OH)_3$	$CH_2CH_2OCH_3$
9d	"	$SO_2NHCH_2CH_2OH$	$CH_2CO_2CH_2CH_3$
9e	"	$SO_2N(CH_2CH_2OH)_2$	$CH_2CO_2CH_2CH_3$
9f	"	$SO_2NHC(CH_2OH)_3$	$CH_2CO_2CH_2CH_3$
9g	4	$SO_2N(CH_2CH_2OH)_2$	H
9h	"	NO_2	"
9m	6	$CH_2PO_3H_2$	Me
9n	4	$CH_2SSCH_2CH(NH_2ClH)CO_2H$	Me
9o	6	"	"
9v	5	CH_2CO_2H	H
9w	6	"	"
9x	7	"	"
9y	8	"	"
9z	6	"	Me
9aa	5	$CH_2N(CH_2CH{=}CH_2)_2$	H
9ab	6	"	"
9ac	7	"	"
9ad	8	"	"
9ae	4	COOH	C_8H_{17}
9an	6	$CH_2NMe_3^+Cl^-$	Me
9aq	6	$SO_2N(CH_2CH_2OH)_2$	Me
9ar	8	"	"
9as	4	$NMe_3^+Cl^-$	Me
9at	6	$NMe_3^+Cl^-$	"
9au	6	$NMe_3^+Cl^-$	C8H17
10a	4	SO_3H	H
10b	5	"	H
10c	6	"	H
10d	8	"	H
10e ***(cone)*** **10f** ***(part.cone)***	4	"	CH_2COOH
10g	6	"	CH_2COOH
10h	6	SO_3Na	$CH_2CH(CH_3)CH_2CH_3$
10i	8	"	"



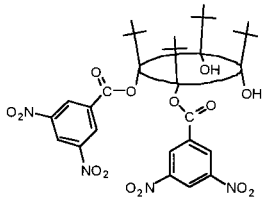
Ligand	R_1	R_2	R_3	R_4
5o	tBu	tBu"	H	
5p	"	"	"	Me
5q	H	"	"	"
5r	"	"	"	
5s	"	H	"	Me
5w	tBu	tBu	Pr	
6g	"	"	$(CH_2)_2SCH_3$	$(CH_2)_2\ N(CH_3)_2$
6h	"	"	"	$(CH_2)_2\ N(CH_2CH_3)_2$
6i	"	"	"	$(CH_2)_2$cyclopentylamine
6j	"	"	"	$(CH_2)_2$cyclohexylamine
6k	"	"	"	$(CH_2)_2$ morpholine
6o	H		$CH_2CH_2OCH_2CH_3$	$CH_2CH_2OCH_2CH_3$
7b	tBu	tBu	CH_2CO_2H	H
7c	"	"	"	CH_2CO_2tBu



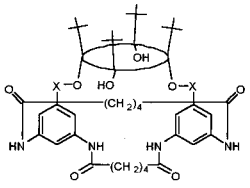
Ligand	R_1	R_2
5d	PhCO	H
5e	3-CNC_6H_4CO	"
5f	4-ClC_6H_4CO	"
5g	4-MeC_6H_4CO	"
5h	4-$NO_2C_6H_4CO$	"
5i	3-ClC_6H_4CO	"
5j	3-$NO_2C_6H_4CO$	"
7d	CH_2CO_2H	CH_2CO_2Et
7e	"	CH_2CO_2tBu
7f	"	H



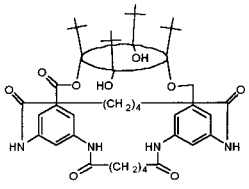
5a, R_2 = Me
5b, R_2 = CH_2CONEt_2
5c, R_2=CH_2CO_2Et



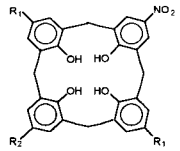
5n



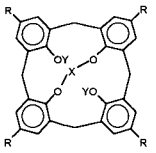
5k (X = C=O)
5l (X = CH_2)



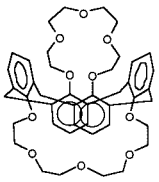
5m



Ligand	R_1	R_2
9i	Me	Me
9j	Me	tBu
9k	tBu	Me
9l	tBu	Dodec



Ligand	X	Y	R
8a *(1,3 - alternate)*	$-CH_2CH_2(OCH_2CH_2)_4-$	iPr	H
8b *(1,3-alternate)*	"	nPr	H
8c *(cone)*	"	Me	H
8d *(cone)*	"	"	tBu
8s *(cone)*	$-CH_2CH_2(OCH_2CH_2)_3-$	iPr	H



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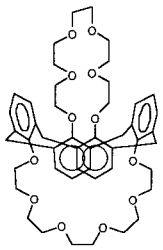

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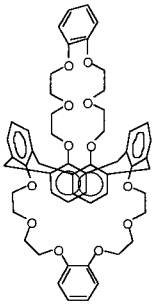

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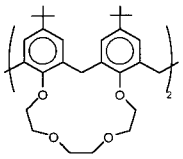

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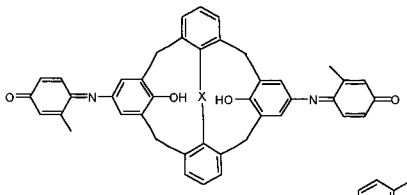
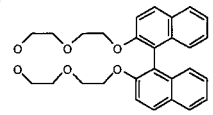
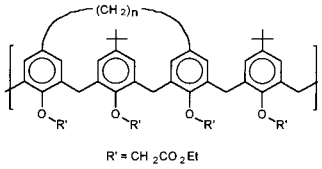
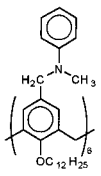


8r



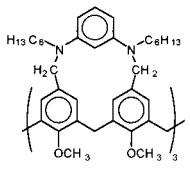


R' = CH_2CO_2Et



9af

Ligand	n	Ligand	n
9p	5	**9s**	8
9q	6	**9t**	9
9r	7	**9u**	10



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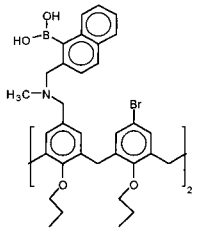
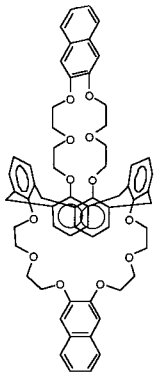
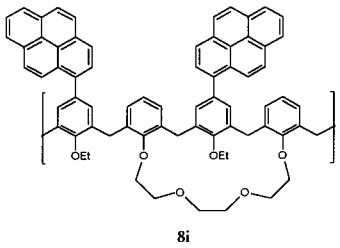


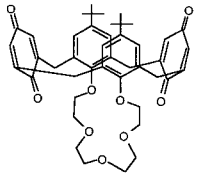
9ah



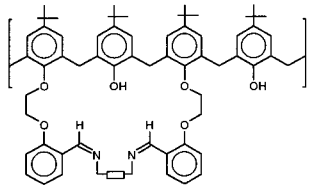
8h



8i



8m

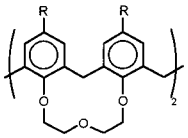


8j-8l

8j = $(CH_2)_3$

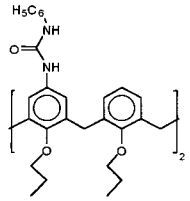
8k = $(CH_2)_4$

8l =

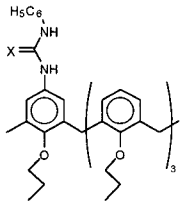


8n-8p

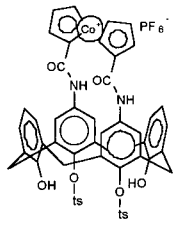
8n, R=H
8o, R=tBu
8p, R=cyclohexyl



9ai

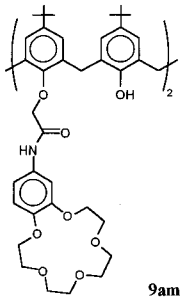


9aj (X=O)
9ak (X=S)

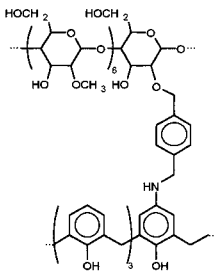


ts = $O_2SC_6H_4Me$ -*p*

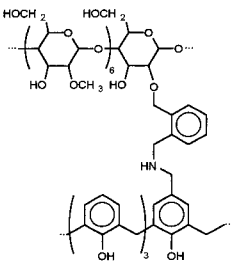
9al



9am



9ao



9ap

1a, the value (expressed as $pK_a = -\log K_a = 19.33 \pm 0.09$) for just the first dissociation was reported. For the cyclic hexamer, **1b**, pK_a values for the first two dissociations ($pK_{a_1} = 17.02 \pm 0.08$, $pK_{a_2} = 20.89 \pm 0.08$) were given, while for the cyclic octamer, **1c**, corresponding data for the first four dissociations ($pK_{a_1} = 17.42 \pm 0.07$, $pK_{a_2} = 20.01 \pm 0.08$, $pK_{a_3} = 27.0$, $pK_{a_4} = 30.4$) were obtained. A strict comparison

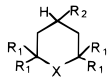
Table 2. Equilibria Data, Enthalpies, and Entropies for the Interaction of Calix(*n*)arenes (*n* = 4, 6, 8) and Neutral Species

ligand	guest[a]	solvent	log K_s	method	T, K	ref
1a	*tert*-butylamine	MeCN	4.68	spect	?	7a
	neopentylamine	MeCN	4.78	spect	?	7a
	G7	MeCN	3.81	spect	298	11
	G8	MeCN	3.6	spect	298	11
	G9	MeCN	3.5	spect	298	11
	G10	MeCN	3.50	spect	298	11
	G11	MeCN	3.61	spect	298	11
	G12	MeCN	3.59	spect	298	11
	G13	MeCN	3.5	spect	298	11
	triethylamine	PhCN	2.39 ± 0.04	cal	298	4b
			$\Delta_c H°$ (kJ mol^{-1}) $= -27.33 \pm 0.02$			
			$\Delta_c S°$ (J K^{-1} mol^{-1}) $= -45.9 \pm 0.7$			
			log $K_p = -1.35$			
	atropine	PhCN	log $K_p = -1.62$	pot.	298	4b
	cryptand 22	PhCN	log $K_p = -1.54$	pot.	298	4b
	cryptand 222	PhCN	log $K_p = -1.35$	pot.	298	4b
	triethylamine	$PhNO_2$	1.57 ± 0.01	cal	298	4b
			$\Delta_c H°$ (kJ mol^{-1}) $= -40.25 \pm 0.01$			
			$\Delta_c S°$ (J K^{-1} mol^{-1}) $= -105.0 \pm 0.1$			
	tert-butylamine	PhCN	log $K_p = -1.54$	cal	298	4b
1b	*tert*-butylamine	MeCN	5.90	spect	?	7a
	tert-butylamine	PhCN	0.77 (log K_p)	pot.	298	4c
	neopentylamine	MeCN	5.90	spect	?	7a
	cryptand 22	PhCN	3.04 ± 0.04	cond	298	4c
			(log $K_p = 1.16 \pm 0.05$)			
			(log $K_{ip} = 1.88 \pm 0.03$)			
			(log $K_p = 0.77$)	pot.	298	4c
		$PhNO_2$	2.06	cond	298	4b
			log $K_p = 0.93$)	cond	298	4b
			(log $K_{ip} = 1.13$)	cond		
	cryptand 222	PhCN	3.18 ± 0.01	cond	298	4b
			(log $K_p = 1.45 \pm 0.01$)	cond		
			(log $K_{ip} = 1.73 \pm 0.01$)	cond		
			(log $K_p = 1.38$)	pot.	298	4c
		$PhNO_2$	3.20	cond	298	4b
			(log $K_p = 1.07$)	cond		
			(log $K_{ip} = 2.13$)	cond		
	triethylamine	PhCN	3.19 ± 0.07	cond	298	4c
			(log $K_p = 0.75 \pm 0.09$)	cond		
			(log $K_{ip} = 2.44 \pm 0.05$)	cond		
			(log $K_p = 0.96$)	pot.	298	4c
		$PhNO_2$	1.69	cond	298	4b
			(log $K_p = 0.33$)	cond		
			(log $K_{ip} = 1.36$)	cond		
	atropine	PhCN	(log $K_p = 0.69$)	pot.		4c
1c	cryptand 22	PhCN	3.24 ± 0.18	cond	298	4c
			(log $K_p = 0.62 \pm 0.19$)	cond		
			(log $K_{ip} = 2.62 \pm 0.07$)	cond		
			(log $K_p = 0.37$)	pot.	298	4c
			3.15 ± 0.04	cal	298	4c
		$PhNO_2$	2.30	cond	298	4b
			(log $K_p = 1.09$)	cond		
			(log $K_{ip} = 1.21$)	cond		
	atropine	PhCN	3.29 ± 0.03	cond	298	4c
			(log $K_p = 0.42 \pm 0.06$)	cond		
			(log $K_{ip} = 2.87 \pm 0.05$)	cond		
			(log $K_p = 0.29$)	pot.	298	4c
			3.30 ± 0.10	cal	298	4c
	cryptand 222	PhCN	3.70 ± 0.20	cond	298	4c
			(log $K_p = 1.18 \pm 0.22$)	cond		
			(log $K_{ip} = 2.52 \pm 0.09$)	cond		
			(log $K_p = 0.98$)	pot	298	4c
			3.84 ± 0.06	cal	298	4c
		$PhNO_2$	2.74	cond	298	4b
			(log $K_p = 0.80$)	cond	298	4b
			(log $K_{ip} = 1.94$)	cond		
	triethylamine	PhCN	3.98 ± 0.18	cond	298	4c
			(log $K_p = 0.75 \pm 0.20$)	cond		
			(log $K_{ip} = 3.23 \pm 0.08$)	cond		
			(log $K_p = 0.56$)	pot.		4c
			3.97 ± 0.24	cal	298	4c

Table 2 (Continued)

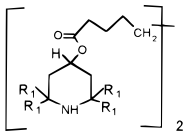
ligand	guest[a]	solvent	log K_s	method	T/K	ref
	tert-butylamine	PhCN	3.18 ± 0.05	cal	298	4c
			(log K_p = 0.37)	pot.	298	4c

[a] Structures:



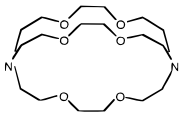
G7- G12

Guest	X	R_1	R_2	Guest	X	R_1	R_2
G7	CH_2	H	NH_2	G10	NH	CH_3	NH_2
G8	NH	H	H	G11	NH	CH_3	OH
G9	NH	CH_3	H	G12	N-CH_3	CH_3	OH

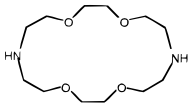


R_1=Me

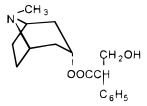
G13



Cryptand 222



Cryptand 22



Atropine

of pK_a values for parent calixarenes in PhCN relative to the monomeric *tert*-butylphenol in the same solvent and temperature cannot be made since its pK_a value in this solvent has not been reported. However, literature data[8] for phenol in acetonitrile (MeCN) (pK_a = 26.6 at 298.15 K), a solvent with similar properties to PhCN, suggests that the acidity of parent calixarenes is higher than that for phenol by about 7−9 pK_a units. In fact, this result is not dramatically far from the differences in acidity predicted for calix(4)arenes and 2,4,6-trimethylphenol from free energy perturbation (FEP) methods.[9a]

2.3. Interactions with Organic Cations and Metal Cations

Extensive studies on interactions of lanthanides and calixarene anions have been carried out by Bünzli and Harrowfield,[10a] and some very interesting chemistry has been reported by these authors. Apparent equilibrium data for 1:1 and 2:1 europium−**1c** (anion) complexes at 298 K in *N*,*N*-dimethylformamide (DMF) have been published by this group. As stated by Bünzli and Harrowfield, the degrees of deprotonation of the cyclic octamer or its Eu(III) complexes in a 10-fold excess of triethylamine are unknown. A further contribution of this group is that of showing interactions between calixarene anions (including L^{2-} and L^{3-}) and quaternary ammonium [choline, acetylcholine, and $(CH_3)_4N^+$] cations in acetone (^{1}H NMR) at 298 K and in MeCN (UV measurements) at 303 K. A relatively strong interaction takes place between the tervalent anion of **1c** and these cations [choline and $(CH_3)_4N^+$] in MeCN (log $K_s \cong 5.50$). No selective behavior is observed by this ligand between these two quaternary ammonium cations in this solvent.[10b]

More recently estimated stability constants for the monoanion of *p*-*tert*-butylcalix(4)arene and alkali-metal cations in Me_2CO (Na^+ and Cs^+) at 293 K and in MeCN (Li^+, Na^+, K^+, Rb^+, and Cs^+) at 298 K have been reported. In acetone, ^{23}Na and ^{13}Cs NMR measurements were carried out while UV spectrophotometry was used to derive equilibrium data in acetonitrile. Fitting the experimental data for lithium required the assumption that 1:1 and 2:1 (metal cation:ligand) complexes are formed with this cation in acetonitrile. On the basis of previous studies in the field of calixarenes, Abidi et al. suggested the possibility of a disproportionation reaction of the monoanion into the dianion and the neutral ligand when an excess of Li^+ is present in solution. It was also noted that X-ray crystallographic studies of a Li_2L calixarene complex was previously reported. Unlike for lithium, data for other alkali metals are consistent with the formation of 1:1 complexes.

Experimental data were complemented by computational studies involving molecular dynamics and free energy perturbation simulation. The theoretical calculations suggest a decrease in complex stability from lithium to cesium.

2.4. Interactions with Neutral Species

Most data reported on these systems are referred to the interaction of calixarenes with amines (G) in solution (Table 2).

The interaction of *p*-substituted calix(*n*)arenes (*n* = 4, 6) and aliphatic amines in MeCN was first discussed by Gutsche and co-workers[7a] as a two-step process involving a proton-transfer reaction from the calixarene to the amine (K_p) followed by the ion-pair formation (K_{ip}) between the protonated amine and the calixarenate anion as described by eq 6.

$$L_n(s) + G(s) \xrightarrow{K_p} L_n^-(s) + GH^+(s) \xrightarrow{K_{ip}} L_n^-GH^+(s) \quad (6)$$

These authors used UV spectrophotometry and ^{1}H NMR spectroscopy to study these interactions. The spectrophotometric study was undertaken at low calixarene concentrations at which ion-pair formation was considered negligible. Spectral changes analyzed by the use of the Benesi−Hildebrand equation and by a computer program based on a similar expression were used to derive the equilibrium constant, K_p, for the proton transfer process. Accord-

ing to the authors, the latter treatment leads to more accurate data than the former, and therefore, these are the data included in Table 2. The NMR study was conducted with the amine and the calixarene concentrations sufficiently high that proton transfer could subsequently be considered effectively complete. Thus, equilibrium constants for the ion-pair process were derived by study of the concentration-dependent chemical shifts and relaxation times of the amine protons in 1:1 calixarene−amine mixtures. On the basis of two-dimensional NOE experiments, a proton transfer followed by the formation of an *endocalix* complex was suggested for the *p*-allylcalix-(4)arene-*tert*-butylamine system in MeCN. Görmar and co-workers[11] reported UV spectrophotometric studies on the interactions of *p*-*tert*-butylcalix(n)-arenes ($n = 4, 8$) and various cyclic amines, including diamines in MeCN. Representative data for the cyclic tetramer **1a** are listed in Table 2. Both exocyclic and endocyclic nitrogen atoms were involved in these interactions. Bidentate amines formed 1:2 amine−calixarene complexes. Complex stoichiometries were determined by the continuous variation method, and the Benesi−Hildebrand method was used to derive equilibrium data for these processes. No indication was given about the processes to which the data are referred.

Danil de Namor et al.[4b,c] have reported equilibrium constants (K_s) for the interaction of amines (including macrocyclic amines such as cryptand 222 and cryptand 22) and *p*-*tert*-butylcalix(*n*)arenes ($n = 4, 6, 8$) in PhCN and nitrobenzene ($PhNO_2$) at 298.15 K with the overall process dissected into component proton transfer (K_p) and ion-pair association (K_{ip}) terms using conductimetry.[4b,c] Unlike **1b**,**c**, very low conductivities were reported for the interaction of **1a** and these amines in these solvents. In addition, equilibrium data for the proton-transfer process (K_p) by potentiometry were calculated from combination of the proton dissociation constants of the calixarenes and the protonation constants of the amines in the appropriate solvents, individually determined by potentiometry. The precision of equilibrium data derived from the latter method was found to be higher than the conductometric equilibrium constants. Calorimetric studies of the overall process have also been used to simultaneously obtain stability constants and derived Gibbs energies, enthalpies, and entropies associated with these processes. A reasonable agreement was found between K_s values obtained calorimetrically and those from conductimetry. These studies were complemented by ^{13}C NMR studies to explain the interactions of these macrocycles and cryptand 222 in PhCN. It was suggested that cryptand 222 is likely to host the proton released by the cyclic octamer in its cavity. No suggestion was made that any of these amines form endo complexes with parent calixarenes.

The interaction of quinones with **1b** in solution has been reported by Chawla[12] with equilibrium data determined in chloroform by UV spectrophotometry. The NMR spectra of calixarene−quinone mixtures at low temperature were said to be consistent with the formation of endo complexes.

3. Solution Thermodynamics of Lower Rim Functionalized Calixarenes

3.1. Calixarene Esters, Amides, Ketones, Acids, and Amines

3.1.1. Interactions with Metal Cations, Organic Cations, and Protons

An interesting development of growing interest in the field of calixarene chemistry is the synthesis of derivatives obtained by the substitution (partial or total) of the phenolic hydrogens in the lower rim of the parent compounds by suitable functional groups. Among these are esters, amides, ketones, acids, amines and others which are able to complex cations. McKervey et al.[13a] have given an account on cation complexation by calixarenes. As far as the thermodynamic content of this article is concerned, there are concepts that deserve some comments. Under the heading of stability and association constants, these authors only defined the stability constant. Within the thermodynamic context of this review, it is important to define carefully the parameters relating to the complexation process, as reported in Table 3. The stability constants ($\log K_s$) and derived standard Gibbs energies, $\Delta_c G°$, enthalpies, $\Delta_c H°$, and entropies, $\Delta_c S°$, of complexation of lower rim calixarene derivatives (L) and cations, M^{n+}, in various solvents (s) refers to the process in eq 7.

$$M^{n+}(s) + L(s) \rightarrow ML^{n+}(s) \qquad (7)$$

The thermodynamic stability constant, K_s (molar scale), is defined by eq 8 in which a and γ denote

$$K_s = \frac{a_{ML^{n+}}}{a_{M^{n+}} \cdot a_L} = \frac{[ML^{n+}]\gamma_{\pm ML^{n+}}}{[M^{n+}]\gamma_{\pm M^{n+}} \cdot [L]\gamma_L} \cong \frac{[ML^{n+}]}{[M^{n+}][L]} \qquad (8)$$

activity and activity coefficients, respectively. The inequality of eq 8 holds provided that the solutions are relatively dilute, in which case $\gamma_L \cong 1$ and $\gamma_{\pm ML^{n+}} = \gamma_{\pm M^{n+}}$. For processes involving charged ligands, particularly multicharged ligands, it may be necessary to consider explicity the activity coefficients of the species concerned in the equilibria. In solvents of low dielectric constants, such as chloroform or water (D_2O)-saturated chloroform, where ion pair formation becomes important, it is common to define an "association constant", K_{assn}, which refers to the following process

$$M^+X^-(s) + L(s) \rightarrow ML^+X^-(s) \qquad (9)$$

involving ion-pairs rather than free ions. It is important not to confuse K_{assn} and K_s as they refer to two different processes. Caution should be attached to the interpretation of association constants determined in low dielectric media, particularly, chloroform and tetrahydrofuran, as they relate to ion-pair as well as binding processes. As these constants do not refer to a well-characterized thermodynamic process, they do not reflect "true" stability constants, and therefore, these data are not included. These are

Table 3. Thermodynamic Parameters of Complexation of Lower Rim Calixarene Derivatives with Cations in Nonaqueous Media

ligand	cation	solvent	T, K	log K_s	method[g]	$\Delta_c G°$, kJ mol^{-1}	$\Delta_c H°$,[h] kJ mol^{-1}	$\Delta_c S°$, J K^{-1} mol^{-1}	ref
2a	Li^+	MeOH	298	2.6	spect (ref 13a), 0.01 M TEAC	−14.84	5.05	66.7	4f
		MeCN	298	6.40 ± 0.30	spect, 0.01 M TEAP				13a
		MeCN	298	6.10 ± 0.20	cond				4d
		MeCN	298	6.10 ± 0.19	pot.(a), 0.05 M TEAP				4d
		MeCN	298	6.20 ± 0.25	av of spect, cond, and pot	−35.39 ± 1.43	−48.78	−44.9	f
		PhCN	298	5.49 ± 0.22	av pot. and cal (micro)	−31.34 ± 0.55	−57.20 ± 1.80	−86.7	4d
	Na^+	MeOH	298	5.0[a]	spect[a] (ref 13a), 0.01 M TEAC	−28.5	−45.60	−57.2	4f
		MeCN	298	5.8	spect, 0.01 M TEAP				13a
		MeCN	298	7.82 ± 0.20	cond				4d
		MeCN	298	7.53 ± 0.15	pot.(a), 0.05 M TEAP				4d
		MeCN	298	7.97 ± 0.04	ISE, 0.05 M TEAP				4e
		MeCN	298	7.77 ± 0.23	av of cond, pot.(a), and ISE	−44.36 ± 1.32	−69.20 ± 0.96	−83.3	f
		PhCN	298	6.17	cal (micro)				4d
		PhCN	298	7.57 ± 0.30	pot.(a), 0.05 M TEAP	−43.22 ± 1.71	−50.70 ± 1.10	−24.9	4d
	K^+	MeOH	298	2.40	spect (ref 13a), 0.01 M TEAC	−13.70	−14.22	−1.7	4f
		MeCN	298	4.5	spect, 0.01 M TEAP				13a
		MeCN	298	4.04 ± 0.03	cal (micro)	−23.06 ± 0.07	−45.75 ± 0.45	−76.1	4d
		PhCN	298	3.51 ± 0.03	cal (micro)	−20.04 ± 0.07	−23.21 ± 0.86	−10.6	4d
	Rb^+	MeOH	298	3.1	spect, 0.01 M TEAC				13a
		MeCN	298	1.9	spect, 0.01 M TEAP				13a
		MeCN	298	2.05 ± 0.03	cal (micro)	−11.70 ± 0.07	−23.34 ± 1.36	−39.0	4d
	Cs^+	MeOH	298	2.7	spect, 0.01 M TEAC				13a
		MeCN	298	2.8	spect (ref 13a), 0.01 M TEAP	−15.98	−11.48 (macro)	15.1	4f
		MeCN	298		spect−cal (micro) (see text)		no heat detected (micro)		4d
	Ag^+	MeOH	298	4.0[b]	spect, 0.01 M TEAC				13a
		MeCN	298	2.5	spect, 0.01 M TEAP				13a
	Tl^+	MeOH	298	1.6	spect, 0.01 M TEAC				13a
	Ca^{2+}	MeCN	298	∼6.0	cal (macro and micro)				4e
	Sr^{2+}	MeCN	298	5.34 ± 0.02	cal (macro and micro)				4e
	Ba^{2+}	MeCN	298	4.19 ± 0.03	cal (macro and micro)				4e
2b	Li^+	MeCN	298	5.61 ± 0.06	pot.(a), 0.05 M TEAP	−32.02 ± 0.17	−37.80 ± 0.80	−19.4	4d
		PhCN	298	5.63 ± 0.06	pot.(a), 0.05 M TEAP	−32.14 ± 0.34			4d
		PhCN	298	5.27 ± 0.03	cal (micro)	−30.08 ± 0.17	−47.02	−56.8	4d
		PhCN	298	5.45 ± 0.21	av cal and pot.(a)	−31.11 ± 0.07	−47.02 ± 0.29	−53.4	4d
	Na^+	MeCN	298	6.97 ± 0.14	pot.(a), 0.05 M TEAP	−39.79 ± 0.80	−63.00 ± 0.50	−77.8	4d
		PhCN	298	6.78 ± 0.04	pot.(a), 0.05 M TEAP	−38.70 ± 0.10	−41.08 ± 1.23	−8.0	4d
	K^+	MeCN	298	4.01 ± 0.03	cal (micro)	−22.89 ± 0.07	−40.63 ± 0.70	−59.4	4d
		PhCN	298	2.70 ± 0.07	cal (micro)	−15.41 ± 0.17	−21.34 ± 0.68	−19.9	4d
2c	Li^+	MeCN	298	6.21 ± 0.05	pot.(a), 0.05 M TEAP	−35.45 ± 0.29	−46.3 ± 1.00	−36.4	4d
		PhCN	298	6.09 ± 0.05	pot.(a), 0.05 M TEAP	−34.76 ± 0.29	−56.70 ± 0.78	−73.6	4d
	Na^+	MeOH	298	5.6	pot.(c), 0.01 M TEAP				13a
		MeCN	298	7.67 ± 0.22	pot.(a), 0.05 M TEAP	−43.78 ± 1.26	−67.80 ± 1.0	−80.6	4d
		PhCN	298	7.56 ± 0.05	pot.(a), 0.05 M TEAP				4d
			298	7.32 ± 0.16	pot.(b), 0.05 M TEAP				
		PhCN	298	7.44	av pot.(a) and pot.(b)	−42.47	−50.7 ± 1.33	−27.6	*f*
	K^+	MeOH	298	2.7	pot.(c), 0.01 M TEAP				13a
		MeCN	298	2.05 ± 0.03	cal (micro)	−11.67 ± 0.20	−26.91 ± 1.54	−51.0	4d
		MeCN	298	4.38	cond				4d
		PhCN	298	3.48 ± 0.06	cal (micro)	−19.86 ± 0.15	−24.30 ± 0.33	−14.9	4d
2d	Li^+	PhCN	298	4.37 ± 0.05	cal	−24.95 ± 0.28	−21.04 ± 1.32	13.1	4h
		MeCN	298	3.7	spect, 0.01 M TEAP				13a
	Na^+	PhCN	298	5.31 ± 0.04	cal	−30.31 ± 0.23	−29.17 ± 0.74	3.8	4h
		MeCN	298	3.5	spect, 0.01 M TEAP				13a
	K^+	PhCN	298	6.14 ± 0.04	cal	−35.05 ± 0.23	−47.68 ± 1.30	−42.4	4h
		MeCN	298	5.1	spect, 0.01 M TEAP				13a
	Rb^+	PhCN	298	4.77 ± 0.04	cal	−27.23 ± 0.23	−29.66 ± 1.33	−8.2	4h
		MeCN	298	4.8	spect, 0.01 M TEAP				13a
	Cs^+	MeCN	298	4.3	spect, 0.01 M TEAP				13a
3a	Li^+	MeOH	298	2.7	spect, 0.01 M TEAC				13a
		MeCN	298	5.8	spect, 0.01 M TEAP				13a
	Na^+	MeOH	298	5.1	spect, 0.01 M TEAC				13a
		MeCN	298	5.6	spect, 0.01 M TEAP				13a
	K^+	MeOH	298	3.1	spect, 0.01 M TEAC				13a
		MeCN	298	4.4	spect, 0.01 M TEAP				13a
	Rb^+	MeOH	298	3.6	spect, 0.01 M TEAC				13a
		MeCN	298	1.7	spect, 0.01 M TEAP				13a
	Cs^+	MeOH	298	3.1	spect, 0.01 M TEAC				13a
		MeCN	298	3.7	spect, 0.01 M TEAP				13a
	Ag^+	MeOH	298	4.7	spect,[b] 0.01 M TEAC				13a
		MeCN	298	2.4	spect, 0.01 M TEAP				13a

Table 3 (Continued)

ligand	cation	solvent	T, K	log K_s	method[g]	$\Delta_cG°$, kJ mol^{-1}	$\Delta_cH°$,[h] kJ mol^{-1}	$\Delta_cS°$, J K^{-1} mol^{-1}	ref
3b	Li^+	MeCN	298	6.3	spect, 0.01 M TEAP				13a
	Na^+	MeCN	298	6.1	spect, 0.01 M TEAP				13a
	K^+	MeCN	298	5.1	spect, 0.01 M TEAP				13a
	Rb^+	MeCN	298	4.5	spect, 0.01 M TEAP				13a
	Cs^+	MeCN	298	5.6	spect, 0.01 M TEAP				13a
3c	Li^+	MeOH	298	1.8	spect, 0.01 M TEAC				13a
	Na^+	MeOH	298	4.3	spect, 0.01 M TEAC				13a
	K^+	MeOH	298	5.0	spect, 0.01 M TEAC				13a
	Rb^+	MeOH	298	1.6	spect, 0.01 M TEAC				13a
	Cs^+	MeOH	298	<1	spect, 0.01 M TEAC				13a
4a	Li^+	MeOH	298	3.9	spect, 0.01 M TEAC				13b
		MeOH	298	4.1 ± 0.2	cal	−22.2 ± 0.6	−7 ± 2	50 ± 10	13b
		MeCN	298	≥8.5	pot.	≥−48.4	−55 ± 2	≥−22	13b
	Na^+	MeOH	298	7.9 ± 0.1	pot.(c), 0.01 M TEAP	−45.0 ± 0.6	−50.6 ± 0.8	−20 ± 3	13b
		MeCN	298	≥8.5	pot.	≥−48.4	−79 ± 4	≥−103	13b
	K^+	MeOH (I = 0.01 M)	298	5.8 ± 0.1	pot.(c)/spect[c]	−33.1 ± 0.6	−42.4 ± 0.2	−31 ± 3	13b
		MeCN	298	≥8.5	pot.	≥−48.4	−64 ± 2	≥−52	13b
	Rb^+	MeOH	298	3.8	spect, 0.01 M TEAC				13b
		MeOH	298	3.8 ± 0.1	pot.	−21.6 ± 0.6	−17.5 ±0.8	13 ± 3	13b
		MeCN	298	5.7 ± 0.1	pot.(c), 0.01 M TEAP	−32.5 ± 0.6	−37.2 ± 0.8	−17 ± 3	13b
	Cs^+	MeOH	298	2.4	spect, 0.01 M TEAC				13b
		MeOH	298	2.5 ± 0.1	cal	−14.0 ± 1.0	−9 ± 3	17 ± 13	13b
		MeCN	298	3.5 ± 0.1	cal (I = 0.01 M)	−19.9 ± 0.6	−26 ± 2	−20 ± 10	13b
	Mg^{2+}	MeOH	298	1.2	spect, 0.01 M TEAC				13a
	Ca^{2+}	MeOH	298	≥9	pot.(c), 0.01 M TEAP	≥−51.3	−25 ± 0.5	≥88.2	13b
	Sr^{2+}	MeOH	298	≥9	pot.(c), 0.01 M TEAP	≥−51.3	−10 ± 0.5	≥138.6	13b
	Ba^{2+}	MeOH	298	7.2 ± 0.1	pot.(c), 0.01 M TEAP	−41.0 ± 0.6	2.5 ± 0.4	144 ± 3	13b
	Ag^+	MeOH	298	7.2	pot.(d), 0.01 M TEAC				13b
		MeCN	298	5.5	pot.(d), 0.01 M TEAC				13a
4b	Li^+	MeOH	298	3.00 ± 0.05	spect, 0.01 M TEAC	−17.1 ± 0.3	6 ± 1	77 ± 3	13b
	Na^+	MeOH	298	7.20 ± 0.05	pot.(c), 0.01 M TEAP	−41.0 ± 0.3	−34.4 ± 0.8	23 ± 3	13b
	K^+	MeOH	298	5.4 ± 0.1	pot.(c), 0.01 M TEAP	−30.8 ± 0.6	−32.6 ± 0.4	−6 ± 3	13b
	Rb^+	MeOH	298	3.10 ± 0.02	cal	−17.1 ± 0.6	−11 ± 1	20 ± 6	13b
		MeOH	298	3.0	spect, 0.01 M TEAc				13a
	Mg^{2+}	MeOH	298	1.2	spect, 0.01 M TEAC				13b
	Ca^{2+}	MeOH	298	7.8 ± 0.1	pot.(c), 0.01 M TEAP	−44.5 ± 0.6	−10.0 ± 0.5	116 ± 3	13b
	Sr^{2+}	MeOH	298	8.1 ± 0.1	pot.(c), 0.01 M TEAP	−46.2 ± 0.6			13b
	Ba^{2+}	MeOH	298	6.8 ± 0.1	pot.(c), 0.01 M TEAP	−38.8 0.6	7.7	156 ± 3[i]	13b
	Ag^+	MeOH	298	6.8 ± 0.1	pot.(d), 0.01 M TEAP				13b
5b	Na^+	MeCN	298	5.2	spect				19a
	K^+	MeCN	298	4.7	spect				19a
	Ba^{2+}	MeCN	298	5.3	spect				19a
	NH_4^+	MeCN	298	3.1	spect				19a
	$BuNH_3^+$	MeCN	298	4.0	spect				19a

ligand	proton	solvent	T, K	log K_p	method	$\Delta_pG°$, kJ mol^{-1}	$\Delta_pH°$, k mol^{-1}	$\Delta_pS°$, J K^{-1} mol^{-1}	ref
5d	H^+	EtOH−H_2O (1:1)	298	12.14 (1)[d]	spect, (I = 1 M)				20
				6.84 (2)					
5d	H^+	EtOH−H_2O (1:1)	298	11.70	spect[e]				20
5e	H^+	EtOH−H_2O (1:1)	298	10.07	spect[e]				20
5f	H^+	EtOH−H_2O (1:1)	298	11.10	spect[e]				20
5g	H^+	EtOH−H_2O (1:1)	298	12.34	spect[e]				20
5h	H^+	EtOH−H_2O (1:1)	298	9.50	spect[e]				20
5i	H^+	EtOH−H_2O (1:1)	298	10.70	spect[e]				20
5f	H^+	EtOH−H_2O (1:1)	298	9.69	spect[e]				20
6a	**6a** + H^+ → **6a**H^+	MeOH	298	9.40 (1)[d]	pot.(d)				4i
	6aH^+ + H^+ → **6a**H_2^{2+}			8.43 (2)					
	6aH_2^{2+} + H^+ → **6a**H_3^{3+}			8.23 (3)					
	6aH_3^{3+} + H^+ → **6a**H_4^{4+}			7.67 (4)					
6l	**6l** + H+ → **6l**H^+	MeOH		5.91					4e
	6lH^+ + H^+ → **6l**H_2^{2+}			5.35					
	6lH_2^{2+} + H^+ → **6l**H_3^{3+}			5.03					
	6lH_3^{3+} + H^+ → **6l**H_4^{4+}			4.70					
6m	**6m** + H+ → **6m**H^+	MeOH		5.71					4i
	6mH^+ + H^+ → **6m**H_2^{2+}			4.52					
	6mH_2^{2+} + H^+ → **6m**H_3^{3+}			4.11					
	6mH_3^{3+} + H^+ → **6m**H_4^{4+}			3.59					
6g	**6g** + H^+ → **6g**H^+	MeOH		9.06					4e
	6gH^+ + H^+ → **6g**H_2^{2+}			7.95					

Table 3 (Continued)

ligand	proton	solvent	T, K	log K_p	method	$\Delta_pG°$, kJ mol^{-1}	$\Delta_pH°$, k mol^{-1}	$\Delta_pS°$, J K^{-1} mol^{-1}	ref
7a	**7a**$^{4-}$ + H$^+$ → **7a**$^{3-}$	MeOH	298	13.39 ± 0.03 (1)[d]	pot.(d), 0.0 1 M TEAP				13a
	7a^{3-} + H$^+$ → **7a**$^{2-}$			10.89 ± 0.05 (2)					
	7a^{2-} + H$^+$ → **7a**$^-$			9.19 ± 0.02 (3)					
	7a$^-$ + H$^+$ → **7a**			8.25 ± 0.09 (4)					

[a] Value checked by competition potentiometry, Ag+ as auxiliary cation. [b] Value checked by direct potentiometry. [c] Value mean of spectrophotometric and potentiometric data. [d] Suffix in parentheses refers to first, second, third, or fourth protonation constant. [e] K_a derived from kinetics of ester hydrolysis, monitored spectroscopically. [f] Recalculated by reviewers. [g] Methods: pot.(a), double competitive potentiometry, with Ag^+ as auxiliary cation, cryptand 222 as auxiliary ligand; pot.(b), double competitive potentiometry, with Ag^+ as auxiliary cation, cryptand 22 as auxiliary ligand; pot.(c), competition potentiometry, silver electrode, Ag^+ auxiliary cation; pot.(d), direct potentiometric titration, glass electrode; cal, titration calorimetry; spect, UV spectrophotometric method. TEAP = tetraethylammonium perchlorate salt. TEAC = tetraethylammonium chloride salt. [h] Calorimetric data. [i] $\Delta_cS°$ value of 196 J K^{-1} mol^{-1} (ref 13b) must be in error.

briefly discussed in the final part of this review (Extraction Processes).

Stability constants for the complexation of cations by calix(*n*)arenes functionalized at the lower rim have been reported mainly for alkali-metal cations and to a lesser extent for alkaline-earth-metal cations (see Table 3). However, the most detailed thermodynamic information on calixarene derivatives and alkali-metal cations is that involving the esters.[4d] This statement is based on the following facts: (i) Stability constants for these systems have been determined by several methods, particularly, for lithium and sodium derivatives in MeCN and PhCN. (ii) Enthalpies of complexation have been measured by classical titration calorimetry and checked by the most sensitive microcalorimetric technique. (iii) For the interpretation of the complexation process, the solution thermodynamics of the free and the complexed cation salts as well as the ligand were considered. (iv) Enthalpies of coordination, $\Delta_{coord}H°$, referred to the process in which reactants and product are in their solid states (eq 10) have been calculated. For a given

$$MX(sol.) + L(sol.) \rightarrow MLX(sol.) \qquad (10)$$

system $\Delta_{coord}H°$ should be the same, independently of the solvent from which this is derived. Therefore, in addition to the information that can be obtained from these data, its calculation provides a useful means of checking the reliability of solution and complexation enthalpies.[4d] Therefore, following a brief discussion regarding the methods currently used for the determination of stability constants of systems involving lower rim derivatives, the thermodynamics of complexation of calix(*n*)arene esters and metal cations are discussed.

Methods of stability constant determination exemplified in the literature surveyed in this review include potentiometry, UV and visible absorption, and fluorescence spectrophotometry, NMR spectroscopy, titration calorimetry, and conductimetry. Of these methods, potentiometry is often considered the most accurate, where particular stable metal ligand complexes are studied, due to the proportionality of the measured potential difference to the logarithm of the metal-ion activity. As a result, measurements are far more sensitive to changes in the extent of complexation when the complexation is nearly complete and the free metal ion activity is low.

The potentiometric method has been extensively used by Cox and Schneider[1b] and others to measure the activity of free silver ions in the presence of a competitive equilibrium involving a second metal cation in order to calculate the stability constants of relevant metal-ion cryptates in a variety of solvents.

It is evident that to apply this method to other systems the ligand must be able to form stable complexes with the silver cation, and this is not always the case. Such is the situation with calix(4)-arene esters in solvents such as MeCN and PhCN. Recently, using silver electrodes, a double competition method involving cryptands and calix(4)arenes esters has been introduced by Danil de Namor and co-workers[4d] for the potentiometric determination of stability constants of highly stable complexes of esters and metal cations (Li^+ and Na^+) in MeCN and PhCN. This approach can be applied to systems in which the first ligand has a high affinity for silver while the second has low or no affinity. Stability constants for **2a**−**c** with lithium and sodium in MeCN and PhCN at 298.15 K show that, for a given system when data derived from different methods are available, there is reasonable agreement between log K_s values derived from UV spectrophotometry, conductimetry, and calorimetry when these are not greater than 6.5. However, large discrepancies are observed in the log K_s values for Na^+ and **2a** in MeCN at 298.15 K. Stability constant data determined by UV spectrophotometry (see Table 3)[13a] show selective binding of this ligand for lithium in MeCN while data determined by the double competitive method[4d] shows selective behavior for sodium in the alkali-metal series. However, direct potentiometry using a sodium selective electrode[4e] shows that the stability constant value for the Na^+-**2a** system in MeCN (see table) at 298.15 K is in reasonable agreement with that derived from the double potentiometric method but differs by about 2.3 log units from the value derived from UV spectrophotometry.[13a] Therefore, an average of log K_s values obtained from three different methods (double competitive potentiometry, ion-selective electrodes, and conductivity) is given in Table 3 as the recommended value for the Na^+-**2a** system in MeCN at 298.15 K. To a lesser extent this is also the case for this system in PhCN, since appreciable differences are observed in the data derived from conductimetry (log K_s = 6.16) relative

to the value obtained from potentiometry.[4e] Again the log K_s value for K^+ and **2c** in MeCN derived from conductimetry differs from that obtained by calorimetry. We believe that the former value is in error. These are representative examples that if the complex is too stable or too weak ($1 > K > 10^6$) data derived from methods based on effects which are proportional to the concentration are not suitable. It is therefore concluded that where the complexation of alkali-metal cations has been studied, calix(4)-arene-based ligands in the *cone* conformation with ester groups appended to the lower rim selectively bind sodium in MeOH, MeCN, and PhCN.

In light of these results some of the discussions and trends in complexation selectivity for calix(4)arene esters and alkali-metal cations in MeCN need to be reconsidered. Furthermore, stability constant data determined by UV spectrophotometry[13a] for ketones (**3a**,**b**) showing higher selectivity for lithium relative to sodium in MeCN should be checked by other methods since, as with esters, log K_s values reported for these ligands with lithium and sodium in this solvent are relatively high.

On the basis of experimental data carried out in MeOH, McKervey et al.[13a] indicated that calixarene esters do not complex alkaline-earth-metal cations to any significant extent. However, the strength of complexation of macrocycles in general and calix(4)-arene derivatives, in particular, is strongly dependent on the nature of the solvent. Thus, Table 3 lists log K_s values for **2a** and alkaline-earth-metal cations in MeCN at 298.15 K. The data show that this ligand is able to recognize selectively these cations in this solvent in the sequence $Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}$ to the extent that some of the metal-ion complexes (Ca^{2+}, Sr^{2+}, Ba^{2+}) have been isolated and thermodynamically characterized.[4e]

Enthalpies of complexation have been determined calorimetrically for the calixarene esters **2a**, with alkali-metal cations in MeOH,[4f] and for **2a**−**c** in MeCN and PhCN.[4d] Initial data for **2a** in MeCN obtained by classical titration calorimetry[4f] were subsequently measured by titration microcalorimetry.[4d] Due to the much higher sensitivity of the latter relative to the former technique, the $\Delta_c H°$ values for **2a** and metal cations (Na^+, K^+, Rb^+) slightly differ from those previously reported, and therefore, these are the data listed in Table 3. It was also noted that no heat was detected in the microcalorimeter for the reaction between cesium ions and **2a** at 298.15 K. Obviously, these findings cannot be taken as an indication that these ligands are unable to interact with this cation in this solvent given that if the heat associated with these processes is close to 0 kJ, calorimetry is not a suitable reporter of molecular events for these systems. Attempts by us to reproduce the spectrophotometric value reported in the literature for **2a** and Cs^+ [13a] were unsuccessful since hardly any changes were observed in the spectra by the addition of cesium salts to solutions containing this ligand in this solvent. McKervey et al.,[13a] while acknowledging the small changes in the UV−visible spectrum, claim that a multiwavelength treatment of such spectral data allows estimation of the desired constant.

The thermodynamics of complexation of Na^+ and K^+ by alkylcalix(4)aryl esters in MeCN and PhCN show more negative enthalpy of complexation in MeCN.[4d] Enthalpies of transfer of the free metal cations show that these are actually better solvated in acetonitrile.[4d] It therefore follows that the metal complexes are better solvated relative to the free ligand in MeCN than in PhCN. The relative contributions of the solvation enthalpies of the free ligand, metal, and metal-ion complexes in the two solvents have been assessed by Danil de Namor et al.[4d] by determining transfer enthalpies from corresponding solution data of the ligand and the complex cation salts in the two solvents as discussed in section 3.1.2.

For the interpretation of $\Delta_c S°$ values of alkali-metal cations and calixarene derivatives in MeOH, MeCN, and PhCN, solvation parameters previously used by Danil de Namor and co-workers[4c,d] for complexation processes involving cryptands and these cations[4g] were explored for these systems. The aim was to assess the role of cation solvation in binding processes involving functionalized calixarenes. Thus, the reverse correlation between complexation and cation solvation entropies was only observed for **2a**−**c** with Li^+ and Na^+ in MeCN and the same cations and **2a** in MeOH and from Li^+ to K^+ with **4a** in the latter solvent,[13b] suggesting that for the larger cations other factors should be considered.

For the ester derivative of the cyclic hexamer, **2d**, and alkali-metal cations, stability constant data in MeCN at 298.15 K were reported.[13a] More recently, the thermodynamics of complexation of alkali-metal cations and **2d** in PhCN at 298.15 K was investigated.[4h] Stability constant data (see Table 3) derived from titration microcalorimetry show a "peak" selectivity with a monotonic increase in stability from lithium to potassium followed by a decrease from the latter to rubidium. In terms of enthalpy, a linear relationship was obtained when $\Delta_c H°$ values were plotted against the stability (log K_s) of the metal-ion complexes. Therefore, these complexes are enthalpy stabilized. In terms of entropy, the destabilizing effect was found to be at its maximun for potassium. It was pointed out that, for these ligands as well as for others, a more favorable enthalpy (more negative) results in a more negative entropy, providing good examples of incomplete enthalpy−entropy effects recently discussed by Grunwald and Steel.[14] The results were analyzed in terms of solute−solvent interactions reflected on the solution thermodynamics of the free and the complexed salts and the ligand in PhCN.

In the case of ligands which bind silver, competitive potentiometry using silver−silver ion electrodes have been employed.[13b] The stability of Li^+, Na^+, K^+, Sr^{2+}, and Ca^{2+} complexes of calix(4)tetramides **4a**,**b** in acetonitrile was deemed too high to obtain quantitative data by this method.[13b] As described by Cox and Schneider,[1b] this method is best applied when the stability constant of the metal−ligand complex is less than that of the silver ligand complex or does not exceed the silver complex stability by more than 1

or 2 orders of magnitude. This ensures that the complexation process can be studied over a suitably wide range of metal or ligand concentrations before extensive complexation of the metal to liberate silver causes the free silver activity to become immeasurably different from the total silver concentration in solution. Clearly other methods need to be explored to study the highly stable complexes of the calix(4)arene amides quantitatively.

Enthalpy data for calixarene amides **4a**,**b** with alkali-metal and alkaline-earth-metal cations in MeOH and MeCN at 298.15 K determined by classical titration calorimetry have been reported by Arnaud et al.[13b]

The calix(4)arene tetramide **4a** displays more negative complexation enthalpies for the alkali-metal cations in MeCN compared with MeOH. Using transfer Gibbs energies of the alkali-metal cations from MeCN to MeOH, it was pointed out that the lithium and sodium cations are better solvated in MeOH, whereas the opposite is true for K^+, Rb^+, and Cs^+.[13b] In the case of these three cations there is some discrepancy in the literature[15] as to whether Gibbs energies of transfer (related to transfer activity coefficients γ by $\Delta_t G° = -RT \ln \gamma$) from MeCN to MeOH are exogonic or endogonic. However, in the assessment of enthalpies of complexation, the relevant parameters to consider are the transfer enthalpies, $\Delta_t H°$, of these cations from MeCN to MeOH (eq 1 expressed in terms of enthalpies) which provide information regarding the difference in stability (in enthalpic terms) of these cations in these solvents. In fact, transfer enthalpies of K^+, Rb^+, and Cs^+ from MeCN → MeOH (based on the Ph_4AsPh_4B convention) are consistently positive reflecting that the stabilities (in enthalpic terms) are higher in MeCN than in MeOH. As the complexation enthalpies for these cations are more negative in MeCN, it follows that the relevant parameter for the free cation is not the dominant factor affecting the relative $\Delta_c H°$ values in the two solvents; the relative transfer enthalpies of the free and complex ligand must be considered. This information can be obtained from experimental data as discussed in section 3.1.2. Arnaud-Neu et al.[13b] attributed the stronger complexation of K^+, Rb^+, and Cs^+ in MeCN to the weaker solvation of the carboxyl groups in this solvent relative to MeOH. This suggestion was based on observations made by Wippf and Varnek[16a] during comparative molecular dynamics (MD) simulations of **4a** and its alkali-metal cations in MeCN and H_2O where water was considered a reasonable model for the behavior of methanol. It was pointed out that for **4a** the increase found in the $\Delta_c S°$ values from K^+ to Cs^+ is consistent with the relative conformational flexibilities of the cationic complexes observed in the MD simulations. For the complexation of **4b** and alkali-metal cations in MeOH, these authors suggested that the lower enthalpic stabilities and more favorable entropies observed for this ligand relative to **4a** may be attributed to a higher cation desolvation upon complexation with the former relative to the latter. This suggestion was based on the higher steric hindrance and greater rigidity resulting from the presence of pyrrolidinyl substituents in **4b** which then is argued to lose less conformational entropy upon complexation. However, entropies[4d] of calixarenate formation, $\Delta_{cf} S°$ referring to the process

$$M^+(g) + \mathbf{4b}(MeOH) \rightarrow M^+\mathbf{4b}(MeOH) \quad (11)$$

essentially describing the complexation of a desolvated cation are more favorable ($\Delta_{cf} S°$ more positive) for **4b** than **4a**, suggesting that ligand desolvation and metal-ion complex solvation are also contributing to the differences observed in the $\Delta_c S°$ values of these metal cations and these ligands in MeOH.

As far as the complexation of alkaline-earth-metal cations and **4a**,**b** in MeOH is concerned, stability constants were determined by competitive potentiometric titrations. The effect of ion-pair formation, known to occur for reactions of alkaline-earth-metal cations even in dilute methanolic solutions, needs to be considered.[1b] No information was given[13b] as to whether this effect was taken into account in the derivation of stability constant data for these systems. For ligand **4b** where quantitative information on complexation Gibbs energies was given, the decrease in enthalpic stability down the group was accompanied by an increase in entropy. The decrease in enthalpy in the series from Ca^{2+} to Ba^{2+} was attributed to the decrease in cation charge densities down the group. Then low enthalpies were explained on the basis of cation solvation in methanol. Undoubtedly, other factors (see eq 1 in terms of enthalpy) need to be considered in the interpretation of these data. As far as amide calixarenes and their metal-ion complexes are concerned, their solution properties in these solvents have not been investigated.

Generally speaking, the complexation processes for esters and amide derivatives and alkali-metal cations are all enthalpy controlled with the exception of Li^+-**2a**, Li^+-**4a**, and Li^+-**4b** in MeOH. All calixarene esters and amides show an exothermic maximum with sodium in MeOH and MeCN. All stability constants show that these ligands form more stable complexes in MeCN than in MeOH or PhCN.

In all cases with the exception of the complexation of lithium and **2a**−**c** in PhCN this is caused by the more negative complexation enthalpies in MeCN which override the contribution of the less favorable complexation entropy terms. In PhCN, the enthalpy term is again dominant; however, there is a definite size effect as far as enthalpies are concerned, with the highest stability for lithium and the lowest for potassium. A final exception is the complex of **2c** with potassium which is more stable in PhCN due to a more favorable enthalpy change.

Comparative complexation enthalpy data for related ligands in this series reflect the expected variation in the strength of cation−ligand interactions with the basicity of the carboxyl oxygen atoms. The $\Delta_c H°$ values of alkali-metal cations become more negative on progressing from methyl (**2b**) to ethyl ester (**2a**) to the tetrakis(diethylamide) (**4a**). The increase in the basicity of the carboxyl oxygens is expected along the series because the σ donating ability of the carboxyl substituents increases along

the series methoxy < ethoxy < *N*,*N*-diethylamino. Comparative enthalpies of complexation in different solvents show that the competing solvation of the free metal cation is often not the dominating factor affecting the extent of complexation. Recently the formation of a 2:1 **2a**-Na^+ complex in CD_3CN-CD_3Cl mixture (50:50) has been reported by Israeli and Detellier.[17] Estimated enthalpy and entropy values were derived from equilibrium measurements (^{22}Na NMR) at various temperatures. The authors suggested that the 2:1 complex may be an intermediate in the pathway of the exchange of sodium cations between 1:1 complexes in this solvent mixture.

As far as other esters (**2e**−**l**), amide (**4c**), and ketones (**3a**−**c**) are concerned, thermodynamic data are limited to stability constants of alkali-metal cations, Ag^+, and Tl^+ in MeOH and MeCN at 298 K.[13a] Stability constant data for the complexation of non-alkali or alkaline-earth-metal cations by ligands in this series appears limited to data reported for interactions of amides of the cyclic tetramer and hexamer with the lanthanide cations (Pr^{3+}, Eu^{3+}, Yb^{3+}, Gd^{3+}) in MeOH in articles by Arnaud[13c] and Roundhill.[18] Both of these articles though are preliminary communications which omit details of the experimental procedures used and the temperature.

Beer[19a] has reported stability constants for the complexation of alkylammonium and ammonium cations by calix(4)arenequinones in which opposite phenolic oxygens are functionalized with methyl ether, (**5a**) amide (**5b**) or ester (**5c**) containing side chains. The data reported in MeCN for **5b** and ammonium cations were compared with corresponding data for Na^+, K^+, and Ba^{2+}.

Studies involving the interaction of lower calixarene derivatives and the proton have been limited to the determination of pK_a ($-\log K_a$) values. These are reported in Table 3 as log K_p values ($\log K_p = -\log K_a = pK_a$). This table also shows the processes to which the data are referred.

Thus, Ray et al.[19] have used spectrophotometry to obtain pK_a values for the phenolic hydroxyls of monobenzonate esters of various *p*-substituted calix(4)arenes (see **5d**−**j**). A titrimetric method was used for the first two dissociation constants of the *p-tert*-butyl-substituted derivative. For other derivatives, values for the second dissociation constants were estimated from an analysis of the kinetics of the benzoate ester hydrolysis, assuming a mechanism involving hydrolysis via both the monoanion and the dianion of the calixarene. The reaction was monitored spectroscopically.

More recently Danil de Namor and co-workers[4i] reported the synthesis of lower rim calix(4)arene derivatives containing aliphatic and alicyclic tertiary amines (**6a**−**f**) in order to enhance the basicity of the nitrogen relative to those of existing lower rim derivatives. In this way the protonated ligand could be used as an efficient extracting agent for anions. In its free form (neutral ligand) calixarene amino derivatives are potential complexing agents for metal cations including Hg^{2+}, Pb^{2+}, and Cd^{2+}. Protonation constants for a representative ligand, **6a**, in methanol at 298.15 K are listed in Table 3. It was observed that as far as aliphatic amines are concerned the increase in the electron-donating capability of the ethyl (**6b**) relative to the methyl (**6a**) increases the basicity of the former relative to the latter and, therefore, the ability of **6b** to interact with the proton. However, the proton affinity is greatly reduced in **6f** due to the oxygen in the 4-position with respect to nitrogen which weakens the basicity of this amine relative to **6d**. Similar studies have been carried out with lower rim derivatives containing amino and thioalkyl functional groups (**6g**−**k**), where only two amino groups are available for protonation. These ligands are slightly less basic in MeOH than the tetraaminocalix(4)arenes (**6a**−**f**) (see data for **6g** in Table 3). In the order from aliphatic and alicyclic amines to pyridinocalix(4)arenes (**6l**,**m**), a sharp decrease in basicity is observed, which, in turn, leads to much lower protonation constants for the latter relative to the former. Among the geometrical isomers of pyridinocalix(4)arenes, the basicity of **6 l** is greater than that for **6m** in MeOH. In fact, the experimental pK_a values ($pK_a = \log K_p$) for pyridinocalix(4)arenes are in agreement with the values predicted for these ligands in water.[9b] In this particular case, a comparison between H_2O and MeOH is justified on the basis that, unlike neutral acids, the medium effects for the dissociation of cationic acids are very small since these processes do not lead to the creation of new fields (see equations in table). In fact, the transfer of equilibrating systems from H_2O to MeOH results in a change of pK_a values for cationic acids of about 0.06 ± 0.02 units (molal scale). Enthalpy and entropy data for the protonation process may lead to a more detailed discussion on these systems.[4e]

Under this heading, the ligands so far discussed are neutral macrocycles able to complex cations mainly through ion−dipolar interactions. However, representative examples of lower rim calix(4)arene derivatives containing ionizable groups are those involving carboxylic acid groups (**7a**−**f**). The strength of complexation of these ligands with metal cations is mainly determined by ion−ion interactions, and therefore, in their fully deprotonated forms these are expected to form stronger complexes with metal cations than neutral ligands.

Protonation constants of *p-tert*-butylcalixarene tetra (**7a**$^{4-}$), di (**7b**$^{2-}$, **7c**$^{2-}$), and mono (**7d**$^-$, **7e**$^-$, **7f** $^-$) carboxylates in MeOH at 298 K have been reported by Arnaud et al.[13a]

Data for **7a**$^{4-}$ are listed in Table 3 (incidentally the autoprotolysis constant, pS, of MeOH at 298 K is about 16.7 and not −16.7 as stated in the original source).[13d]

The weak acidities of these ligands (except **7f**) with respect to the monomer was explained in terms of intramolecular hydrogen bonding of the protonated forms of these ligands.

Through competitive equilibria between the proton and metal ions by titrating the ligand with an acid alone and in the presence of a metal cation using a glass electrode, stability constants (in terms of concentrations) of alkali-metal, alkaline-earth-metal,[13a] and lanthanide cations[13d] for protonated and fully

Table 4. Solution Thermodynamics of Lower Calix(4)arene Derivatives and Metal-Ion Complexes in Various Solvents at 298.15 K with Derived Transfer Parameters from Acetonitrile

ligand	solvent	solubility, mol dm^{-3}	$\Delta_sG°$, kJ mol^{-1}	$\Delta_sH°$,[b] kJ mol^{-1}	$\Delta_sS°$, J K^{-1} mol^{-1}	$\Delta_tG°$, kJ mol^{-1}	$\Delta_tH°$, kJ mol^{-1}	$\Delta_tS°$, J K^{-1} mol^{-1}	ref
2a	MeCN	$(1.12 \pm 0.08) \times 10^{-2}$	11.13	22.67	38.7	0	0	0	4d
	MeOH	$(3.65 \pm 0.12) \times 10^{-3}$	13.91	32.67	62.9	2.78	10.00	24.2	4f,4d
	PhCN			14.03			−8.64		4d
2b	MeCN			25.03		0			4d
	PhCN			17.51			−7.52		4d
2c	MeCN	$(4.80 \pm 0.16) \times 10^{-2}$	7.53	20.80	44.5	0	0	0	4d
	MeOH	$(9.44 \pm 0.12) \times 10^{-3}$	11.56			4.03			4d
	PhCN			12.20			−8.60		4d
2d	PhCN	1.72×10^{-3}	15.78	4.96	−36.3				4h
4d	MeCN	$(2.64 \pm 0.05) \times 10^{-3}$	14.72			0			4e
	1-BuOH	$(1.23 \pm 0.03) \times 10^{-2}$	10.90	15.41	15.1	−3.82			4e
	1-BuOH satd with H_2O	$(9.23 \pm 0.05) \times 10^{-3}$	11.61	0.76	−36.4	−3.11			4e
	Me_2CO	$(1.62 \pm 0.01) \times 10^{-2}$	10.22			−4.50			4e
	DMF	$(4.53 \pm 0.09) \times 10^{-3}$	13.38			−1.34			4e
	THF	0.152 ± 0.07	4.67			−10.05			4e
	1,2-DCE[a]	v soluble							4e
6n	MeCN	$(4.08 \pm 0.04) \times 10^{-4}$	19.35			0			4e
	MeOH	$(1.24 \pm 0.03) \times 10^{-3}$	16.59			−2.76			4e
	EtOH	$(5.73 \pm 0.08) \times 10^{-3}$	12.80			−6.55			4e
	1-PrOH	$(2.26 \pm 0.01) \times 10^{-2}$	9.39			−9.96			4e
	1-BuOH	$(3.74 \pm 0.05) \times 10^{-2}$	8.15			−11.2			4e
	PhCN	$(1.05 \pm 0.03) \times 10^{-2}$	11.30			−8.05			4e
	CH_2Cl_2	v soluble							4e
	$PhNO_2$	$(2.58 \pm 0.02) \times 10^{-3}$	14.77			−4.58			4e
	DMF	$(1.88 \pm 0.04) \times 10^{-3}$	15.56			−3.79			4e
	PC[a]	$(3.44 \pm 0.19) \times 10^{-4}$	19.77			0.42			4e
6h	MeCN	$(3.30 \pm 0.04) \times 10^{-3}$	14.16	24.36	34.2	0	0	0	4e
	MeOH	$(1.16 \pm 0.03) \times 10^{-2}$	11.05	12.93	6.3	−3.11	−11.43	−27.9	4e
	EtOH	$(2.07 \pm 0.03) \times 10^{-2}$	9.61	11.68	6.9	−4.55	−12.68	−27.3	4e
	1-BuOH	$(1.36 \pm 0.04) \times 10^{-1}$	4.95	9.13	14.0	−9.21	−15.23	−20.2	4e
	PhCN	too soluble		7.44			−16.92		4e
	CH_2Cl_2	too soluble							4e
	$PhNO_2$	too soluble							4e
	DMF	$(1.68 \pm 0.10) \times 10^{-2}$	10.13	23.02	43.2	−4.03	−1.34	9.1	4e
	PC[a]	too low sol.							4e
	THF	too soluble		7.20			−17.16		4e
	Hex	too soluble							4e
	EtAc	too soluble							4e
Li^+**2a**ClO_4^-	MeCN			−9.17					4d
	PhCN			−10.42					4d
Na^+**2a**ClO_4^-	MeCN	6.25×10^{-2}	16.11	−34.62	−170.1				4d
	PhCN			−12.70					4d
	MeOH		20.14[c]	−2.91[c]	−77.3[c]	4.03[d]	31.71[d]	92.8[d]	4f
Na^+**2d**PhB_4^-	PhCN			−19.77					4h
K^+**2d**PhB_4^-	PhCN			−20.72					4h

[a] 1,2-DCE, 1,2 dichloroethane; PC, propylene carbonate. [b] Calorimetric data [c] Calculated by the authors from thermodynamic parameters of transfer of dissociated electrolyte from acetonitrile to methanol and corresponding data of solution in acetonitrile. [d] From ref 4f taking acetonitrile as the reference solvent.

deprotonated ligands in MeOH at 298.15 K were obtained. As expected for these types of ligand, the ability to complex metal cations is strongly dependent on the solution pH.

3.1.2. Interactions in Nonaqueous Media

Detailed studies of the changes in the thermodynamics of uncomplexed 1:1 electrolytes on transfer from one solvent to another have been extensively reported.[1b] Therefore, under this heading the solution thermodynamics of calixarene derivatives (nonelectrolytes) and their metal-ion complexes (electrolytes) are considered. The aim of these investigations has been the derivation of transfer parameters for these species between two solvents. The relevance of these data in assessing the medium effect on the complexation process is explicity shown in eq 1. Thus, solubilities (molar scale) and derived standard Gibbs energies, $\Delta_sG°$, enthalpies, $\Delta_sH°$, and entropies, $\Delta_sS°$, of solution of lower rim calixarene derivatives (**2a**,**b**,**d**,**e**, **4d**, **6h**,**n**) in various solvents at 298.15 K are listed in Table 4. These data have been used by Danil de Namor and co-workers[4d,e] to derive the thermodynamic parameters of transfer ($\Delta_tG°$, $\Delta_tH°$, $\Delta_tS°$) of these ligands to various solvents (s) using acetonitrile (MeCN) as reference (eq 12)

$$\text{L(MeCN)} \rightarrow \text{L(s)} \qquad (12)$$

Gibbs energy data provide a quantitative measure of the solvation changes of the solute in its transfer from one medium to another, and therefore, transfer parameters are instructive, particularly in calixarene chemistry where the presence of hydrophobic and hydrophilic regions confers unusual properties to these molecules to the extent that specific solute−

solvent interactions often occur. These may have profound implications in many processes such as binding, choice of reaction media for recrystallization, solvent extraction technology, and design of ion selective electrodes.[4b]

The derivation of transfer data for metal-ion complex salts (M^+LX^-) (see Table 4) deserves some comments. Solubility data for these electrolytes are referred to the process

$$ML^+X^-(sol.) \rightarrow ML^+(s) + X^-(s) \qquad (13)$$

Thus, the thermodynamic solubility product, K°_{sp} (corrected for ion-pair formation when there is evidence of its occurrence) referred to the standard state (1 mol dm^{-3}) is given by

$$K^\circ_{sp} = a_{ML^+} \cdot a_{X^-} = [ML^+][X^-]\gamma_\pm{}^2 \qquad (14)$$

where a, [ ], and $\gamma_\pm$ denote activity, molar concentrations, and mean ionic molar activity coefficients (calculated by the extended Debye−Hückel equation), respectively. These data were used to calculate $\Delta_s G°$ and $\Delta_t G°$ values. The latter refers to the transfer of the fully dissociated electrolyte from MeCN to s (eq 15).

$$ML^+(MeCN) + X^-(MeCN) \rightarrow ML^+(s) + X^-(s) \quad (15)$$

The K°_{sp}, $\Delta_s G°$, and $\Delta_t G°$ values were calculated only for cases in which the composition of the solid phase was not altered by solvate formation when this was exposed for several days to a saturated atmosphere of the solvent. For the calculation of $\Delta_t H°$ values for 1:1 electrolytes, $\Delta_s H°$ data used were the values at $c = 0$ from a plot of $\Delta_s H$ (calorimetric measurement) against $c^{1/2}$, where c is the molar concentration of the electrolyte.

Gibbs energies for these ligands (nonelectrolytes) show that the transfer from one solvent to another alters the equilibrium position in a selective manner. Indeed, differences of up to 10−11 kJ mol^{-1} are observed in the $\Delta_t G°$ values of **4d** and **6n**, respectively. Ligand **6h** is of particular interest as $\Delta_t G°$, $\Delta_t H°$, and $\Delta_t S°$ are available. Thus, the solvation sequence observed in terms of $\Delta_t G°$, PhCN, EtAc, Hex, THF, $PhNO_2$, CH_2Cl_2, 1,2DCE > 1-BuOH > EtOH > MeOH > DMF > MeCN > PC is found to be parallel with $\Delta_t H°$ values, with the highest enthalpic stability in THF and the lowest in MeCN. However, two distinctive patterns are observed in terms of entropy. Thus, the transfer to a dipolar aprotic solvent (DMF) is slightly positive while the corresponding parameter to protic solvents (MeOH, EtOH, 1-BuOH) is negative. The loss of freedom of this ligand in moving to the alcohols was partially attributed to interactions via hydrogen bond formation between these solvents and the basic amino groups of **6h**.

There are important points to stress regarding the data in Table 4: (i) The fact that these ligands undergo solvate formation in a wide variety of solvents underlines the possibility that the use of these solvents for crystallization purposes may lead to the isolation of their complexes rather than the pure ligands. (ii) It has been implied that the solvation of calixarene derivatives may be related to Gutmann's donor numbers of the solvent.[13b] However, the fact that parent calixarenes and their derivatives are highly solvated in low donor number solvents (1,2-DCE, DN = 0; $PhNO_2$, DN = 4.4; PhCN, DN = 11.9)[1b] provides experimental evidence that this is not a suitable parameter to predict the solvation of these ligands and therefore, any suggestion regarding this type of correlation should be taken with caution. (iii) Much of the current interest in calixarene chemistry is the use of these ligands as extracting agents for metal cations from water to the organic phase where the two solvents involved are mutually saturated. Within this context, the results in Table 4 for **4d** in butan-1-ol and the water-saturated solvent are immediately striking. Indeed, the observed decrease in entropy and the concomitant increase in enthalpic stability in moving from the pure to the water saturated solvent has been attributed to specific water−ligand interactions.[4e]

Quite clearly the data show that the system is seriously perturbed by the presence of water in the nonaqueous phase. The outcome is a complete enthalpy−entropy compensation effect since hardly any changes are observed in the $\Delta_t G°$ value for this system from the pure to the water saturated solvent. In fact, these findings provided further support to the interesting formalism (solvent reorganization associated with chemical and physical processes and enthalpy−entropy compensation effects) recently developed by Grunwald and Steel[14] in that $\Delta_t G° \cong 0$ kJ mol^{-1} for **4d** from 1-BuOH to water saturated 1-BuOH and consequently, $\Delta_t H° \cong T\Delta_t S°$.

These results provide a sharp illustration that misleading conclusions can be drawn from data based solely on Gibbs energies. Furthermore, the presence of water in the organic phase, particularly in the H_2O−1-BuOH solvent system where the mutual solubility of the solvents involved is high, may seriously alter the strength of complexation of these ligands with metal cations. Transfer and partition of 1:1 electrolytes in various solvent systems have been previously discussed by Danil de Namor and coworkers.[4j] A direct implication of this statement is that, in reporting the thermodynamics of complex formation or solution, the water content of the solvent should be specified.

As far as metal-ion complexes of calixarene derivatives are concerned, the solution thermodynamics of the esters (see Table 4) are the only systems that have been investigated.[4d]

The enthalpies of transfer of the sodium perchlorate complex of **2a** from MeCN to both MeOH and PhCN are positive. An interesting aspect of the transfer parameters from MeCN to PhCN is that for the free ligand the equivalent $\Delta_t H°$ value is negative in contrast with the positive value for the sodium complex. This indicates that in MeCN compared to PhCN the sodium−calixarenate complex salt is markedly more stable (in enthalpic terms) than the free ligand. This is the dominant factor causing the more negative $\Delta_c H°$ value for sodium and **2a** in MeCN and overrides the fact that the free sodium cation itself

is better solvated in MeCN (as shown by its transfer enthalpy between the solvents[14]). These results therefore illustrate quantitatively the statement made in section 3.1.1 that with calixarene ligands the influence of the solvation of the host, guest, and host−guest complex must be accounted for when discussing the complexation thermodynamics of these systems in different media.

In the case of the transfer parameters from MeCN to MeOH, the positive $\Delta_t H°$ and $\Delta_t S°$ values for both the ligand and its sodium complex reflect a gain in solvation in MeCN. It has been pointed out that this can be considered consistent with the complexation of a solvent molecule in the hydrophobic cavity of the calixarene in MeCN but not in MeOH.[4d] Such a specific ligand−solvent interaction may explain the unusually large downfield shifts of the aromatic protons of the ligand seen in its ^{1}H NMR spectrum in CD_3CN compared to $CDCl_3$.[4e] Evidence for such interactions between MeCN and the hydrophobic cavity of calixarene derivatives of this nature is found in the X−ray crystal structure of a similar derivative, metal *p-tert*-butylcalix(4)arene tetracarbonate complexes, in which one solvent molecule resides in the cavity with the methyl group orientated toward the cation.[13a]

3.1.3. Interaction with Neutral Species

The binding of aliphatic and aromatic amines, carboxylic acids, and phenols to Gutsche's "double cavity" calixarenes (**5k**−**m**) to form 1:1 complexes has been quantified by ^{1}H NMR spectroscopy in $CDCl_3$ at 298 K[7b] and compared with single-cavity O-disubstituted calix(4)arene (**5n**−**s**). The strength of complexation for imidazoles, phenols, carboxylic acids, and amines is weak as shown in representative data listed in Table 5.

The variation in the magnitude of K_s values with different host−guest combinations was attributed to variations in the strength of intermolecular hydrogen bonding. In addition to the hydrogen bond forming capacity of host and guest, steric complementarity was deduced to be important. Molecular mechanics calculations suggested the important role of $\pi-\pi$ stacking interactions between the phenolic ring of the guest and the exterior aromatic surface of the calixarene. However, in a solvent like $CHCl_3$, guest species such as carboxylic acids, phenols, and primary and secondary amines self-associate via hydrogen bond formation and this is also likely to contribute to the relative low interaction (or lack of it) observed for these systems in this solvent.

Using the donor properties of calix(4)arenes with epoxy moieties (**5t**) and hydroxy amino groups (**5u**) at the lower rim and the electron acceptor properties of iodine, Vural[21] measured equilibrium constants for 1:1 complexes in $CHCl_3$ at 298 K by UV spectrophotometry. The larger stability constant found for **5u** relative to **5t** (see Table 5) was attributed to the higher electron donor ability of the former with respect to the latter ligand.

UV spectrophotometry has similarly been used to determine equilibrium constants for 1:1 complexes formed by aromatic dyes and a water-soluble calix(8)arene derivative with poly(ethylene oxide) chains appended to the lower rim (**5v**) in water.[22] However, the temperature at which these measurements were carried out was not reported. Interest in these molecules relies on their properties to enhance the fluorescence of guest molecules.

Hydrogen bonding of the cyclic secondary amide γ-butyrolactam to a 2-pyridyl moiety at the lower rim of a calix(4) derivative (**5w**) complexed with Na^+ in $CDCl_3-CD_3CN$ (9:1) at 223 K to form a 2:1 (guest−host) complex has been determined by ^{1}H NMR spectroscopy.[6b] The sodium complex interacts with the amide but not the free ligand. This was associated with the complexation of sodium inducing disruption of intramolecular hydrogen bonding between neighboring functional groups at the lower rim, thus making the appropriate groups available for intermolecular hydrogen bonding host−guest interactions.

Shinkai[6c] has studied the interaction of pyrene with calix(*n*)arenes functionalized with sulfonate groups at the lower rim in water at 303 K using the fluorescence spectroscopic method. Equilibrium data for 1:1 complexes show that the strength of interaction is greater for the *p-tert*-butylcalix(6)arene derivative. This was attributed to the complementarity between the calix(6)arene cavity and the pyrene guest as observed in CPK models and to the extended cavity built by *p*-substitution. The induced circular dichroism technique extensively used for studying the interaction of cyclodextrins to guest species has been applied to assess quantitatively interactions between a *p-tert*-butylcalix(6)arene derivative bearing (*S*)-5-oxo-2-pyrrolidinylcarbonyloxyl groups in the lower rim (**5ab**) with ferrocenecarboxylic acid (F).[6d] The predominant guest species of the 1:1 adduct in $CHCl_3$ at 293 K is the molecular acid presumably self-associated in this solvent. Using a competitive reaction between the **5ab**-F complex and benzoic acid (BA) (assuming that 1:1 substitution occurs), the equilibrium constant was derived for the **5ab**-BA system in $CHCl_3$ at 293 K.

3.2. Calixcrowns

3.2.1. Interactions with Metal Cations and Organic Cations

Spectrophotometry, potentiometry, and calorimetry have been mainly used to determine the stability constants of calixcrowns (**8a**−**m**) and cations (mainly alkali metals and silver) in MeOH and MeCN at 298 K.[13e,23a] Where values have been determined by calorimetry,[23a] they are said to show full agreement with those derived from potentiometric or spectrophotometric techniques.

Enthalpy and entropy data have been reported for the three monosubstituted calixcrown 6 ligands (**8a**,**c**,**d**)[23a] in MeOH plus three bis-substituted calixcrown 6 ligands (**8f**−**h**) and a bis(calix crown 5) ligand (**8e**)[13e] in MeOH and MeCN at 298.15 K, and these are reported in Table 6.

Interest in these ligands is mainly centered around their selectivity for Cs^+ in favor of Na^+ and their potential applications as carrier molecules to extract

Table 5. Stability Constants for Calixarene Derivatives and Neutral Species in Various Solvents

ligand	guest	solvent	log K_s	method	T, K	ref
5n	imidazole	$CDCl_3$	1.08	NMR	298	7b
5k	phenol	$CDCl_3$	0.85	NMR	298	7b
	4-nitrophenol	$CDCl_3$	1.74	NMR	298	7b
	3-nitrophenol	$CDCl_3$	1.60	NMR	298	7b
	4-cyanophenol	$CDCl_3$	1.49	NMR	298	7b
	4-(trifluoromethyl)phenol	$CDCl_3$	1.32	NMR	298	7b
	4-bromophenol	$CDCl_3$	1.32	NMR	298	7b
	iodoacetic acid	$CDCl_3$	0.95	NMR	298	7b
	dichloroacetic acid	$CDCl_3$	0.78	NMR	298	7b
	3-chloropropionic acid	$CDCl_3$	0.70	NMR	298	7b
	bromoacetic acid	$CDCl_3$	0.70	NMR	298	7b
	dibromoacetic acid	$CDCl_3$	0.70	NMR	298	7b
	butyric acid	$CDCl_3$	1.26	NMR	298	7b
	isobutyric acid	$CDCl_3$	0.85	NMR	298	7b
	2-bromopropionic acid	$CDCl_3$	1.18	NMR	298	7b
	4-n-butylbenzoic acid	$CDCl_3$	1.11	NMR	298	7b
	pyridine	$CDCl_3$	1.52	NMR	298	7b
	3-methylpyridine	$CDCl_3$	0.78	NMR	298	7b
	imidazole	$CDCl_3$	1.20	NMR	298	7b
	4-methoxybenzylamine	$CDCl_3$	1.28	NMR	298	7b
	(4-methoxyphenyl)ethylamine	$CDCl_3$	1.20	NMR	298	7b
	(4-methoxyphenyl)propylamine	$CDCl_3$	1.28	NMR	298	7b
	isobutylamine	$CDCl_3$	1.11	NMR	298	7b
	n-butylamine	$CDCl_3$	1.08	NMR	298	7b
	isopropylamine	$CDCl_3$	1.11	NMR	298	7b
	2-aminopropanol	$CDCl_3$	1.30	NMR	298	7b
	3-aminopropanol	$CDCl_3$	1.18	NMR	298	7b
	2-hydroxypropylamine	$CDCl_3$	1.04	NMR	298	7b
5l	4-nitrophenol	$CDCl_3$	1.60	NMR	298	7b
	3-nitrophenol	$CDCl_3$	1.56	NMR	298	7b
	4-bromophenol$CDCl_3$	$CDCl_3$	1.00	NMR	298	7b
	dibromoacetic acid	$CDCl_3$	1.18	NMR	298	7b
	2-bromopropionic acid	$CDCl_3$	1.00	NMR	298	7b
	4-n-butylbenzoic acid	$CDCl_3$	1.08	NMR	298	7b
5m	phenol	$CDCl_3$	0.7	NMR	298	7b
	4-nitrophenol	$CDCl_3$	1.68	NMR	298	7b
	4-bromophenol	$CDCl_3$	1.20	NMR	298	7b
	dibromoacetic acid	$CDCl_3$	1.28	NMR	298	7b
	2-bromopropionic acid	$CDCl_3$	1.11	NMR	298	7b
5o	imidazole	$CDCl_3$	0.84	NMR	298	7b
	1-methylimidazole	$CDCl_3$	0.60	NMR	298	7b
5p	imidazole	$CDCl_3$	1.15	NMR	298	7b
	1-methylimidazole	$CDCl_3$	0.70	NMR	298	7b
	4-methylimidazole	$CDCl_3$	0.95	NMR	298	7b
5q	imidazole	$CDCl_3$	1.0	NMR	298	7b
	1-methylimidazole	$CDCl_3$	0.7	NMR	298	7b
	4-methylimidazole	$CDCl_3$	0.8	NMR	298	7b
5s	imidazole	$CDCl_3$	1.0	NMR	298	7b
5t	iodine	$CHCl_3$	0.58	spect	298	21
5u	iodine	$CHCl_3$	1.85	spect	298	21
5v	*N*-phenyl-2-naphthylamine	H_2O	5.1	spect	298?	22
5w (Na^+ complex)	γ-butyrolactam	$CDCl_3-CD_3CN$ (10:1)	2.12 (1) 2.02 (2)[a]	NMR	248	6b
5x	pyrene	H_2O	5.79	fluo	303	6c
5y	pyrene	H_2O	6.61	fluo	303	6c
5z	pyrene	H_2O	5.57	flue	303	6c
5aa	pyrene	H_2O	5.80	fluo	303	6c
5ab	ferrocenecarboxylic acid	$CHCl_3$	2.83	CD spect	293	6d

cesium radionuclide selectively from nuclear waste solutions containing large excesses of sodium.

From the standard deviations given in Table 6 it appears that, among these ligands, the highest complex stabilities as reflected in the log K_s values are found for the monocalixcrowns (**8a**,**b**) with Rb^+- and Cs^+ in MeOH where the maximun $\Delta_c H°$ (more negative) is that for the complexation of **8a** and Cs^+ in this solvent. In interpreting thermodynamic data, the authors point out that the $T\Delta_c S°$ value for the Cs^+-**8a** system in MeOH is less negative than equivalent values for the monocyclics 18-crown-6 and 21-crown-7, explainable in part in terms of the more rigid calixcrown losing less conformational flexibility, hence less entropy of complexation. On the basis of different conformations of **8a** (1,3 alternate) relative to **8c** (cone) in MeOH, solvation effects have been invoked to account for the differences in enthalpy and entropy observed for the complexation of Cs^+ and these ligands. However, the solution thermodynamics of these ligands and their Cs^+ complexes have not been investigated. Therefore, the approach used for the interpretation of complexation data based on solvation effects remains speculative.

Table 6. Thermodynamic Parameters of Complexation of Calixcrown Ligands and Metal Cations in Nonaqueous Solvents at 298 K

ligand	cation	solvent	log K_s	method[c]	$\Delta_cG°$, kJ mol^{-1}	$\Delta_cH°$,[d] kJ mol^{-1}	$\Delta_cS°$, J K^{-1} mol^{-1}	T/K	ref
8a	Li^+	MeOH	≤1	spect, 0.01 M TEAC				298	23a
	Na^+	MeOH	≤1	spect, 0.01 M TEAC				298	23a
	K^+	MeOH	4.5 ± 0.1	spect/pot.(b)[a]	−25.6 ± 0.6	−18.1 ± 0.4	25 ± 3	298	23a
	Rb^+	MeOH	5.93 ± 0.06	pot.(b), 0.01 M TEAP	−33.8 ± 0.3	−40 ± 2	−21 ± 2	298	23a
	Cs^+	MeOH	6.1 ± 0.2	pot.(b), 0.01 M TEAP	−35 ± 1	−50.2 ± 0.4	−52 ± 3	298	23a
	Ag+	MeOH	4.52 ± 0.09	pot., 0.01 M TEAP	−25.8 ± 0.5	−13.5 ± 0.4	41 ± 3	298	23a
8b	Li^+	MeOH	≤1	spect, 0.01 M TEAC				298	23a
	Na^+	MeOH	≤1	spect, 0.01 M TEAC				298	23a
	K^+	MeOH	4.3 ± 0.2	pot.(b), 0.01 M TEAP				298	23a
	Rb^+	MeOH	5.96 ± 0.01	pot.(b), 0.01 TEAP				298	23a
	Cs^+	MeOH	6.4 ± 0.2	pot.(b), 0.01 M TEAP				298	23a
	Ag^+	MeOH	4.60 ± 0.09	pot., 0.01 M TEAP				298	23a
8c	Li^+	MeOH	≤1	spect, 0.01 M TEAC				298	23a
	Na^+	MeOH	≤1	spect, 0.01 M TEAC				298	23a
	K^+	MeOH	2.13 ± 0.08	spect, 0.01 M TEAC				298	23a
	Rb^+	MeOH	3.18 ± 0.03	spect, 0.01 M TEAC				298	23a
	Cs^+	MeOH	4.2 ± 0.2	spect, 0.01 M TEAC, cal	−24.0 ± 1	−23 ± 0.1	2 ± 6	298	23a
8d	Li^+	MeOH	≤1	spect, 0.01 M TEAC				298	23a
	Na^+	MeOH	≤1	spect, 0.01 M TEAC				298	23a
	K^+	MeOH	2.54 ± 0.08	spect, 0.01 M TEAC	−14.5			298	23a
	Rb^+	MeOH	3.5 ± 0.3	spect, 0.01 M TEAC	−20.0			298	23a
	Cs^+	MeOH	4.6 ± 0.1	spect, 0.01 M TEAC	−26.2 ± 0.6	−36 ± 3	−30 ± 10	298	23a
8e	Li^+	MeOH	≤1	spect, 0.01 M TEAC				298	13e
		MeCN	1.80 ± 0.08	spect, 0.01 M TEAP	−10.3			298	13e
	Na^+	MeOH	2.1 ± 0.2	spect, 0.01 M TEAC	−12.0[b]			298	13e
		MeCN	3.5 ± 0.1	spect, 0.01M TEAP	−19.9 ± 0.6	−4.56 ± 0.06	51 ± 2	298	13e
	K^+	MeOH	4.76 ± 0.04	spect, 0.01 M TEAC	−27.1 ± 0.2	−57.0 ± 0.1	−100 ± 1	298	13e
		MeCN	4.47 ± 0.09	spect, 0.01 M TEAP	−25.5 ± 0.5	−59 ± 1	−114 ± 3	298	13e
	Rb^+	MeOH	4.8 ± 0.2	spect, 0.01 M TEAC	−27. ± 1	−61 ± 2	−114 ± 10	298	13e
		MeCN	4.61 ± 0.08	spect, 0.01 M TEAP	−26.3 ± 0.4	−57 ± 2	−104 ± 7	298	13e
	Cs^+	MeOH	5.1 ± 0.1	spect, 0.01 M TEAC	−29.1 ± 0.6	−44 ± 1	−50 ± 5	298	13e
		MeCN	5.4 ± 0.1	spect, 0.01 M TEAP	−30.8 ± 0.6	−40.5 ± 0.1	−32 ± 2	298	13e
8f	Li^+	MeOH	≤1	spect, 0.01 M TEAC				298	13e
		MeCN	2.3 ± 0.2	spect, 0.01 M TEAP	−13.1[b]			298	13e
	Na^+	MeOH	1.52 ± 0.07	spect, 0.01 M TEAC	−8.7[b]			298	13e
		MeCN	1.97 ± 0.08	spect, 0.01 M TEAP	−11.2[b]			298	13e
	K^+	MeOH	4.1 ± 0.1	spect, 0.01 M TEAC	−23.4 ± 0.6	−31.7 ± 0.8	−28 ± 5	298	13e
		MeCN	4.12 ± 0.08	spect, 0.01 M TEAP	−23.5 ± 0.4	−17 ± 1	23 ± 3	298	13e
	Rb^+	MeOH	4.3 ± 0.1	spect, 0.01 M TEAC	−24.5 ± 0.6	−52 ± 1	−92 ± 5	298	13e
		MeCN	4.41 ± 0.04	spect, 0.01 M TEAP	−25.1 ± 0.2	−25.2 ± 0.1	0 ± 1	298	13e
	Cs^+	MeOH	4.8 ± 0.3	spect, 0.01 M TEAC	−27 ± 2	−56.2 ± 2	−98 ± 13	298	13e
		MeCN	4.9 ± 0.1	spect, 0.01 M TEAP	−27.9 ± 0.6	−29.7 ± 0.1	−6 ± 2	298	13e
8g	Li^+	MeCN	1.5 ± 0.2	spect, 0.01 M TEAP				298	13e
	Na^+	MeCN	1.5 ± 0.2	spect, 0.01 M TEAP				298	13e
	K^+	MeCN	4.32 ± 0.05	spect, 0.01 M TEAP				298	13e
	Rb^+	MeCN	4.39 ± 0.04	spect, 0.01 M TEAP	−25.0 ± 0.2	−12.6 ± 0.2	42 ± 1	298	13e
	Cs^+	MeCN	4.9 ± 0.2	spect, 0.01 M TEAP	−28 ± 1	−11.4 ± 0.7	57 ± 7	298	13e
8h	Li^+	MeCN	1.2 ± 0.1	spect, 0.01 M TEAP				298	13e
	Na^+	MeCN	1.4 ± 0.2	spect, 0.01 M TEAP				298	13e
	K^+	MeCN	4.2 ± 0.3	spect, 0.01 M TEAP				298	13e
	Rb^+	MeCN	4.4 ± 0.1	spect, 0.01 M TEAP	−25.1 ± 0.6	−12.5 ± 0.8	42 ± 5	298	13e
	Cs^+	MeCN	4.9 ± 0.2	spect, 0.01 M TEAP	−28 ± 1	−11 ± 1	57 ± 7	298	13e
8i	Li^+	MeCN−THF (1000:1 v/v)	4.65	spect				298	6e
		MeCN−THF (1000:1 v/v)	4.84	fluo				298	6e
	Na^+	MeCN−THF (1000:1 v/v)	5.16	spect				298	6e
		MeCN−THF (1000:1 v/v)	5.48	fluo				298	6e
8j	Pb^{2+}	MeOH	5.0	spect, 0.01 M TEAC				298	13a
	Eu^{3+}	MeOH	4.8	spect, 0.01 M TEAC				298	13a
8k	Cu^{2+}	MeOH	4.3 ± 0.1	spect, 0.01 M TEAC				298	13a
	Pb^{2+}	MeOH	3.8 ± 0.3	spect, 0.01 M TEAC				298	13a
	Eu^{3+}	MeOH	4.11 ± 0.04	spect, 0.01 M TEAC				298	13a
8l	Pb^{2+}	MeOH	≤1	spect, 0.01 M TEAC				298	13a
	Eu^{3+}	MeOH	3.7 ± 0.2	spect, 0.01 M TEAC				298	13a

[a] Value checked by competition potentiometry. [b] Calculated by the reviewers. [c] Pot.(b): competition potentiometry, silver electrode, Ag^+ auxiliary cation. Pot.: direct potentiometry, silver electrode. Spect: UV spectrophotometric method. Fluo: fluorescence spectrophotometric method. TEAP: tetraethylammonium perchlorate. TEAC: tretraethylammonium chloride. [d] Calorimetric data.

As far as calix(4)-bis-crowns (**8e**−**h**) and alkali-metal and silver cations in MeOH and MeCN are concerned, in terms of stability (log K_s) these ligands are able to discriminate between the smaller cations (weak complexes are formed with Li^+ and Na^+) and the large ones (relatively stable complexes with K^+, Rb^+, and Cs^+), leading to a greater selectivity for the latter relative to the former. This was explained on the basis of the cavity size-selection principle. For processes involving **8e**,**f** and alkali-metal cations (K^+, Rb^+, Cs^+) in MeOH and MeCN, the contribution of $\Delta_cH°$ to $\Delta_cG°$ relative to $\Delta_cS°$ is dominant. For **8g**

and Rb^+ in MeCN, both parameters ($\Delta_c H°$ and $T\Delta_c S°$) contribute almost equally to complex stability while representative examples of entropy-stabilized complexes are found for **8e** with Na^+ and for **8g**,**h** with Cs^+ in MeCN. However, the most notable feature of the thermodynamics of these systems is the decrease in enthalpic stability and the entropy gain observed in the complexation of ligands containing six oxygens in the crown moieity (**8f**−**h**) and these cations in MeCN relative to MeOH. These were attributed to the different states of solvation of alkali-metal cations in these solvents and to the possibility that these ligands may be better solvated in MeCN than in MeOH. Although omitted by the authors, it should be noted that there is considerable evidence in the literature regarding specific interactions between 18-crown-6 and MeCN in the solid state and in solution. These have been carefully considered in the interesting paper by Ohtsu et al.[24] on the thermodynamics of 18-crown-6 and alkali-metal cations where similar but more dramatic effects than those observed for **8f** and these cations were found in MeCN relative to other solvents including MeOH. The authors also mention the possibility that the benzene and naphthalene substituents in **8g**,**h**, respectively, may enable cation−π interactions to be established. The implications of such interactions on the observed enthalpy and entropy data were not mentioned. A more refined insight into ligand and metal-ion complex solvation may be needed to decide what are the predominant factors contributing to the thermodynamics of complexation of these interesting systems in solution.

The binding of cations to a calix-5-crown (**8m**) has been investigated by Beer and co-workers.[19b] Stability constants in MeCN at 298 K were found to be too large to be accurately determined by UV−vis spectroscopy, and therefore, the authors correctly reported lowest limits of log K_s values that can be obtained by this technique. However, competition experiments were carried out to establish the strength of complexation of this ligand and metal cations in MeCN ($Ba^{2+} > K^+ > NH_4^+ > Na^+ > BuNH_3^+$). In this ligand the nonbridge aromatic rings in the calix(4) were quinone units. The reduction potential of the cyclic voltammogram of the ligand displayed an anodic shift upon cation complexation.

Shinkai[6e] has determined the stability constants for the complexation of Li^+ and Na^+ in MeCN−THF (1000:1) at 298 K by a calixcrown-4 with pyrene moieties appended to the upper rim (**8i**) (see Table 6). This ligand interacts selectively with Na^+. ^1H NMR measurements showed the ability of the pyrene moieties to bind a trinitrobenzene guest; complexation of sodium induced the dissociation of this complex. This was attributed to the perturbation of the conformation of the upper rim binding site, induced by change in the shape of calix(4)arene cone accompanying metal binding at the lower rim.

Other contributions involving these ligands and bivalent (Pb^{2+}, Cu^{2+}) and tervalent cations (Eu^{3+}) include stability constants of these cations with **8j**−**l** in MeOH.[13a]

Table 7. Stability Constants of Calixcrowns and Neutral Species in Various Solvents

ligand	guest	solvent	log K_s	method	T, K	ref
8n	nitromethane	$CDCl_3$	0.7 ± 0.2	NMR	303	23b
	nitromethane	CCl_4	1.4 ± 0.1	NMR	303	23b
	malonitrile	$CDCl_3$	1.2 ± 0.1	NMR	303	23b
8o	nitromethane	$CDCl_3$	1.4 ± 0.1	NMR	303	23b
	nitromethane	CCl_4	2.4 ± 0.1	NMR	303	23b
	malonitrile	$CDCl_3$	0.8 ± 0.1	NMR	303	23b
8p	nitromethane	$CDCl_3$	1.5 ± 0.1	NMR	303	23b
	nitromethane	CCl_4	2.1 ± 0.1	NMR	303	23b
	malonitrile	$CDCl_3$	1.4 ± 0.1	NMR	303	23b
8q	nitromethane	CCl_4	1.7 ± 0.1	NMR	303	23b
8r	Bu^nNH_2	EtOH, 99%	2.0 ± 0.1	spect	298	25
	Bu^iNH_2	EtOH, 99%	2.5 ± 0.1	spect	298	25
	Bu^sNH_2	EtOH, 99%	2.82 ± 0.05	spect	298	25
	Bu^tNH_2	EtOH, 99%	3.04 ± 0.05	spect	298	25

Further aspects of the thermodynamics of alkali-metal complexation by these ligands are discussed in section 6 in light of their relevance to the results of recent MD simulation studies.

3.2.2. Interactions with Neutral Species

Equilibria data for these systems are listed in Table 7.

Arduini et al.[23b] has studied the binding of neutral molecules containing acidic C−H groups (nitromethane, malonitrile) by calixcrowns with syn phenolic oxygens linked by a three-oxygen poly(ethyleneoxy) chain (**8n**−**p**) in CCl_4 and $CDCl_3$ at 303 K. ^1H NMR spectroscopy indicates that the interaction takes place between the acidic protons of the guest and π electrons of the calixarene cavity. These data show that more flexible derivatives with a longer, four-oxygen poly(ethyleneoxy) chain displayed weaker binding for both guests. A representative example is the log K_s value reported for **8q** and nitromethane in CCl_4 at 303 K, which is lower than the corresponding data for **8o** and this guest in this solvent. This was attributed to the latter, more rigid ligand possessing a more open hydrophobic cavity better able to accommodate neutral guests. It was suggested that the short crown ether strap at the lower rim helps constrain the cone into a shape closer to 4-fold symmetry than the elongated, 2-fold symmetrical shape common in the X-ray crystal structures of nonbridged lower rim functionalized calix(4)arenes. The X-ray structure of the **8p**−nitromethane adduct was reported. Kubo et al.[25] has synthesized a calix(4)crown with a binaphthyl spacer in the crown unit and 4-aminoquinone substituents at the upper rim (**8r**). Equilibrium data for this ligand and butylamine isomers in ethanol at 298 K determined by UV spectrophotometry reflects that **8r** is able to recognize selectively the various isomers. The sequence observed for a 1:1 host−guest process is as follows: $Bu^tNH_2 > Bu^sNH_2 > Bu^iNH_2 > Bu^nNH_2$.

4. Solution Thermodynamics of Upper Rim Functionalized Calixarenes

4.1. Solubilities

Gansey et al.[9c] reported the solubilities in water at 298 K of a series of calixarene derivatives substi-

tuted at the upper rim with *p*-sulfonylamino groups (**9a**−**f**) (solubility data range from 10^{-5} to 0.31 mol dm^{-3}). It was demonstrated that the introduction of one additional hydroxyl group per aromatic unit of the calix(4)arene increases the water solubility of these compounds by a factor of 100. The analytical method used to determine the concentration of the macrocycle in the saturated solution was UV spectrophotometry. Although solubility studies of these macrocycles have been conducted for purposes other than calculating thermodynamic properties, it should be emphasized that in reporting these data it is useful to provide information regarding (i) the method used to attain equilibrium between the solid and the saturated solution, and (ii) the composition of the solid phase at the equilibrium.

Without this information solubility data are of little use for thermodynamic purposes. For a comprehensive account on solubility of solids in liquids readers are referred to the guidelines provided by Cohen Adad et al. in the Solubility Data Series (IUPAC).[26]

4.2. Interactions with Protons, Metal Cations, and Organic Cations

Compared with the parent calixarenes (practically insoluble in water), considerably more proton dissociation equilibrium constants [($pK_a = -\log K_a$) or the reverse process; protonation constants ($\log K_p$)] have been reported for the phenolic protons of calix(*n*)arene derivatives suitably functionalized at the upper rim to confer water solubility. If the initial controversy regarding proton dissociation constants for the tetramer is neglected, $\log K_p$ values for these systems (**10a**−**d**) reported by various authors[3,6f,27,28a,b,29a,b] are listed in Table 8. In cases where more than one set of data is available for a given system, good agreement is found between these data. As far as the thermodynamics on these systems is concerned, the most significant contribution is that by Arena et al.[29a−c] in which the partition of $\log K_p$ (hence $\Delta_pG°$) into $\Delta_pH°$ and $T\Delta_pS°$ is reported. Thus, the large difference between the second dissociation of the phenolic groups of **10a**,**c** (6.5 pK units) is under enthalpic control. The much more positive phenolic proton dissociation enthalpy for the monoanion of the tetramer compared to the hexamer was attributed to stronger hydrogen bonding between the phenolic groups in the monoanion and the larger electrostatic repulsion between the deprotonated phenoxide groups in the dianion of the smaller, more rigid tetramer ring system. pK_a values for **10c** compared with corresponding data for acyclic triphenols and the monomer led to the conclusion that the phenolate anions (mono and di) of **10c** are stabilized by hydrogen bond formation with the neighboring undissociated phenolic groups. This was reflected in the similar $\Delta_pH°$ and $\Delta_pS°$ values observed for the last protonation steps of the water-soluble calix(4)- and calix(6)arenes. The higher entropy gain observed for the hexamer relative to the tetramer was attributed to the larger flexibility of the former derivative.

A further contribution by Arena et al.[29c] includes the four successive deprotonations of cone (**10e**) and partial cone (**10f**) conformers of *p*-sulfonylcalix(4)arene derivatives with oxyacetic moieties at the lower rim. Differences of 1.5 and 2.4 log K units between the first and fourth protonation constants of **10e** (cone) and **10f** (partial cone) were attributed to the differences in stereochemistry of these two ligands. For the cone conformer, the trends observed in the $\Delta_pS°$ values for each successive deprotonation are said to reflect the occurrence of intramolecular hydrogen binding between adjacent protonated and deprotonated carbonyl groups in the adjacent anions. For **10f**, the observed decrease in entropy gain (partially compensated by a more favorable enthalpy) in the successive protonations appears to reflect the expected decrease in dehydration effects likely to occur upon complexation with the proton in moving from the most highly hydrated tetraanionic base to the fully protonated ligand.

As regards pK_a values for neutral upper rim calixarene derivatives, Shinkai et al.[6g] have reported data for *p*-sulfonylaminocalix(4)arenes (**9g**) in water and *p*-nitrocalix(4)arenes (**9h**) in water−ethanol mixtures determined by potentiometric methods. The unusually low pK_a value for the dissociation of the first proton in **9g** (1.8) and **9h** (2.9) when compared with the acyclic analogue was attributed to the formation of strong intramolecular hydrogen bonds in these macrocycles.

Dissociation constants for the first deprotonation of a series of mono-*p*-nitrocalix(4)arenes (**9i**,**j**) in aqueous methanolic solutions have been reported by Böhmer et al.[30a] Representative data are included in Table 8. The nature of the alkyl group (**9i**,**j**) at the upper rim of these ligands were shown to influence the determined pK_a values markedly. The authors suggested that the upper rim substituents influence the proton dissociation constants by affecting the strength of hydrogen bonding in the monoanion by an indirect influence on the conformation of the phenolic groups at the lower rim. These aspects have been discussed in the interesting chapter on *Special Calixarenes* written by Böhmer and Vicens[30b] in which meaningful comparisons between pK_a values for these macrocycles and those for the monomer and corresponding trinuclear compounds have been made.

As regards the complexation of metal and organic cations, Shinkai[6h−o] has reported extensively on the behavior of upper rim derivatized calixarenes as ligands in aqueous solutions.

Starting with the metal cations, stability constants have been determined for **10a** and the lanthanides[6h] in water at 298 K, by using pH potentiometric titrations (m = 0.1 M KNO_3) where the ligand is in its deprotonated form (LH_2, omitting ionization of the sulfonate groups). The overall stability constants ($\log K_s$) for the process involving all lanthanides [M^{3+}; except scandium(III)] and LH_2 range from ~19.3 (La^{3+}) to 22.8 (Yb^{3+}). The standard deviation of the data was not reported.

The higher stability of **10c**,**g** for UO_2^{2+} (1:1 complexes) in water at 298 K ($\log K_s$ values ≅ 19.0 determined by competitive spectrophotometric titrations; pH = 10.4; I = 0.1 mol dm^{-3}) relative to other metal cations [$\log K_s$ values: **10c**-Ni^{2+}, 2.2; **10c**-Zn^{2+},

Table 8. Thermodynamics of Complex Formation of Upper Rim Functionalized Calixarenes[a] with the Proton in Water, Water−Methanol, and Water−Ethanol Mixtures

ligand	cation/ proton	solvent	process	log K_p	method[b]	$\Delta_pG°$, kJ mol^{-1}	$\Delta_pH°$, kJ mol^{-1}	method	$\Delta_pS°$, J K^{-1} mol^{-1}	T/K	ref
9g	H^+	H_2O	$L^{4-} + H^+ \rightarrow HL^{3-}$	>14	spect(b), KCl 0.1 M					298	6g
		H_2O	$H_L{}^{3-} + H^+ \rightarrow H_2L^{2-}$	≅12.5	spect(b), KCl 0.1 M					298	6g
		H_2O	$H_2L^{2-} + H^+ \rightarrow H_3L^-$	9.7 ± 0.1	spect(b), KCl 0.1 M					298	6g
		H_2O	$H_3L^- + H^+ \rightarrow H_4L$	1.8 ± 0.3	spect(b), KCl 0.1 M					298	6g
9h	H^+	85.4 wt % EtOH	$L^{4-} + H^+ \rightarrow HL^{3-}$	>14	pot.(a)					298	6g
		85.4 wt % EtOH	$HL^{3-} + H^+ \rightarrow H_2L^{2-}$	12.3 ± 0.2	pot.(a)					298	6g
		85.4 wt % EtOH	$H_2L^{2-} + H^+ \rightarrow H_3L^-$	10.9 ± 0.1	pot.(a)					298	6g
		85.4 wt % EtOH	$H_3L^- + H^+ \rightarrow H_4L$	2.9 ± 0.3	pot.(a)					298	6g
9i	H^+	MeOH−H_2O (1:1)	$L^- + H^+ \rightarrow HL$	6.0	spect(b)					298	30a,b
9j	H^+	MeOH−H_2O (1:1)	$L^- + H^+ \rightarrow HL$	4.3	spect(b)					298	30a,b
9m	H^+	H_2O	$L^{2-} + H^+ \rightarrow HL^-$	8.86	pot.(a), KCl 0.1 M					298	6o
		H_2O	$HL^- + H^+ \rightarrow H_2L$	2.91	pot.(a), KCl 0.1 M					298	6o
10a	H^+	H_2O	$H_2L^{2-} + H^+ \rightarrow H_3L^-$	11.5 ± 0.01	pot.(a), $NaNO_3$ 0.1 M	−65.7	−25.9 ± 1.7	cal(c)	134 ± 4	298	29a
		H_2O	$H_3L^- + H^+ \rightarrow H_4L$	3.34 ± 0.04	pot.(a), $NaNO_3$ 0.1 M	−19.04	2.59 ± 0.12	cal(c)	72.5 ± 1.2	298	29a
		H_2O	$L^{4-} + H^+ \rightarrow HL^{3-}$	~14	spect(b), KCl 2 M					298	6f
		H_2O		13.6	pot.(a), KNO_3 0.1 M					298	6f
		H_2O	$HL^{3-} + H^+ \rightarrow H_2L^{2-}$	12.8 ± 0.3	spect(b), KCl 2 M					298	6f
		H_2O		12.9	pot.(a), KNO_3 0.1 M					298	6f
		H_2O	$H_2L^{2-} + H^+ \rightarrow H_3L^-$	11.3 ± 0.3	spect(b), KCl 2 M					298	6f
		H_2O		11.8 ± 0.3	pot.(a), KNO_3 0.1 M					298	6f
		H_2O	$H_3L^- + H^+ \rightarrow H_4L$	3.26 ± 0.02	pot.(a), KNO_3 0.1 M					298	6f
10b	H^+	H_2O	$H_2L^{3-} + H^+ \rightarrow H_3L^{2-}$	10.96 ± 0.08	pot.(a), KNO_3 0.1 M					298	28a
		H_2O	$H_3L^{2-} + H^+ \rightarrow H_4L^-$	7.63 ± 0.05	pot.(a), KNO_3 0.1 M					298	28a
		H_2O	$H_4L^- + H^+ \rightarrow H_5L$	4.31 ± 0.01	pot.(a), KNO_3 0.1 M					298	28a
10c	H^+	H_2O	$H_4L^{2-} + H^+ \rightarrow H_5L^-$	5.02	pot.(a), $NaClO_4$ 0.1 M					298	27
		H_2O		4.99 ± 0.09	pot.(a), $NaNO_3$ 0.1M	−28.45	0.6 ± 0.2	cal(c)	97.6 ± 0.9	298	29a
				4.76 ± 0.03	pot.(a), $NaNO_3$ 0.1 M					298	28a
		H_2O	$H_5L^- + H^+ \rightarrow H_6L$	3.45	pot.(a), $NaClO_4$ 0.1 M					298	27
		H_2O		3.37 ± 0.09	pot.(a), $NaNO_3$ 0.1 M	−19.23	5.8 ± 0.3	cal(c)	84.1 ± 0.9	298	29b
				3.44 ± 0.04	pot.(a), $NaNO_3$ 0.1 M					298	28b
10d	H^+	H_2O	$H_6L^{2-} + H^+ \rightarrow H_7L^-$	9.10	pot.(a), $NaClO_4$ 0.1 M					298	27
		H_2O	$H_7L^- + H^+ \rightarrow H_8L$	7.70	pot.(a), $NaClO_4$ 0.1 M					298	27
10e	H^+	H_2O	$L^{4-} + H^+ \rightarrow HL^{3-}$	4.57 ± 0.03	pot.(a), $NaNO_3$ 0.1 M	−26.07	−2.1 ± 0.4	cal(c)	79.9 ± 1.2	298	29a,c
		H_2O	$HL^{3-} + H^+ \rightarrow H_2L^{2-}$	3.97 ± 0.02	pot.(a), $NaNO_3$ 0.1 M	−22.63	−4.6 ± 0.4	cal(c)	61.5 ± 2.1	298	29a,c
		H_2O	$H_2L^{2-} + H^+ \rightarrow H_3L^-$	3.27 ± 0.03	pot.(a), $NaNO_3$ 0.1 M	−18.66	1.7 ± 0.8	cal(c)	68.2 ± 2.1	298	29a,c
		H^2O	$H_3L^- + H^+ \rightarrow H_4L$	3.03 ± 0.03	pot.(a), $NaNO_3$ 0.1 M	−17.28	12.5 ± 0.8	cal(c)	100.4 ± 2.1	298	29a,c
10f	H^+	H_2O	$L^{4-} + H^+ \rightarrow HL^{3-}$	5.11 ± 0.01	pot.(a), $NaNO_3$ 0.1 M	−29.16	8.4 ± 0.4	cal(c)	126.0 ± 1.7	298	29c
		H_2O	$HL^{3-} + H^+ \rightarrow H_2L^{2-}$	4.61 ± 0.01	pot.(a), $NaNO_3$ 0.1 M	−26.07	3.8 ± 0.4	cal(c)	100.2 ± 1.7	298	29c
		H_2O	$H_2L^{2-} + H^+ \rightarrow H_3L^-$	3.35 ± 0.01	pot.(a), $NaNO_3$ 0.1 M	−19.2	4.6 ± 0.8	cal(c)	80.3 ± 2.1	298	29c
		H_2O	$H_3L^- + H^+ \rightarrow H_4L$	2.71 ± 0.01	pot.(a), $NaNO_3$ 0.1 M	−15.48	−1.7 ± 0.8	cal(c)	46.0 ± 2.5	298	29c

[a] For S calixarenes, charges due to the ionized sulfonating groups are omited for simplicity. [b] (a) Direct potentiometric titration; (b) UV spectrophotometric method; (c) classical titration calorimetry.

5.5; **10c**-Cu^{2+}, 8.6; **10g**-Ni^{2+}, 3.2; **10g**-Zn^{2+}, 5.6; **10g**-Cu^{2+}, 6.7 (m = 0.1 mol dm^{-3}; pH = 9.50; polarographic method)] was ascribed by Shinkai[6i] to the rigidity of the calixarene skeleton in **10c**,**g** providing a pseudoplanar arrangement of phenoxy or carboxylate oxygens to wrap around the cation. The same concepts were applied to **10b** ($\log K_s \cong 19$) but not to **10a** ($\log K_s \cong 3.2$).

However, Atwood[28b] pointed out that the X-ray crystal structures of the hexamer (**10c**), both as the parent acid and sodium salt, do not show the phenoxide groups to be arranged in any such pseudoplanar arrangement. In both structures the phenolic oxygens are arranged into two independent groups of three which are not coherently arranged to complex a central cation. The pK_a values of the phenolic hydroxyl groups show that, at the pH at which Shinkai studied the uranyl complexation, the octaanion (H_4L^{2-} in Table 8 omitting ionization of six sulfonate groups) seen in the sodium salt X-ray structure should be the dominant species.

Atwood[28c] has also pointed out recently that the binding of the uranyl cation to the sulfonate moieties cannot be ruled out. X-ray crystal structures of lanthanide complexes of the pentamer (**10b**) and transition metal complexes of the hexamer (**10c**) show the occurrence of such metal-sulfonate oxygen binding.

Indeed, Shinkai has in fact interpreted the pH-dependent uranyl cation complexation by **9m** in terms of binding occurring through the upper rim phosphonate oxygens.[6o] The pK_a values of the phosphonyl groups (Table 8) and the pH dependence of the extent of complexation (a difference of ~1.2 log K_s units for a pH change from 10.4 to 11.5 for the UO_2^{2+}−**9m** system) are consistent with the proton competing with the uranyl cation for coordination of the phosphonyl group. Complexation is optimized at the pH at which all phosphonate groups are fully dissociated as anions.

As regards the binding of organic cations (**G1**−**6**) and upper rim functionalized calixarenes (**10a**,**c**,**d**, **9m**−**o**), some representative stability constant data ($\log K_s$) are reported in Table 9 where the appropiate references are given.[6k,q,t,u] Shinkai et al.[6k] have reported stability constants and derived Gibbs energies, enthalpies, and entropies for the interactions of **10a**,**c**,**d** and ammonium cations (**G1, G2**) in D_2O. Enthalpy data were derived by the use of the van't Hoff equation.[6k] The accuracy of enthalpy (and, consequently, entropy) data should be regarded with caution due to the limitations of the van't Hoff equation which omits heat capacity changes associated with a given process, in this particular case complexation. Representative examples are comparisons made by Danil de Namor and co-workers[4j] between $\Delta_c H°$ values obtained from the temperature variation of stability constant data (van't Hoff) and those measured calorimetrically. Stödeman and Wadsö[5a,b] have recently described quantitatively how errors in the stability constants accumulate in the derived ΔH value when using this equation.

Stability constants for **10a**,**c**,**d** with protonated forms of phenol blue (**G3**) and anthrol blue (**G4**) in aqueous solutions, indicative of the order of selective host−guest interaction for each of the dyes with the different size calix(n)arenes were said to reflect a "hole size selectivity", the large anthrol blue host binding best to the octamer (**10d**) (although small differences in $\log K_s$ are observed) and the smaller phenol blue to the hexamer.[6q] A detailed calorimetric study on these systems will be useful to assess the thermodynamic origin of these interactions.

The influence of modifications to the cone shape on the preorganization of calix(4)arene-based ligands for interacting with metal cations has been carried out in MeOH.[13a] Stability constants were determined for 1:1 metal−ligand complexation processes for a series of calix(4)arene esters linked at the upper rim by a variable chain length methylene spanner (**9p**−**u**) and a limited number of cations (Na^+, K^+, and in some cases Ag^+). Derivatives with a chain length of between 8 and 10 methylene groups showed enhanced cation binding compared to the analogous tetraester with a *tert*-butyl substituent at the upper rim (**2a**). The spectrum of the ligand with eight methylene units in the bridge was consistent with the cone being nearest to 4-fold symmetry in this ligand of all in the series; this was the ligand of all in the series which showed optimum binding of all cations. The data reported [Na^+-**9s**, $\log K_s = 6.0$; K^+-**9s**, $\log K_s = 3.9$; Ag^+-**9s**, $\log K_s = 4.5$; Na^+-**9u**, $\log K_s = 6.1$; K^+-**9u**, $\log K_s = 3.8$; Ag^+-**9u**, $\log K_s = 4.5$; potentiometry and spectrophotometry; MeOH; I = 0.01 M; 298 K) hardly show any stability change in moving from **9s** to **9u**.

4.3. Interactions with Neutral Species

Stability constants of upper rim functionalized calixarenes and neutral species mostly in H_2O and $CHCl_3$ have been reported for more than 200 systems.[6r,s,7c,d,9d,31] Among the methods used, solid−liquid (sol.−liq.) and liquid−liquid (liq.−liq.) extraction techniques carefully described by Diederich and Dick[32] for measuring K_s values for 1:1 stoichiometry complexes deserve some additional comments. The sol.−liq. extraction technique requires solubility data for the guest (G) in the absence and in the presence of different concentrations of the macrocycle (L). K_s values derived from this method are referenced to the pure solvent. The liq.−liq. extraction technique requires experimental data for the partition of the guest between two mutually saturated solvents (e.g. H_2O saturated with organic phase, s_1, and organic phase saturated with water, s_2) in the absence of the ligand

$$G_{(s_1)} \rightarrow G_{(s_2)} \qquad K_{part} \tag{16}$$

and in the presence of the ligand (extraction process).

$$G_{(s_2)} + L_{(s_1)} \rightarrow GL_{(s_1)} \qquad K_{ex} \tag{17}$$

Combination of eqs 16 and 17 leads to the calculation of K_s for the complexation process

$$G_{(s_1)} + L_{(s_1)} \rightarrow GL_{(s_1)} \qquad K_s \tag{18}$$

Clearly the stability constants derived from the sol.−liq. and liq.−liq. procedures are not the same since the composition of the solvent in these processes is not the same. However, when the mutual solubility of the solvents involved is very small or negligible, approximate values of K_s are obtained as shown for the water−hexane solvent system discussed by Diederich and Dick.[32] Having stated this, the liq.−liq. extraction technique provides important quantitative information regarding the factors (K_s, K_p) controlling the selective extraction of neutral species from one solvent to another in the presence of the macrocycle.

The sol.−liq. extraction technique has been used by Gutsche to determine equilibrium data in aqueous media for aromatic hydrocarbons and tetrameric, pentameric, hexameric, heptameric, and octameric calixarene derivatives with carboxy (**9v**−**z**) and dialkylamino moieties (**9aa**−**ad**) appended to the lower rim.[7c,d] For the lower unsubstituted calixarenes the site of interaction was provided by the hydroxyl array at the lower rim which partially hosts the aromatic guest. Different size calixarenes display different patterns of selectivity for the aromatic guest which was said to be in part attributed to the steric complementarity of the guest for the host's cavity. Representative examples shown in Table 10 indicate that the strength of interaction for some systems is moderately high as reflected in the log K_s values listed in this table.

A reduction in the number of ordered water molecules at the lower rim (within the cavity) is perhaps the driving force for the complexation of these macrocycles with hydrophobic guests. One is tempted to speculate about the thermodynamic origin of these interactions. However, the fact that little is known about the solution thermodynamic behavior of these ligands and their adducts in different media particularly in water makes any discussion meaningless.

The work of Vreekamp et al.[9b] provides an excellent example of the use of geometrical isomers to demonstrate the importance of preorganization in aggregation processes, using lower rim pyridinocalix(4)arenes (**6l**,**m**) and carboxylic acids appended to the upper rim of the tetramer (**9ae**) in $CDCl_3$. Interaction through hydrogen bond formation (between hydroxyl of COOH (**9ae**) and pyridyl nitrogen of **6m/6l**) rather that a proton-transfer reaction from acid to base was the outcome of these investigations (IR in the solid state and solution). This finding is in accord with the behavior of acid−base reactions in a low-permittivity medium such as $CDCl_3$. Readers are referred to the excellent article by King[33] regarding correlations of pK_a values in water with corresponding data in a low dielectric solvent (best referred to as association rather dissociation). The reaction stoichiometry (1:1) assessed by extraction of **9ae** by the appropriate pyridinocalixarene in $CDCl_3$ was supported by vapor pressure osmometric measurements in the same solvent (302 K). Equilibrium data (estimated error 10%, uncorrected for self-association of carboxylic groups due to their low solubility in $CDCl_3$) show that **9ae** interacts more strongly with **6 l** than with **6m**. This was suggested to be due to the higher basicity of the former relative to the latter which is accord with the pK_a values for these ligands in MeOH. Discusssions regarding acid−base strength of components and their decisive role in hydrogen bond/proton transfer reactions are nicely corroborated by the work by Danil de Namor et al. on amine−calixarene interactions discussed above.[4b,c]

A procedure to correct for self-association through hydrogen bond formation which takes place in aprotic media has been reported by Reinhoudt's group[9d] for the determination of the stability constant involving two neutral species (host−guest). In this paper the concept of using calix(4)arenes (**6o**) as building blocks was illustrated.

The circular dichroism technique (CD) to determine the extent of interaction for systems involving macrocycles with chiral centers was successfully applied by Shinkai et al.[6r] to determine the equilibrium data for *p*-sulfonate calix(6)- (**10h**) and calix(8)arene (**10i**) derivatives containing chiral substituents at the lower rim. Representative data for **10h** shown in Table 10 indicate that this macrocycle is able to interact selectively with the alcohols with the formation of 1:1 inclusion complexes. Changes in the CD spectra upon complexation were attributed to the conformational changes that the macrocycle undergoes upon complexation (from alternate to cone/winged conformation) with these species. The outcome of CD spectroscopic studies was correlated with ^{1}H NMR (solvent not specified) measurements. Within the framework of thermodynamics, a great deal of information about the origin of the selective behavior of these macrocycles for the alcohols would be useful, particularly heat capacity measurements which are likely to reflect these conformational changes.

Shinkai[6s] has also designed a calix(6)arene derivatized with (arylamino)alkyl moieties at the upper rim (**9af**,**ag**) for inclusion of buckminster fullerene (C60). Data reported in Table 10 show the higher affinity of **9ag** for C60 relative to **9af**. This was attributed to both the stronger donating ability and higher preorganization of the *m*-phenylenediamine groups in the former ligand. For other contributions by Shinkai involving upper rim functionalized calixarenes (**9ah**) and neutral species, readers are referred to the original sources.[6y]

The past decade has witnessed some outstanding developments in the field of molecular biology[34] as far as "subtle" interactions are concerned. Within this context, the contribution by Schneider[31] regarding attractive interactions involving negative charges and polarizable aryl regions in host−guest systems should be mentioned with particular reference to the K_s value determined for **10a** and toluene (see Table 10), where ^{1}H NMR studies in CD_3OD indicated an upward orientation of the methyl group of toluene.

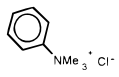
5. Solution Thermodynamics of Anion Complexation

In sharp contrast to calixarene-based cation complexing agents, only a few anion receptors have been synthesized. Factors to be considered in the design of macrocycles for anion complexation have been discussed in an excellent review paper by Dietrich.[35]

Table 9. Stability Constants of Upper Rim Functionalized Calixarenes and Organic Cations in Amphitrotic Solvents

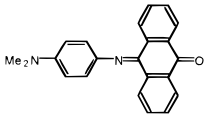
ligand	guest[b]	solvent	log K_s	method	$\Delta_c G°$, kJ mol^{-1}	$\Delta_c H°$,[a] kJ mol^{-1}	$\Delta_c S°$, J K^{-1} mol^{-1}	T, K	ref
9m	G5	I = 0.2 M, pH 9.0	2.88	spect				303	6u
9n	G6	0.025 M KCl, pH = 10	4.02	fluo				303	6t
9o	G6	0.25 M KCl, pH = 10	3.95	fluo				303	6t
10a	G1	D_2O, pD = 7.3, I = 0.1 M	3.75 ± 0.02	NMR	−21.3 ± 2.1	−25.9 ± 1.3	−15.1 ± 3.3	298	6k
	G2	D_2O, pD = 7.3, I = 0.1 M	4.32 ± 0.03	NMR	−24.7 ± 1.7	−23.8 ± 1.2	2.7 ± 2.5	298	6k
	G3	H_2O	4.67	spect				303	6q
	G4	H_2O	3.26	spect				303	6q
10c	G1	D_2O (I = 0.1 M), pD = 7.3	2.74 ± 0.03	spect	−15.5 ± 0.8	−1.05 ± 0.4	48.9 ± 1.3	303	6k
	G2	D_2O (I = 0.1 M), pD = 7.3	3.0 ± 0.1	spect	−17.2 ± −0.8	−0.6 ± 0.4	55.6 ± 1.3	303	6k
	G3	H_2O	4.75	spect				303	6q
	G4	H_2O	3.97	spect				303	6q
10d	G1	D_2O, I = 0.1 M, pD = 7.3	3.72 ± 0.01 (1)	NMR	−21.3 ± 0.8	0.0 ± 4.2	71.1 ± 1.3	303	6k
		D_2O, I = 0.1 M, pD = 7.3	3.66 ± 0.01 (2)		−20.9 ± 0.4	0.0 ± 4.2	69.9 ± 0.4		
	G2	D_2O, I = 0.1 M, pD = 7.3	4.28 ± 0.01 (1)	NMR	−24.3 ± 0.8	0.0 ± 0.4	82.0 ± 1.2	303	6k
			4.23 ± 0.01 (2)		−24.3 ± 2.1	0.0 ± 0.4	80.7 ± 0.8	303	
	G3	H_2O	4.13	spect				303	6q
	G4	H_2O	4.18	spect				303	6q

[a] Obtained from the use of the van't Hoff equation (see text). [b] Structures:

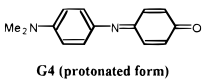


G1

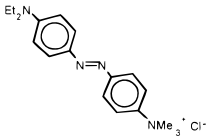
G2



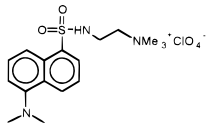
G3 (protonated form)



G4 (protonated form)



G5



G6

Table 10. Stability Constants of Upper Rim Functionalized Calixarenes and Neutral Guests

ligand	guest	solvent	log K_s	method	T, K	ref
6o	phenobarbital	$CDCl_3$	2.72	NMR	?	9d
9v	anthracene	aq 0.01 M K_2CO_3	3.96	sol.−liq. ext[a]	?	7c
9w	anthracene	aq 0.01 M K_2CO_3	4.11	sol.−liq. ext[a]	?	7c
9x	anthracene	aq 0.01 M K_2CO_3	4.04	sol.−liq. ext[a]	?	7c
	pyrene	aq 0.01 M K_2CO_3	4.04	sol.−liq. ext[a]	?	7c
9aa	anthracene	aq 0.01 M HCl	3.95	sol.−liq. ext[a]	?	7c
9ab	anthracene		3.20	sol.−liq. ext[a]	?	7c
9ac	anthracene		3.92	sol.−liq. ext[a]	?	7c
9ad	anthracene	aq 0.01 M HCl	3.88	sol.−liq. ext[a]	?	7c
9ae	6m	$CDCl_3$	3.1	NMR	298	9b
	6l	$CDCl_3$	3.9	NMR	298	9b
9af	C60	toluene	0.9	spect	298	6s
9ag	C60	toluene	2.0	spect	298	6s
10a	toluene	20% CD_3OD in D_2O	0.85	NMR	300	31
10h	1-hexanol	H_2O, 3% vol DMF (I = 0.067 M, pH = 6.9)	2.15	CD spect[b]	293	6r
	1-heptanol	H_2O, 3% vol DMF (I = 0.067 M, pH = 6.9)	3.08	CD spect[b]	293	6r
	1-octanol	H_2O, 3% vol DMF (I = 0.067 M, pH = 6.9)	3.89	CD spect[b]	293	6r
	1-decanol	H_2O, 3% vol DMF (I = 0.067 M, pH = 6.9)	3.71	CD spect[b]	293	6r
	1-dodecanol	H_2O, 3% vol DMF (I = 0.067 M, pH = 6.9)	4.15	CD spect[b]	293	6r
	2,2-dimethyl-3-hexanol	H_2O, 3% vol DMF (I = 0.067 M, pH = 6.9)	2.40	CD spect[b]	293	6r
	cyclohexanol	H_2O, 3% vol DMF (I = 0.067 M, pH = 6.9)	1.90	CD spect[b]	293	6r

[a] Liquid−solid extraction. [b] Circular dichroism spectroscopy.

As far as calixarene-based ligands able to interact with anions are concerned, the main contributions are due to the synthetic efforts of Beer et al.[19c] and Casnati et al.[23c] Thermodynamic data for these systems are limited to stability constant measurements. Representative values are given in Table 11.

Casnati et al.[23c] has synthesized calix(4)arenes mono- and disubstituted at the upper rim with urea and thiourea moieties. Stability constants for these ligands and anions in DMSO-d_6 (see table) show that the disubstituted derivative (**9ai**) binds acetate selectively in favor of butyrate, halide, and aromatic carboxylate anions. The higher stability for acetate compared with other urea-containing ligands was attributed to a cooperative chelatelike interaction of the acetate carboxylate group with two urea units forming four hydrogen bonds. A relatively high self-association constant (300 mol^{-1} dm^3) was reported for **9ai** in DMSO-d_6 at 298 K. The monosubstituted derivatives (**9aj**,**ak**) appear to interact more selec-

Table 11. Stability Constants of Calixarene Derivatives and Anions in Water and Nonaqueous Solvents

ligand	anion	solvent	log K_s	method	T, K	ref
5v	ANS	water	4.54	fluo	298	22
9n	ANS	0.025 M KCl, pH 2.5	3.39	fluo	303	6t
9o	ANS	0.025 M KCl, pH 2.5	3.26	fluo	303	6t
9ai	Br^-	DMSO-d_6	<1	NMR	298	23c
	I^-	DMSO-d_6	<1	NMR	298	23c
	Cl^-	DMSO-d_6	<1	NMR	298	23c
	benzoate	DMSO-d_6	2.46 ± 0.07	NMR	298	23c
	acetate	DMSO-d_6	3.3 ± 0.1	NMR	298	23c
	butyrate	DMSO-d_6	2.1 ± 0.2	NMR	298	23c
	o-phthalate	DMSO-d_6	2.5 ± 0.2	NMR	298	23c
	m-phthalate	DMSO-d_6	2.36 ± 0.09	NMR	298	23c
	p-phthalate	DMSO-d_6	2.3 ± 0.2	NMR	298	23c
9ak	Br^-	DMSO-d_6	<1	NMR	298	23c
	I^-	DMSO-d_6	<1	NMR	298	23c
	Cl^-	DMSO-d_6	<1	NMR	298	23c
	$H_2PO_4^-$	DMSO-d_6	<1	NMR	298	23c
	benzoate	DMSO-d_6	2.23 ± 0.04	NMR	298	23c
	acetate	DMSO-d_6	2.0 ± 0.2	NMR	298	23c
	butyrate	DMSO-d_6	2.53 ± 0.09	NMR	298	23c
	p-nitrobenzoate	DMSO-d_6	1.76 ± 0.02	NMR	298	23c
	phenylacetate	DMSO-d_6	2.4 ± 0.1	NMR	298	23c
	lactate	DMSO-d_6	<1	NMR	298	23c
9al	Cl^-	DMSO-d_6	1.85	NMR	298?	19c
	NO_3^-	DMSO-d_6	2.10	NMR	298?	19c
	HSO_4^-	DMSO-d_6	1.60	NMR	298?	19c
	$H_2PO_4^-$	DMSO-d_6	3.80	NMR	298?	19c
	acetate	DMSO-d_6	4.62	NMR	298?	19c
	benzoate	DMSO-d_6	4.58	NMR	298?	19c
	phenylacetate	DMSO-d_6	4.35	NMR	298?	19c
	β-naphthylcarboxylate	DMSO-d_6	4.30	NMR	298?	19c
9am (K^+ complex)	Cl^-	CD_3CN	3.54	NMR	298?	19d
	NO_3^-	CD_3CN	3.11	NMR	298?	19d
	HSO_4^-	CD_3CN	3.75	NMR	298?	19d
	$H_2PO_4^-$	CD_3CN	>4	NMR	298?	19d
9an	ANS	CD_3CN	3.08	fluo	303	6t
		0.2 M borate buffer, pH 9.0	3.1	fluo	303	6u
9ao	ANS	H_2O, pH 7.0	4.39	fluo	298	9e
9ap	ANS	H_2O, pH 7.0	3.36	fluo	298	9e
9aq	ANS	17% EtOH	4.36	fluo	30	6v
9ar	ANS	15% EtOH	4.99	fluo	30	6v
9as	ANS	H_2O	3.41	fluo	30	6w
9at	ANS	H_2O	3.93	fluo	30	6w
9au	ANS	H_2O	4.58	fluo	30	6w

[a] ANS = 1-anilino-8-naphthalenesulfonate. $C_{10}H_7CO_2^-$ = β-naphthylcarboxylate anion.

tively with butyrate and aromatic carboxylates than with acetate. Representative examples for **9ak** are given in the Table 11. The weak binding of acetate was attributed to the inability of this anion to establish $CH_3-\pi$ interactions with the hydrophobic cavity of the ligand. The long alkyl chain in the butyrate anion was said to enable the methyl group to extend sufficiently in the hydrophobic cavity for such binding forces to operate. Derivatives with a thiourea substituent at the upper rim (**9ak**) form stronger complexes with the anions than the equivalent derivative with an urea moiety (**9aj**). This is said to be commensurated with the higher acidity of the amide protons in thiourea and subsequent stronger hydrogen bond to the anion.

It is now well established that amide protons in proteins are able to interact with anions through hydrogen bond formation.[35] Thus, a new cobaltocenium calix(4)arene receptor containing CONH functional **9al** has been synthesized by Beer et al.[19c] The high affinity of this ligand for carboxylate containing anions is reflected in the relatively large stability constants (log K_s; see Table 11) obtained for this ligand in DMSO-d_6. For benzoate and acetate anions, the stability of this ligand is greater by 2.1 and 1.3 log units, respectively, relative to **9ai** and these anions in this solvent. In both cases, acetate appears to interact more strongly than benzoate. High stabilities for carboxylate-containing anions were attributed to the rigidity of the cobaltocenium bridging unit of the ligand which confers the amide groups the complementary topology for anion recognition.

Although the role of the solvent has not been discussed, the data deserve some comments. As far as the anions are concerned, DMSO is an excellent medium for anion complexation because of its poor solvating ability for anions. This has been attributed to the nucleophilic property of the sulfur atom, and it is reflected in the higher ionic conductivities observed in this solvent for anions relative to cations.[33] However, in this medium (dipolar aprotic) as the polarizability of the anion increases, solvation increases. Therefore, if the solvation of the anion plays a role in the binding process, stability constants are expected to decrease as a result of the competitive effect of the ligand and solvent for the anion. This

appears to be corroborated by the data shown in Table 11. Indeed, the strength of complexation follows the sequence

$$CH_3CO_2^- > PhCO_2^- > PhCH_2CO_2^- > C_{10}H_7CO_2^-$$
$$\xrightarrow{\text{increased in solvation}}$$

Having stated this, an investigation on the solution thermodynamics of the ligand and whenever possible their complex electrolytes in different media would provide a better insight into the factors controlling the selective behavior of these ligands for anions.

Another contribution by Beer et al.[19d] involves anion stability constant data for potassium and ammonium calix(4)arene complexes of individual crown ether moieties appended to the lower rim (**9am**-K^+, **9am**-NH_4^+ complexes) determined by NMR in CD_3CN.[19d] Representative stability constant data for **9am**-K^+ and anions in CD_3CN are listed in Table 11.

Among the anions, 1-*N*-anilino-8-naphthalene-sulfonate (ANS) and its interaction with calix(4)arene derivatives (**5v**,**ac**, **9n**,**o**, **9an**−**au**) to give inclusion type complexes have received considerable attention due to the enhancement in fluorescence intensity observed for this anion in the presence of these ligands.[6u−w,9e,22] Among these, **5v**, **9ao**, and **9au** show the highest affinity for this anion in aqueous medium.

An excellent example of ligand preorganization is provided by **9ao**, where the inherent hosting ability of β-cyclodextrin for this anion is enhanced by the additional environmental shielding provided by the upper rim of the calixarene.[9e]

6. Molecular Mechanics Studies

Warnek and Wipff[16b] have used molecular dynamics to simulate calix(4)bis(crowns) and the alkali-metal cations in MeOH, MeCN, H_2O, and $CHCl_3$. Free energy perturbation calculations predicted that, in MeOH, calixbis(crown 5) (**8e**) selectively bound K^+ or Rb^+ while calixbis(crown 6) (**8f**) selectively binds Cs^+. Thermodynamic parameters of complexation of alkali-metal cations and these ligands in MeOH and MeCN were discussed in section 3.2.1 (Table 6). Within the experimental error quoted in the log K_s values in methanol it is difficult to state that **8e** is able to selectively recognize among the K^+, Rb^+, and Cs^+ cations. From log K_s values for **8f** and alkali-metal cations, it appears that this ligand is slightly more selective for Cs^+ in MeOH.

Wipff and Lauterbach[16c] have simulated the calix-mono(crowns) in the gas phase, water, chloroform, and the $CHCl_3-H_2O$ interface. An issue of interest with regard to available thermodynamic complexation data for these ligands and analogous (**8c**,**d**) in MeOH and MeCN is the effect of introducing butyl substituents at the *p*-position. Experimentally it is found that introduction of a *p*-*tert*-butyl substituent (**8d**) increases the $\Delta_c H°$ (more negative) and decreases $\Delta_c S°$ relative to **8c** (see Table 6) in the complexation processes with Cs^+ in methanol. It has been suggested that this is attributable in part to a weaker solvation of the hydrophilic regions of the calixcrown containing the *tert*-butyl substituent.[23a] Experimental studies show that **8c**,**d** interchange between cone, 1,3 alternate, and partial cone conformers in MeOH; the cone conformer is predominant at 298 K.

These authors[16c] did not report calculated solvation energies of the two ligands in MeOH, but MD simulations of the alkali-metal complexes in H_2O did show that the *tert*-butyl substituent reduced the solvation of the hydrophilic cavity. The steric bulk of the *tert*-butyl group hinders the passage of water into the cavity via the annulus at the upper rim of the cone. This effect is most likely to be reflected in the solvation behavior of these ligands in MeOH and will be strongly dependent on the nature of the solvent. However, the solution thermodynamics of these ligands and their metal-ion complexes are unknown in MeOH let alone in other solvents.

Free-energy perturbation methods have been used to investigate the origins of the observed extraction selectivity of calixbis(crown-6) (**8f**) among the alkali-metal cations from water to the organic phase.[16d] An underlying message that arises from this particular article is that it is not easy to relate extraction selectivities to the thermodynamics of a single binding process, given the multitude of interactions and processes occurring in the extraction process. In fact, this has been previously emphasized by Danil de Namor and co-workers.[4c] A quantitative assessment of the individual processes which contribute to the selective extraction of metal cations from aqueous to the organic phase containing calix(4)arene esters has been recently reported.[4k]

The same authors[16e] have simulated the complexation of the uranyl cation by *p*-methylcalix(*n*)arenate ($n = 5$, 6) anions in order to investigate the origins of the observed selectivity of the related *o*-sulfonatocalix(*n*)arenes for this cation over competing divalent cations.[6i] These *p*-methylcalix(6)arene metal complexes cannot adequately represent any interactions which might occur between the cation and the upper rim sulfonate groups present in the ligands experimentally studied by Shinkai. Examination of the preferred coordination geometries found in the course of the simulation of the corresponding uranyl and copper(II) cation complexes in water led the authors to suggest that the large selectivity for the uranyl cation is driven by stronger cation−ligand interactions and stronger solvation of the uranyl−calixarenate complex. It was argued that more efficient desolvation of the metal cation may favor the complexation to the uranyl cation entropically. No relevant experimental enthalpy or entropy change data have been reported for these systems. As stated by Guilbaud and Wipff, it would be desirable to investigate the thermodynamics involved in these processes.

More recently the same authors[16f] used free-energy perturbation methods to calculate the difference between the free-energy of complexation of the uranyl and strontium cations by *p*-methylcalix(6)arene in water. Nonbonding interactions were represented by a simple Lennard−Jones potential and using Coulomb's law; necessary parameters for the uranyl

cation were first obtained by fitting calculated differences in the hydration free-energies of the two cations to experimental data. Subsequent calculations showed the differences in free energies of complexation to the ligand to favor uranyl cation over strontium. The calculated difference between the two binding free energies was less than the differences between experimentally determined free energies of binding of the uranyl and copper cations to *p*-sulfonlycalix(6)arene. It was argued that this was expected because strontium should bind more favorably to the calix(6)arene than copper due to a better steric fit in the ligand cavity and to the preference of the calixarene for binding harder metal cations.

Gibbs energy perturbation calculations predict that the ligand **4a** binds the alkali metals in the selectivity order $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$ [16a] in MeCN. To our knowledge the complexation Gibbs energies for Li^+, Na^+, and K^+ (see Table 3) are not well characterized experimentally in MeCN because the stability constants were too large to be determined accurately.[13b] However, in terms of complexation enthalpies, this ligand is selective for sodium in MeCN. Therefore, unless entropic factors dominate the complexation it is likely that in MeCN this ligand will bind sodium selectively.

The same authors have undertaken similar calculations for the binding of alkaline-earth-metal cations by the same ligand.[16g] The ligand was found to prefer to bind cations in water in the sequence $Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}$. However, for calcium and strontium the stability constants in MeOH were too large to be determined accurately (see Table 3). To justify a comparison of relative binding Gibbs energies calculated in water with experimental data in MeOH it was argued that there should be a similar relative solvation of different alkaline-earth cations in the two solvents, both for free and complexed metal cations.

Kollman has undertaken MD studies on complexes of calix-spherands with alkali-metal cations in the gas phase and H_2O.[36] The author calculated the absolute binding Gibbs energy of the calix-spherand with Rb^+ in water. This was compared with association constant data determined in $CDCl_3$ saturated with H_2O.[9a]

7. Extraction Processes

The ability of calixarene derivatives (highly insoluble in water) to extract metal cations from the aqueous to the nonaqueous phase has been investigated.[6x,9f,13a,23b] Cram's method[36] has been extensively used for the determination of the association constants, K_{assn} (eq 9). These are derived from distribution data in the mutually saturated $H_2O-CHCl_3$ solvent system in the absence, K_d (eq 19), and in the presence, K_{ex} (eq 20), of the ligand (L)

$$M^+(H_2O) + X^-(H_2O) \xrightarrow{K_d} MX(s) \qquad (19)$$

$$M^+(H_2O) + X^-(H_2O) + L(s) \xrightarrow{K_{ex}} MLX(s) \qquad (20)$$

Therefore, K_{assn} values are referenced to water-saturated $CHCl_3$. As stated by Cram,[37] this is a low precision method which provides useful correlations between K_{assn} and structure (ligand binding power and number of active sites) for systems involving alkali-metal cations and macrocycles (spherands, cryptands, crown ethers). Indeed, provided that the free and complexed species (insoluble in H_2O) as ion pairs are the predominant species in the organic phase, these data are useful since they provide quantitative information on the ability of the ligand to extract ion pairs in the organic phase. Apart from temperature, the magnitude of K_{assn} is dependent on the nature of the anion as well as the concentration of both ligand and salt (which will affect its partitioning). However, the fact that this method appears to work reasonably well in the $H_2O-CHCl_3$ solvent system does not imply that it can be universally used without seeking confirmation that ion pairs for both the free and complexed salts are the predominant species in the organic phase in the working range of concentrations. The extent of ion-pair formation for the free metal salt in the organic phase is most likely to differ from that of the complex metal salt, since the latter involves a large cation expected to have a lower tendency to form ion pairs than the former, although this may not be always the case. From several literature reports, it appears that this method as well as others have been applied in a nondiscriminatory manner to an extent that some of the data reported may prove to be the result of the numerical analysis which always produces an answer rather than the outcome of a careful investigation trying to identify the processes taking place in the organic phase under the experimental conditions used. Typical examples are the studies carried out in $H_2O-CH_2Cl_2$[13a] and H_2O-THF.[6x] It has been demonstrated[1b] that ion-pair formation constants of crown ether complexes in CH_2Cl_2 are around 10^5. As stated by Cox and Schneider,[1b] at concentrations of 10^{-4} mol dm^{-3} or lower, the ionic concentrations become appreciable. On the other hand, in CH_2Cl_2, the K^+ complex of monactin appears to be fully dissociated. Little is known about the ion-pair formation of complexed salts involving calixarenes in low dielectric media.[4k]

As far as the anion effect on extraction processes is concerned, on the basis of previous work on the use of macrocycles in liquid−liquid and liquid−solid (resins containing crown ethers as anchor groups)[4e] systems, a good starting point for anion selection is to consider single-ion values for transfer Gibbs energies (eq 21), $\Delta_t G°$, or, more conveniently, partition Gibbs energies (eq 22), $\Delta_{part} G°$, of anions from H_2O to the nonaqueous phase (the trend in $\Delta_t G°$ and $\Delta_{part} G°$ values for anions and cations is independent of the extrathermodynamic convention used).

$$X^-_{(H_2O)} \rightarrow X^-_{(s)} \qquad (21)$$

$$X^-_{(H_2O\ satd\ s)} \rightarrow X^-_{(s\ satd\ H_2O)} \qquad (22)$$

The sequence found in these data is mirrored at least qualitatively (very few exceptions are found) by K_{ex} when different anion-containing electrolytes are used in the aqueous phase. $\Delta_t G°$ values for anions

from H_2O to various solvents[1b] including $H_2O-CH_2Cl_2$ (also $\Delta_{part}G°$) have been reported.[4l] In the latter solvent system, the K_{part} value for picrate is higher by a factor of 21 than the corresponding data for ClO_4^-, which, in turn, is usually higher or equal to that of the thiocyanate anion. It therefore follows from these data that the use of SCN^- instead of picrate as the counterion in extraction processes in $H_2O-CH_2Cl_2$ involving calixarenes will lead to a considerable decrease in the magnitude of K_{ex} and, therefore, the outcome of the work carried out in this solvent system using a calixarene amide and metal-ion salts containing picrate and thiocyanate anions only confirms the expected behavior.[13f] From the above discussion, it is concluded that without disputing the validity of K_{ex} as an equilibrium constant (eq 20) its numerical value is only useful as a measure of the extracting ability of the system under a limited set of conditions. This is the reason we have deliberately omitted establishing comparisons between extraction data reported in the literature.

Caution should be taken in using extraction data as a way of assessing the selective behavior of the macrocycle for a particular guest in a single water-saturated solvent. Indeed the different parameters involved in the overall extraction process recently discussed[4k] hardly justify some of the correlations made between extraction data in a given solvent system with log K_s values in an unrelated solvent.[13a]

8. Conclusions

An essential requirement for assessing quantitatively the selective behavior of calixarenes and their derivatives for a particular guest relative to others in a given solvent and at a given temperature is the availability of accurate stability constant data. Furthermore, in order for such an assessment to be meaningful, the speciation in the system under study must be known. The trend in the field of calixarene chemistry has been to generate equilibrium data. The reliability of some of these data needs to be verified by other methods. As reflected in the information provided through the text, the thermodynamic origin of complex stability is known for a few systems in a limited number of solvents. While solvation of the ligand and its complexes in different media is often invoked to account for the thermodynamic behavior observed in the complexation process, the solution thermodynamics for most of these new nonelectrolytes (neutral ligands and their adducts with neutral species) and electrolytes (metal-ion complex salts) remain unknown. The above statements explain clearly why only few attempts[4h] have been made to establish meaningful comparisons between the thermodynamic behavior of calixarenes and their derivatives for guest species relative to that involving crown ethers and cryptands.[3]

While the contributions made on molecular dynamics for the simulation of the selective binding of these ligands with guest species are encouraging, the outcome of these efforts need to be tested. Such a test requires reliable thermodynamic data. It may be correctly argued that thermodynamics do not provide structural information; on the other hand, it is indisputable that any model proposed must fit the experimental thermodynamic data.

An important aspect to consider in the field of thermodynamics involving calixarenes is the effect of temperature on (i) the solution properties of parent calixarenes and their derivatives in a wide variety of solvents and (ii) the complexation of these macrocycles with neutral or ionic species. As reflected in the tabulated data listed in this review, these are in most cases referred to the standard temperature of 298 K. Particular emphasis should be placed on heat capacity measurements. These quantities are important since these can provide information concerning structural changes taking place in solution. In addition, the application of these systems to biological and biochemical processes requires thermodynamic data at the biological temperature.

While the outstanding synthetic and structural developments in the field of calixarene chemistry are acknowledged, the present status of thermodynamics involving these systems can be greatly benefited if more experts in the field are called into action. Within this context, the initiative taken by Commission V.8 (IUPAC) in the field of macrocyclic chemistry is most encouraging.

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