Entropic origin of the sulfonate groups' electrostatic assistance in the complexation of quaternary ammonium cations by water soluble calix[4]arenes

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The inclusion of symmetrical tetramethylammonium cation (TEMA) by the water soluble calixarene hosts **1**–**8** was studied at neutral pH by ^{1}H NMR spectroscopy and compared with that of the ditopic trimethylanilinium cation (TMA). The hosts blocked in the *cone* conformation and bearing sulfonate groups at the upper rim (**2**, **3**, **5**, **7** and **8**) bind selectively the aromatic portion of TMA, whereas compound **4** which lacks sulfonate groups interacts only with the charged head group of TMA. The conformationally mobile compound **1** and the partial cone calixarene **6** include TMA cation in an unselective fashion. TEMA is complexed by hosts **1**–**7**, but not by the tetraether-tetrasulfonate receptor **8**. The binding constants for all the systems, as determined by ^{1}H NMR spectroscopy, show that inclusion is favoured by the presence of the sulfonate groups and that the complexes of the conformationally mobile receptor **1** with both guests are more stable. The thermodynamic parameters of inclusion determined by direct calorimetry for **2**–TEMA and **4**–TEMA systems show that in both cases the inclusion process is enthalpically driven and that the greater stability constant observed for **2**–TEMA with respect to that of **4**–TEMA mainly results from a less unfavourable entropic contribution, suggesting that in the **2**–TEMA complex the charged sulfonate groups cause a better desolvation of the host–guest system upon inclusion.

Introduction

Molecular recognition in water is a fundamental chemical event which controls many significant biological processes such as enzyme catalysis,[1] transport through membranes[2] and antibiotic activity.[3] In order to understand the factors which affect molecular recognition in water at a very basic level several natural and synthetic receptors have been employed. Many studies have been performed on cyclodextrins[4] since 1950, but more recently water soluble synthetic macrocycles and especially cyclophanes have been widely investigated, since they have well defined cavities with a wide range of sizes and shapes, which allow a much larger number of host–guest systems to be studied.[5]

More recently water soluble calixarenes have also been exploited as molecular hosts for the recognition of charged and neutral guest species.[6] The complexation of tetraalkylammonium salts by synthetic receptors has received extensive attention in the last few years,[7] especially after the discovery that acetylcholine can be bound to acetylcholine esterase (AChE) through interaction with some of the 14 aromatic residues present in a narrow gorge of the enzyme.[8] These studies led to the disclosure of the important role played by weak cation–π interactions[9] in the recognition process.

Shinkai and co-workers[6a] addressed the problem of trimethylanilinium cation (TMA) complexation by conformationally mobile, water soluble calix[4]arene tetrasulfonate **1** and were able to show that the guest was included into the apolar cavity of the host *via* its aromatic nucleus at acidic pH, whereas at neutral pH both the polar methylammonium head group and the apolar aromatic moiety of TMA were unselectively complexed.

Later we showed[6f] that the tetrasulfonate host **2**, which is blocked in the *cone* conformation thanks to the presence of four ionisable acetic acid units at the lower rim, and host **3**, which is rigidified by microsolvation,[6d] were both able to complex selectively only the aromatic portion of TMA. In contrast, host **4**, which is also blocked in the *cone* conformation, but lacks the sulfonate groups at the upper rim,[6f] is able to complex only the polar head group of TMA and of benzyltrimethylammonium salts. These data suggested that the cooperation between electrostatic and π–π interactions could determine the selectivity in the binding of TMA by host **2**.

However, because of this dual mode of binding, it was not possible to assess the relative importance of electrostatic or cation–π interactions in the binding of quaternary ammonium cations by the two hosts **2** and **4**. Therefore we decided to investigate this problem more deeply by using the more symmetrical tetramethylammonium cation (TEMA) as guest and by determining the thermodynamic parameters of inclusion (ΔH° and ΔS°) of these systems by direct calorimetry. Only a few examples of the complexation of the symmetrical TEMA by calixarenes are known[6c,10] and in only one case has the association constant in water been determined.[6c] In addition a more extensive investigation of TMA and TEMA complexation by the water soluble calixarenes **1**–**8**, two of which are newly synthesized compounds (**5** and **7**), was also undertaken. The results of these studies are reported in this paper.

Results and discussion

^{1}H NMR studies

Compound **1** is conformationally mobile,[6a] compound **6** is

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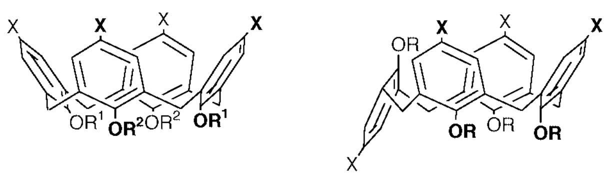
Table 1 Log *K* values for complex formation of TMA and TEMA with hosts **1**–**8**; pD = 7.3 at 25 °C[a]

	Guest		
	TMA		TEMA
Host	log *K*	Included moiety	log *K*
1	4.6(1)[b]	Ar or $N^+(CH_3)_3$	4.9(2)[b]
2	3.4[c]	Ar	3.6(1)
3	3.4[d]	Ar	2.6(1)
4	2.2[c]	$N^+(CH_3)_3$	2.4(1)
5	3.4(1)	Ar	2.6(1)
6	3.1(1)	Ar or $N^+(CH_3)_3$	3.7(1)
7	3.3(1)	Ar	3.6(1)
8	2.4(1)	Ar	No inclusion

[a] σ in parentheses. [b] The same log *K* values were reported in ref. 6*c*. [c] Data from ref. 6*f*. [d] Data from ref. 6*d*.



1 X = SO_3^-, $R^1 = R^2$ = H
2 X = SO_3^-, $R^1 = R^2 = CH_2COOH$
3 X = SO_3^-, R^1 = H, $R^2 = CH_2COOH$
4 X = H, $R^1 = R^2 = CH_2COOH$
5 X = SO_3^-, R^1 = H, $R^2 = CH_2CH_2OEt$
6 X = SO_3^-, R = CH_2COOH
7 X = SO_3^-, $R^1 = R^2 = CH_2CON(CH_3)_2$
8 X = SO_3^-, $R^1 = R^2 = CH_2CH_2OEt$

blocked in the *partial cone* structure,[11] and all other receptors studied are in the *cone* conformation.

^{1}H NMR spectra of all hosts **1**–**8**, recorded at different concentrations (10^{-4}–10^{-2} mol dm^{-3}) show no change in the signals of the various protons, thus ruling out micelle formation within the explored concentration range.

We first checked the complexation of TMA with *cone* tetrasulfonated derivatives **5**, **7** and **8** and compared the results with the data available for compounds **1**–**4**. Adding variable amounts of hosts **5**, **7** and **8** to a 10^{-3} mol dm^{-3} water solution of TMA at pD = 7.3 causes significant upfield shifts of the aromatic protons of the guest and very small upfield shifts of the methyl protons of the ammonium head group. This clearly indicates that the *cone* tetrasulfonate hosts behave as host **2**,[6f] and are able to include selectively the aromatic nucleus of TMA.

The upfield shifts observed at different host–guest ratios were used to evaluate the binding constants for the inclusion process (Table 1) through a non linear least squares analysis.[12]

The log *K* values for **5**–TMA and **7**–TMA are comparable with the values previously found for the complexes of compounds **2** and **3** (Table 1), whereas the value found for the tetraether-tetrasulfonate **8** is lower by one order of magnitude. In the case of *partial cone* tetrasulfonate-tetracarboxylic acid **6** both the methyl protons of the ammonium head group as well as the aromatic protons of the benzene residue are shifted upfield (Fig. 1).

This indicates that both moieties are unselectively included in the apolar cavity of **6** (Fig. 2) and that **6** does not behave like the cone isomer **2**, which selectively includes the aromatic nucleus of TMA, but rather looks like the conformationally mobile tetrasulfonate host **1**. These data are a clear example of the stereochemical control of guest inclusion in calix[4]-arenes; such a control, whereas well documented in metal ion complexation,[13] has seldom been detected in the recognition of molecular species.

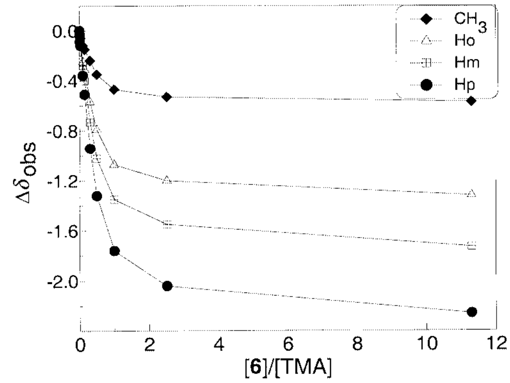


Fig. 1 Plot of $\Delta\delta_{obs}$ (ppm) *versus* [**6**]/[TMA] in D_2O; 25 °C; [**6**] = 1×10^{-3} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer).

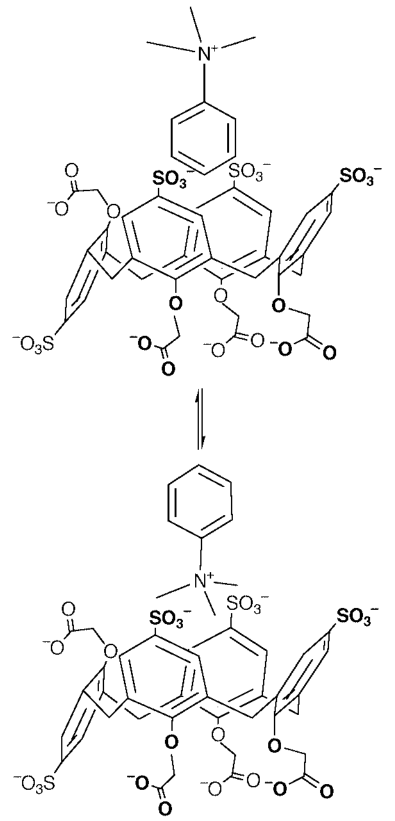


Fig. 2 Modes of inclusion of TMA into host **6**.

In the case of the more symmetrical TEMA, complexation is indicated by the methyl protons' upfield shifts, which were used to evaluate the binding constants (Table 1). No evidence for the complexation of TEMA by the *cone* tetrasulfonate tetraether **8** was obtained. Since we had ruled out *self*-association phenomena (*vide supra*), which could have reduced the availability of the apolar cavity of the host, the observed behaviour of compound **8** must be the result of conformational and steric effects. It is known that *cone* tetraalkoxy calix[4]arenes do not have a perfect C_{4v} *cone* structure in solution, but experience a residual conformational mobility between two C_{2v} flattened cone structures. In these C_{2v} conformations two opposite rings are close and the other two rings are far apart from one another.[14] Molecular mechanics calculations have previously shown that compound **8** adopts a more elongated C_{2v} shape, as a minimum energy structure, for example, with respect to compounds **2** and **5**.[15] In this structure the atomic distances between the sulfur atoms at the upper rim of two parallel aromatic rings are significantly lower than those calculated for hosts **1**, **2** and **5**. Therefore the flat aromatic ring of TMA can enter a cavity that is, on average, less regular, whereas the spherical and sterically more demanding TEMA cannot. This also explains why the

Table 2 Log K values and thermodynamic parameters of complex formation of TEMA[a] and TMA[b] with Hosts **2** and **4**; pH = 7 at 25 °C[c]

Reaction	log K	$\Delta G°$/ kcal mol^{-1}[d]	$\Delta H°$/ kcal mol^{-1}	$T\Delta S°$/ kcal mol^{-1}
2 + TEMA = (**2** TEMA)	3.5(1)	−4.8(1)	−5.8(3)	−0.9(3)
4 + TEMA = (**4** TEMA)	2.1(1)	−2.9(1)	−5.2(3)	−2.4(3)
4 + TMA = (**4** TMA)	2.2	−3.0	−4.9	−1.9

[a] This work. [b] Data from ref. 6*f*. [c] σ are given in parentheses. [d] Non SI units: 1 cal = 4.184 J.

association constant found for TMA and **8** is one order of magnitude lower than those found with the more regular and symmetrical *cone* tetrasulfonate compounds **2**, **3**, **5**, and **7**. Comparison of the complexation of TEMA by hosts **2**, **7** and **4** answers our initial question on the role of electrostatic interactions in determining both selectivity and efficiency in guest binding. The *cone* tetrasulfonate derivatives **2** and **7** form with TEMA complexes stronger than those of tetracarboxylate **4** which has no charged groups in the proximity of the binding region. For hosts **2** and **7** the electrostatic assistance to binding provided by the upper rim sulfonate groups adds to the primary cation–π interaction between the $N(CH_3)_4^+$ group and the calixarene apolar cavity and thus causes an increase of a factor of 10 in the association constant. The TEMA complexes with the difunctionalized tetrasulfonate hosts **3** and **5** show a lower stability constant in comparison with the complexes of **2** and **7** with the same guest. In this case the water molecule bridging two opposite phenolate anions blocks the difunctionalized calixarenes in a C_{2v} structure[6d] which hinders the entrance of TEMA (*vide supra*). The conformationally mobile receptor **1** shows the highest association constants both with TEMA and TMA in spite of the lack of selectivity in the binding of TMA. This is probably due to the ability of host **1** to adapt its cavity to the size of the guest and represents more evidence that induced fit recognition is often more efficient (although in this case less selective) than complexation by more preorganized receptors.[16]

Calorimetric studies

To gain a deeper insight into the factors controlling the inclusion process and in particular into the role of electrostatic interactions in the recognition of quaternary ammonium cations, we determined the $\Delta G°$, $\Delta H°$ and $\Delta S°$ for the inclusion of TEMA into the cavity of hosts **2** and **4** by calorimetry. This allowed us not only to dissect $\Delta G°$ into enthalpic and entropic contributions, but also to verify that the association constants determined by ^{1}H NMR (Table 1) and by calorimetry (Table 2) are in good agreement. $\Delta H°$ and $\Delta S°$ values obtained by direct calorimetry are known to be more accurate than those obtained through classical van't Hoff plots.[17] All the thermodynamic parameters for **2**–TEMA and **4**–TEMA systems are reported in Table 2 together with the values previously determined for the complexation of TMA by host **4**, which selectively includes the charged trimethylammonium head group of TMA.

In all cases the inclusion process is enthalpically favoured ($\Delta H° < 0$) and entropically unfavoured ($\Delta S° < 0$). The negative entropic term results from two different contributions: *i*) a favourable term ($\Delta S° > 0$) due to the desolvation of host and guest upon complexation and the consequent release of water molecules; and *ii*) an unfavourable term ($\Delta S° < 0$) due to the stiffening of the system upon inclusion of the guest in the host cavity. Methylammonium salts have a positive charge and their inclusion into host cavities leads to a desolvation greater than that found for neutral guests. In fact, all the systems reported here show, on average, a less unfavourable entropic contribution compared with the inclusion of neutral guests in cyclophane hosts.[18] However, although the desolvation term is important, the overall process is enthalpically driven for all TEMA and TMA complexes, which indicates that the cation–π interaction is driving the inclusion process.

The complexes of **4** with TEMA and TMA have the same stability and, within experimental error, the same $\Delta H°$. However they are both less stable than the complex of **2** with TEMA. Although the greater stability of **2** with TEMA results both from a more favourable enthalpic contribution and a less unfavourable entropic contribution, the $\Delta\Delta S°$ values indicate that the entropic term plays the most important role in determining the differences in the binding ability of hosts **2** and **4**. This is the result of a larger desolvation of the system due to the interaction of the $N^+(CH_3)_4$ positive charge with the negative charges of the sulfonate groups. The contribution to the overall stability of such an interaction is absent in both **4**–TEMA and **4**–TMA since **4** lacks the sulfonate groups.

Conclusions

In this paper we have shown that subtle conformational, steric and electrostatic effects determine efficiency and selectivity in the complexation of quaternary ammonium cations by water soluble calixarene hosts. Symmetrical, and sterically more demanding, TEMA is efficiently complexed by the hosts **1**–**7**, but not by the very similar host **8**, which was shown by molecular modeling to have a narrower cavity. The ditopic guest TMA is selectively complexed *via* the aromatic ring by all hosts in the *cone* conformation bearing sulfonate groups at the upper rim, whereas the upper rim unfunctionalised *cone* tetracarboxylate **4** is able to recognise only the polar alkylammonium head group of TMA. The *partial cone* conformational isomer **6** shows a behaviour similar to the conformationally mobile receptor **1**, since it complexes TMA in an unselective fashion.

The stability constants reveal that the receptor **1** is more efficient than all the other more rigid hosts **2**–**8**. It is likely that the conformational mobility of **1** renders the host cavity more adaptable to the geometrical features of the guests. The presence of sulfonate groups at the upper rim of calixarene hosts enhances the efficiency of binding of quaternary ammoniun cation by the calixarene apolar cavity, showing that the inclusion process is charge assisted.

The calorimetric data show that in all the systems reported here the complexation is enthalpically driven and thus cation–π interactions are the forces driving the inclusion process. These data also highlight the role played by the negatively charged sulfonate groups and indicate that the larger stability of the cavity with sulfonate groups (host **2**) results from a larger desolvation of this host–guest system.

Experimental

Materials

Compounds **1**,[19] **2**,[20] **3**,[21] **4**,[20] **6**,[22] and **8**[20] were synthesized as previously reported. The purity of **1**, **2**, **3** and **6** was also checked potentiometrically following the procedure described by us previously.[22,23] This could not be done for **4**, since this host is not soluble over the entire pH range in which the acid–base titration was performed, or for **7** and **8**, since these hosts do not have groups that can be protonated in the pH range of interest (pH 2–11). *N*,*N*,*N*-Trimethylanilinium (TMA) and tetramethylammonium (TEMA) chloride were obtained from Aldrich and purified by crystallization from acetonitrile and from methanol respectively. Their analytical concentrations were determined by titrating chloride ions by the Mohr method.

NaH_2PO_4 and Na_2HPO_4, used to prepare the buffer solution, were obtained from Carlo Erba. NaD_2PO_4 and Na_2DPO_4 were prepared by deuteration of the above commercial products. Doubly distilled water and Grade A glassware were used throughout.

25,27-Bis(2-ethoxyethoxy)calix[4]arene (*cone* conformation). To a suspension of calix[4]arene (2.1 g, 4.9 mmol) and K_2CO_3 (0.71 g, 5.4 mmol) in dry CH_3CN (100 ml) heated under reflux and N_2, was added, after half an hour, 2-bromoethyl ethyl ether (1 cm^3, 9.8 mmol). The mixture was refluxed under N_2 for 72 h. The solvent was evaporated and HCl (10% w/w) was added to the residue. This mixture was extracted three times with CH_2Cl_2 and the organic layer was washed with water and dried with Na_2SO_4. The solvent was evaporated and the residue was dissolved in the minimum quantity of CH_2Cl_2 and after addition of MeOH a white solid was obtained (2.1 g; 78%), mp 160 °C[24] (Found: C, 76.0; H, 7.1. Calc. for $C_{36}H_{40}O_6$: C, 76.1; H, 7.0%); δ_H (500 MHz; $CDCl_3$) 7.80 (2H, s, O*H*), 7.05 (4H, d, *J* 7.5, Ar*H*–OR *meta*), 6.88 (4H, d, *J* 7.5, Ar*H*–OH *meta*), 6.72 (2H, t, *J* 7.5, Ar*H*–OR *para*), 6.64 (2H, t, *J* 7.5, Ar*H*–OH *para*), 4.42 (4 H, d, *J* 13, ArCH_2Ar), 4.18 (4 H, t, *J* 5, ArOC$H_2$$CH_2$OEt), 3.94 (4 H, t, *J* 5, ArOCH$_2$$CH_2$OEt), 3.71 (4 H, q, *J* 7, OCH_2-CH_3), 3.36 (4 H, d, *J* 13, ArCH_2Ar), 1.28 (6 H, t, *J* 7, OCH$_2$-CH_3).

5,11,17,23-Tetrasulfonato-25,27-bis(2-ethoxyethoxy)calix[4]-arene hexasodium salt (*cone* conformation) (5). 25,27-Bis-(ethoxyethoxy)calix[4]arene (0.5 g, 0.88 mmol) was dissolved in H_2SO_4 (96% w/w; 3 cm^3) and stirred at room temperature for 24 h. The suspension obtained was frozen for 2 h and filtered. The solid was dissolved in the minimum quantity of MeOH and after addition of ethyl acetate a white solid was precipitated. This solid was filtered, dissolved in water and carefully titrated till pH 7.4. The solvent was evaporated to obtain compound **5** (0.66 g; 65%), mp 320 °C (decomp.) (Found: C, 37.2; H, 4.2; Na, 11.9%. Calc. for $C_{36}H_{34}Na_6O_{18}S_4\cdot 8H_2O$: C, 37.1; H, 4.3; Na 11.8%); ν_{max} KBr/cm^{-1} 3700–3100, 3070, 2980, 2940, 2880, 1660, 1470, 1450, 1200, 1130, 1050; δ_H (200 MHz; D_2O) 7.77 (4 H, s, Ar*H*–OR), 7.17 (4 H, s, Ar*H*–OH), 4.43 (4 H, d, *J* 12, ArCH_2Ar), 4.28 (4 H, t, *J* 4.8, ArOC$H_2$$CH_2$OEt), 4.00 (4 H, t, *J* 4.8, ArOCH$_2$$CH_2$OEt), 3.73 (4 H, q, *J* 7, O$CH_2$$CH_3$), 3.71 (4 H, d, *J* 12, ArCH_2Ar), 1.22 (6 H, t, *J* 7, OCH$_2$$CH_3$); δ_C (200 MHz; D_2O) 158.0 (Ar, *ipso*), 157.6 (Ar *ipso*), 142.4 (Ar, *para*), 137.0 (Ar, *ortho*), 136.6 (Ar, *ortho*), 130.9 (Ar, *meta*), 129.7 (Ar, *meta*), 78.4 (ArO$CH_2$$CH_2$OEt), 72.0 (ArOCH$_2$$CH_2$OEt), 69.9 (O$CH_2$$CH_3$), 34.0 (Ar$CH_2$Ar), 17.4 (OCH$_2$$CH_3$).

5,11,17,23-Tetrasulfonato-25,26,27,28-tetrakis(*N*,*N*-dimethyl-aminocarbonylmethoxy)calix[4]arene tetrasodium salt (*cone* conformation) (7). A suspension of 5,11,17,23-tetrakis-(chlorosulfonyl)-25,26,27,28-tetrakis(*N*,*N*-dimethylaminocarb-onylmethoxy)calix[4]arene[25] (0.3 g, 0.26 mmol) in a mixture of acetone (5 cm^3), pyridine (0.5 cm^3) and H_2O (0.2 cm^3) was refluxed for 16 h. The solvent was evaporated and the residue obtained was dissolved in a minimum quantity of water and carefully titrated with NaOH (0.1 mol dm^{-3}), until neutrality. The volume was reduced at 2 cm^3 and after addition of *n*-butanol a white powder was obtained. This solid was purified by reverse phase column chromatography, using water as eluent, to yield compound **7** (0.3 g; 80%), mp 250 °C (decomp.) (Found: C, 36.0; H, 5.4; N, 4.1; Na, 39.2. Calc. for $C_{44}H_{48}N_4$-$Na_4O_{20}S_4\cdot 16H_2O$: C, 36.15; H, 5.5; N, 3.9; Na, 39.4%); ν_{max} KBr/cm^{-1} 3700–3200, 1660, 1460, 1210, 1050; δ_H (200 MHz; D_2O) 7.63 (8 H, s, Ar*H*), 4.85 (8 H, s, OCH_2CO), 4.61 (4 H, d, *J* 13.5, ArCH_2Ar), 3.63 (4 H, d, *J* 13.5, ArCH_2Ar), 2.97 (12 H, s, NCH_3), 2.89 (12 H, s, NCH_3).

NMR Spectroscopy

^{1}H and ^{13}C NMR spectra were obtained at 25 °C with a Varian Inova 500 MHz spectrometer and with a Bruker AC-200 MHz spectrometer. Chemical shifts (δ, ppm) in water were externally referenced to DSS in order to avoid any possible interaction with the calix[4]arene derivatives as well as with the guest molecule; *J* values are given in Hz. All experiments were performed in deuterated phosphate buffer (0.1 mol dm^{-3}) to have a pD value of 7.3. ^{1}H NMR titrations were carried out in the two following ways: a) the guest concentration was kept constant (usually 1×10^{-3} mol dm^{-3}) while the host concentration was varied from 1×10^{-4} to 5×10^{-3} mol dm^{-3}; b) the guest concentration was varied over the concentration range 1×10^{-2} to 3.5×10^{-4} mol dm^{-3} whereas the host concentration was set to be 1×10^{-3} mol dm^{-3}. Each experiment consisted of about ten points.

Calorimetric measurements

The calorimetric runs were performed under both isothermal and isoperibolic conditions. The isothermal titrations were carried out by using a LKB 2277 microcalorimeter equipped with a perfusion system having a 2.5 cm^3 stainless steel cell; the term *micro* refers to both the volume of the titrant used and the amount of heat that can be detected under appropriate conditions. Integration of the power curve gives the heat involved in the reaction, provided the calorimeter has been calibrated by introducing known power values through a built-in precision resistor.

The isoperibol measurements were performed with a Tronac 450 calorimeter equipped with a 4 cm^3 dewar cell. This calorimeter measures the temperature changes following the addition of the titrant, through a precision thermistor which generates a voltage output; this output is converted into a heat quantity by a precision heater.[26] As recommended,[27] the dewar was calibrated beforehand, to make sure that the volume increase resulting from the addition of titrant did not cause an increase of the heat leakage constant of the calorimetric vessel. For the specific cells used for the experiments described here, the volume upper limit was found to be 3.4 cm^3; consequently, the addition of titrant never exceeded 0.3 cm^3.

General

Infrared spectra were measured on a Perkin-Elmer 648 IR spectrometer. The thermogravimetric analysis was performed on a Mettler Ta 3000 (sensitivity 2.5×10^{-6} g).

Calculations

In order to obtain *K* values from ^{1}H NMR titrations, the data were treated by using a non-linear least squares curve fitting procedure.[12] *K* and $\Delta H°$ values were obtained by using a modified version of the computer program EQDH.[27] Other details can be found in refs. 21, 22 and 28.

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