Thermodynamic study of *p*-sulfonated calixarene complexes in aqueous solution

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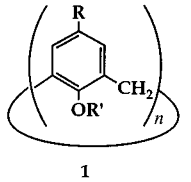
Association equilibrium constants and thermodynamic parameters (*i.e.*, ΔH and ΔS) for complexation between *N*,*N*-dimethylindoaniline and *p*-sulfonated calix[*n*]arenes in aqueous solution have been determined by means of UV–VIS spectroscopy. Equilibrium constants corresponding to calix[*n*]arene-*p*-sulfonates increase in the order [4] < [6] ≈ [8]. ΔH and ΔS values, which are interpreted in terms of the importance of the various interactions responsible for complexation, lead to a linear $\Delta H - T\Delta S$ relationship. Such a linear correlation is interpreted in terms of the extent of calixarene conformational change and of host and guest desolvation involved in the complexation process.

Introduction

There are a large number of organic and inorganic systems that are able to include a variety of organic guest molecules. Among the organic hosts, cyclodextrins represent one of the most commonly used host systems, largely due to the ready accessibility of these macrocyclic compounds.[1,2] Availability also accounts for the increasing attention that artificial bridged aromatic oligomers called calixarenes (**1**) have received over the last decades.[3] The shape and size of **1** depend on the number of phenolic units, *n*, and on the type of substituent on the aromatic nuclei, R (upper rim), and at the phenolic oxygen atoms, R′ (lower rim). Thus, calixarenes are particularly attractive for systematic studies of inclusion phenomena as a function of these parameters.



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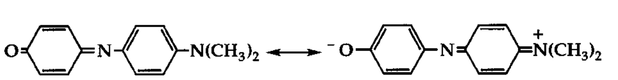
Host	*n*	R'
S4	**4**	**H**
S6	**6**	**H**
S8	**8**	**H**
SM	**6**	$\mathbf{CH_3}$
SH	**6**	$\mathbf{C_6H_{13}}$

$\mathbf{R = SO_3Na}$

There are only a handful of publications on association equilibrium constants[4–12] and thermodynamic parameters[5,7] for complexes of calixarenes and organic molecules in aqueous solution. In this context, complexation between *N*,*N*-dimethylindoaniline and *p*-sulfonated calix[6]arenes in water at 30 °C has been reported by Shinkai and co-workers.[13–15] *N*,*N*-dimethylindoaniline† (phenol blue, **2**), a well known solvent polarity indicator, is characterized by a long wavelength absorption band of intramolecular charge-transfer character.[16] According to the resonance theory, the ionic structure **2b** makes a larger contribution to the excited state. Thus, the visible absorption band undergoes a red (bathochromic) shift as the polarity of the solvent increases (*e.g.*, λ_{max} = 552 and 668 nm in cyclohexane and water, respectively).[16]



2a **2b**

In the presence of calix[6]arene-*p*-sulfonate the visible absorption band of **2** shows a significant bathochromic shift, which suggests that the host molecule is providing an environment 'more polar' than water. This observation was rationalized by postulating that the polar excited state of **2** is stabilized in the *p*-sulfonated calix[6]arene cavity both by hydrogen bonding with the hydroxy groups, and by electrostatic interactions with the sulfonate groups.[13–15] On the other hand, shifts to shorter wavelengths were detected in the presence of calix[6]arenes bearing alkyl chains (*e.g.*, **SH**). The blue (hypsochromic) shift was attributed to binding into the hydrophobic domain constituted by the aliphatic chains.[13–15] From these studies, and assuming the formation of 1 : 1 complexes, only two values of association equilibrium constants (*i.e.*, 560 M^{-1} for **S6**; 2.0×10^5 M^{-1} for $n = 6$, $R' = C_{12}H_{25}$) were determined.[14]

The dependence of association equilibrium constants and thermodynamic parameters (*i.e.*, ΔH and ΔS) on host and guest structures provides a tool to elucidate the factors governing the ability of macromolecules such as calixarenes to selectively 'host' organic molecules. Furthermore, it has been demonstrated that host–guest complexations are characterized by linear $T\Delta S - \Delta H$ relationships.[17,18] The slope (α) and intercept ($T\Delta S_0$) of linear $T\Delta S - \Delta H$ plots can be used, respectively, as quantitative measurements of the extent of conformational change of the host, and of host and guest desolvation involved in complex formation.[17,18] In fact, comparison of such parameters provides a general understanding of both the similarities and the differences in the complexation behavior of several host molecules. Thus, in order to characterize further the driving forces leading to complexation by water-soluble calixarenes, a thermodynamic study on the effects of complex formation of **2** with *p*-sulfonated calix[*n*]arenes was undertaken. ΔH and ΔS values are interpreted in terms of the importance of the various interactions responsible for complexation, and analyzed in the context of the enthalpy–entropy compensation effect.

Results and discussion

Complex formation studies were carried out by means of UV–VIS spectrophotometric titrations, and were based on the use of a series of *p*-sulfonated calix[*n*]arenes (**1**, $R = SO_3Na$) differing in the number of phenolic units, and/or the type of substituent at the phenolic oxygen atoms.

p-Sulfonated calixarenes, although water-soluble, are known to form aggregates in aqueous solution.[6,14,19] Except for **SH**, however, host molecules employed in this study have been

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† IUPAC name: 4-[[4-(dimethylamino)phenyl]imino]cyclohexa-2,5-dien-1-one.

Table 1 Association equilibrium constants for *N*,*N*-dimethylindoaniline–calix[*n*]arene-*p*-sulfonate complexes in aqueous solution as a function of temperature[a]

	T/°C					
Host	5	10	20	30	37	45
S4	511 ± 14	406 ± 24	262 ± 6	171 ± 6		106 ± 25
S6	886 ± 48	745 ± 66	491 ± 8	300 ± 32		220 ± 39
S8	884 ± 41	650 ± 21[b]	505 ± 14	369 ± 48[c]	212 ± 28	
SM	95 ± 11	82 ± 4[b]	73 ± 11	64 ± 9	53 ± 6[d]	48 ± 11
SH	3300 ± 140	3270 ± 280 2950 ± 450[b] 3250 ± 270[g]	2720 ± 360 3060 ± 380[f]	2630 ± 270	3550 ± 380[e] 3200 ± 570	

[a] pH = 9.00 (0.05 M borax buffer). [b] At 12 °C. [c] At 27 °C. [d] At 36 °C. [e] At 35 °C. [f] At 25 °C. [g] At 15 °C.

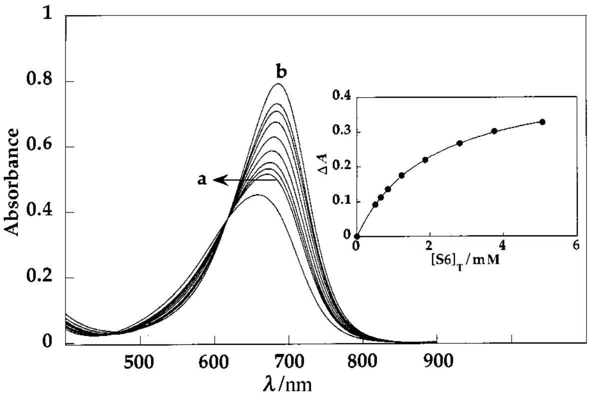

Fig. 1 Absorption spectra of *N*,*N*-dimethylindoaniline in aqueous solution (pH = 9.00, 0.05 M borax buffer) at variable concentrations of calix[6]arene-*p*-sulfonate (5×10^{-4} to 5×10^{-3} M, from a to b) at 20 °C. Inset: dependence of the change in *N*,*N*-dimethylindoaniline absorption as a function of calix[6]arene-*p*-sulfonate concentration at 20 °C.

shown not to aggregate at concentrations of at least 0.2 M in water at 30 °C.[19] **SH**, on the other hand, has a critical micelle concentration (c.m.c.) of *ca.* 0.5 mM in water at 30 °C.[6,14,19] Therefore, in order to ensure that all our determinations were carried out at **SH** concentrations strictly below the corresponding c.m.c., the latter was determined under our experimental conditions (*i.e.*, pH = 9.00, 0.05 M borax buffer) by means of surface tension measurements. The c.m.c. values obtained at temperatures between 5 and 45 °C (temperature limits of this study, see below) were systematically larger than 0.7 mM.

The addition of increasing amounts of calix[*n*]arene-*p*-sulfonate (*i.e.*, **S4**, **S6** and **S8**) to buffered aqueous solutions of **2** (pH = 9.00, 0.05 M borax buffer) results in a bathochromic shift of the wavelength of maximum absorption (*e.g.*, Fig. 1, Table 2); addition of hexamethoxycalix[6]arene-*p*-sulfonate (**SM**), in turn, causes a very small bathochromic shift (Table 2), whereas the addition of hexahexyloxycalix[6]arene-*p*-sulfonate (**SH**) results in a hypsochromic shift (Fig. 2, Table 2). These observations are overall in good agreement with those previously reported for studies in water at 30 °C.[13–15] Furthermore, in all cases an increase in the intensity of the absorption band is also detected, the magnitude depending on the type of host employed.

Spectral changes of the type depicted in Figs. 1 and 2 arise from alterations of the energy difference between the ground and excited states of the absorbing guest. These alterations are attributed to specific host–guest interactions as the result of the formation of 1 : 1 inclusion complexes [eqn. (1)]. Formation of single complexes is indeed supported by the observation of clear isosbestic points in all cases (*e.g.*, Figs. 1 and 2).

$$\mathbf{1} + \mathbf{2} \xrightleftharpoons{K_{\text{assoc}}} \mathbf{1{\cdot}2} \qquad (1)$$

Table 2 Wavelength change (Δλ) and thermodynamic parameters for *N*,*N*-dimethylindoaniline–calix[*n*]arene-*p*-sulfonate complexes in aqueous solution[a]

Host	Δλ/nm[b]	Δ*H*/kcal mol^{-1}	Δ*S*/e.u. (*T*Δ*S*/kcal mol^{-1})[c]
S4	28	−7.0 ± 0.2	−12.7 ± 0.6 (−3.8 ± 0.2)
S6	27	−6.4 ± 0.5	−9.6 ± 1.5 (−2.86 ± 0.45)
S8	22	−7.4 ± 0.6	−13 ± 2 (−3.9 ± 0.6)
SM	5	−3.0 ± 0.2	−1.7 ± 0.6 (−0.75 ± 0.18)
SH	−11	0.0 ± 0.6	16 ± 2 (4.8 ± 0.6)

[a] pH = 9.00 (0.05 M borax buffer). [b] Change relative to the wavelength of maximum absorption of *N*,*N*-dimethylindoaniline. [c] Calculated at 25 °C.

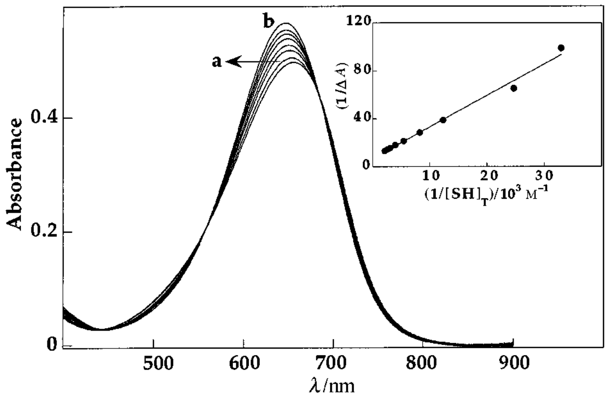

Fig. 2 Absorption spectra of *N*,*N*-dimethylindoaniline in aqueous solution (pH = 9.00, 0.05 M borax buffer) at variable concentrations of 5,11,17,23,29,35-hexasulfonato-37,38,39,40,41,42-hexakis(hexyloxy)-calix[6]arene (3×10^{-5} to 4×10^{-4} M, from a to b) at 15 °C. Inset: double reciprocal plot.

The changes observed in absorbance (Δ*A*) as a function of total calixarene concentration ($[\mathbf{1}]_T \gg [\mathbf{2}]_T$, where T refers to total concentration) can be related to the corresponding association equilibrium constant K_{assoc} according to eqn. (2), where

$$\Delta A = \frac{K_{\text{assoc}}\Delta\varepsilon[\mathbf{1}]_T[\mathbf{2}]_T}{1 + K_{\text{assoc}}[\mathbf{1}]_T} \qquad (2)$$

Δε is the difference between the molar extinction coefficients for complexed and free guest. Plots of Δ*A* as a function of total calixarene concentration are indeed non-linear, and approach asymptotically a plateau region (*e.g.*, Fig. 1, inset). Non-linear fitting of these data according to eqn. (2) leads to the association equilibrium constants (K_{assoc}) of Table 1. While a non-linear fit was preferred, the double reciprocal plots (*i.e.*

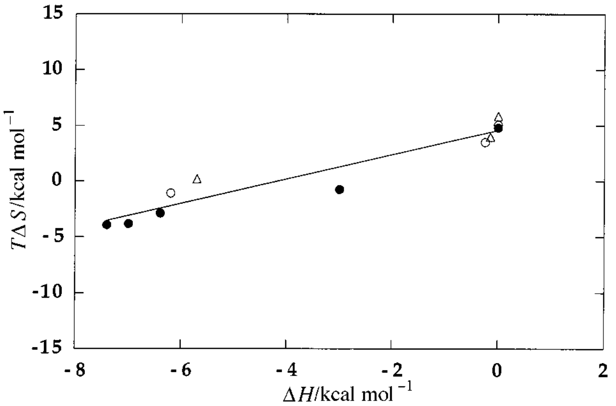

Fig. 3 Enthalpy–entropy compensation plot for complexation of various organic guests with *p*-sulfonated calix[*n*]arenes in aqueous solution: *N*,*N*-dimethylindoaniline (●, Table 2), trimethylanilinium chloride (○, refs. 5 and 7) and 1-adamantyltrimethylammonium chloride (△, ref. 7)

Table 3 Slope (a) and intercept ($T\Delta S_o$) values from $T\Delta S$ *vs.* ΔH plots for complexation by various host molecules in homogeneous solution

Host	a	$T\Delta S_o$
Antibiotic[a]	0.95	5.6
Bis(crown ether)[b]	1.03	4.6
Cyclodextrin[c]	0.90	3.1
Modified cyclodextrin[d]	1.07	5.0
Cyclophane[d]	0.78	3.4
Calixarene[e]	1.10	4.6

[a] Ref. 20. [b] Ref. 21. [c] Ref. 17. [d] Ref. 18. [e] This work.

Benesi–Hildebrand plots) are satisfactorily linear (*e.g.*, Fig. 2, inset), and the resulting K_{assoc} values are in excellent agreement with those obtained from the non-linear fittings. K_{assoc} values for calix[*n*]arene-*p*-sulfonates, for example, increase in the order **S4** < **S6** ≈ **S8**, this probably reflecting the ability of the larger calixarenes to better accommodate the guest molecule within their cavities.

Values of K_{assoc} were determined at at least five different temperatures between 5 and 45 °C in buffered aqueous solutions at pH = 9.00 (Table 1). From the linear plots (not shown) of ln(K_{assoc}) *vs.* $1/T$, thermodynamic parameters (*i.e.*, enthalpy change, ΔH, and entropy change, ΔS) for the formation of complexes were calculated. Resulting values are summarized in Table 2. Analysis of these thermodynamic values indicate that in the case of **S4**, **S6**, **S8** and **SM**, complexation is driven by a favorable change in enthalpy. In the case of **SH**, on the other hand, complexation is driven by an increase in entropy.

The enthalpy change results from several factors, one of the most important being the nature of the intermolecular host–guest interactions (*e.g.*, hydrogen bonding, electrostatic interactions, van der Waals forces). The fact that complexation with **S4**, **S6**, **S8** and **SM** is driven by a favorable change in enthalpy supports the rationalization of the observed bathochromic shift as being due to the stabilization of the polar excited state of **2** by hydrogen bonding with the hydroxy groups, and/or by strong electrostatic interactions with the sulfonate groups.

The entropy change also consists of several factors. One factor is the entropy gain from the loss of the arrangement of water molecules originally surrounding the organic molecules in a highly ordered fashion; at the same time, there is entropy loss due to the 'freezing' of motional freedom of the guest molecule as a result of the association with the host species. This balance of entropic factors clearly depends on the nature of *p*-sulfonated calix[*n*]arene employed. Entropy loss due to restricted mobility of the guest molecule predominates in the case of complexation with calix[*n*]arene-*p*-sulfonates, *i.e.*, **S4**, **S6** and **S8**, and the methyl ether derivative of calix[6]arene-*p*-hexasulfonate, **SM** (complexes characterized by hydrogen bonding and/or strong electrostatic interactions), whereas the entropy gain from the loss of the arrangement of water molecules prevails in the case of complexation with the hexyl ether derivative of calix[6]arene-*p*-hexasulfonate, **SH**.

Comparison of the values summarized in Table 2 also shows that there is a good correlation between ΔH and ΔS, *i.e.*, the less negative the change in enthalpy, the larger the corresponding change in entropy. In fact, a good linear relationship between $T\Delta S$ and ΔH is observed (correlation coefficient $r = 0.98$). Such a linear relationship implies that, whatever the cause is, the change in $T\Delta S$ is proportional to the corresponding change in ΔH. Although the origin of this 'compensatory' effect is not entirely clear, it is not unreasonable to think that, as the host–guest interactions become stronger, the degrees of freedom of the resulting complex will be significantly reduced due to the increased rigidity of the system. As a result, part of the enthalpic gain will be cancelled by the entropic loss. Similarly, as the host–guest interactions become weaker, the corresponding enthalpic loss will be partially compensated by a simultaneous entropic gain due to the greater degrees of freedom of the resulting complex.

It has been proposed that the slope (a) and the intercept ($T\Delta S_o$) of $T\Delta S - \Delta H$ plots can be rationalized, respectively, in terms of the degree of conformational change of the host and the extent of host and guest desolvation involved in the complexation.[17,18] From the data of Table 2, the resulting slope and intercept values are $a = (1.12 \pm 0.14)$ and $T\Delta S_o = (4.1 \pm 0.8)$ kcal mol^{-1}. In fact, compilation of the (few) thermodynamic parameters reported here and elsewhere[5,7] for complexation of organic guests with *p*-sulfonated calix[*n*]arenes in aqueous solution (Fig. 3, correlation coefficient $r = 0.96$) leads, within experimental error, to the same set of values, *i.e.*, $a = (1.10 \pm 0.11)$ and $T\Delta S_o = (4.6 \pm 0.5)$ kcal mol^{-1}. Interestingly, these values are quite comparable to those obtained for host–guest complexation of cationic species with macrocyclic antibiotics[20] and bis(crown ether)s,[21] and for complexation of organic molecules with cyclodextrins[17,18] and cyclophanes,[18] as shown in Table 3. Values for cyclophanes were obtained from data for a variety of cyclophanes, including *p*-sulfonated calix[*n*]arenes. However, we believe the values reported in this work provide a more specific description of *p*-sulfonated calix[*n*]arenes as hosts.

The large a and $T\Delta S_o$ values obtained for *p*-sulfonated calix[*n*]arenes imply that complexation with these host molecules is accompanied by substantial conformational changes and extensive desolvation. Calixarenes are characterized by conformational flexibility and, in general, can easily alter their conformations upon complexation.[3] In fact, the 'cone' conformation seems to be favorably adopted when a guest molecule is included in the cavity of **1** in solution.[22] Thus, a large value of a is not unexpected. Furthermore, *p*-sulfonated calix[*n*]arenes must be heavily solvated and therefore a fairly extensive desolvation is likely to occur upon complexation. In fact, reorganization of the hydrogen-bond network has been shown to play a significant role in host–guest complex formation.[1,23]

In conclusion, association equilibrium constants and the thermodynamic parameters for complexation between **2** and *p*-sulfonated calix[*n*]arenes are shown to depend on the size of the cavity and, particularly, on the type of substituent on the lower rim of the host molecule. A good linear relationship between ΔH and $T\Delta S$ values is observed. The large slope (a) obtained indicates that, upon complex formation, *p*-sulfonated calix[*n*]arenes suffer a large conformational change, which practically cancels out the enthalpic gain arising from binding. Complexation, however, is favored even in the absence of an enthalpic stabilization due to extensive desolvation as reflected by a large intercept ($T\Delta S_o$).

Experimental

N,N-Dimethylindoaniline (Aldrich) was recrystallized from ethanol before use. p-Sulfonated calix[n]arenes were prepared according to methods described in the literature,[14,24,25] and their purity and identity were checked by UV and NMR spectroscopy. Buffered aqueous solutions were made up with water purified by passage through a Millipore Milli-Q system, and reagent grade chemicals (BDH).

pH measurements were carried out on an Orion Perphect Model 350 digital pHmeter. UV–VIS absorption spectra were recorded on a Varian Cary 1 Bio UV–VIS spectrophotometer with thermostated cell compartments (VWR Model 1160A circulating bath). Surface tension measurements were performed on a Fisher Surface Tensiometer, Model 20.

To obtain the association equilibrium constants corresponding to p-sulfonated calix[n]arene complexes, changes in absorbance (ΔA) were determined, as a function of p-sulfonated calix[n]arene concentration, at the wavelength of maximum absorption for N,N-dimethylindoaniline (*ca.* 3×10^{-5} M) in buffered aqueous solution (pH = 9.00, 0.05 M borax buffer). Typical p-sulfonated calix[n]arene concentration ranges were as follows: **S4**, 0.5–6.5; **S6**, 0.5–5.0; **S8**, 0.5–5.0; **SM**, 1.0–12; **SH**, 0.04–0.40 mM.

Acknowledgements

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