First Report on Electrochemical, Thermodynamic and Structural Aspects of the Interaction of *p-tert*-Butylcalix[8]arene and Cryptands in Benzonitrile†

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p-tert-Butylcalix[8]arene interacts with cryptands 22 and 222 in benzonitrile to give 1 : 1 electrolytes, and thermodynamic, electrochemical and structural aspects of this interaction are reported for the first time; the results suggest that cryptand 222 hosts a proton from the calixarene in its cavity.

Interactions between calix[*n*]arenes **1**, particularly calix[4]arenes and amines, is a matter of considerable recent interest.[1–5] An important consequence of the interactions involving neutral molecules is the generation of new electrolytes resulting from proton transfer reactions from the calixarene molecule to the amine. An interesting group of macrocyclic diamines is that of the cryptands discovered by Lehn.[6] Macrobicyclic cryptands are characterised by an intramolecular cavity and, therefore, these compounds have distinctive properties with respect to (*a*) amines, already considered in calixarene chemistry, and (*b*) the monocyclic cryptands (loops). Therefore, the study of the interactions between calix[n]arenes and cryptands is of interest.

Although few quantitative studies have been carried out,[7] calix[n]arenes are known to have relatively low solubility in a wide variety of solvents. Encouraged by the observation that addition of cryptands to saturated solutions of calix[*n*]arenes in various solvents increases their solubility in these media, we proceeded to study these interactions. We have now completed a preliminary electrochemical (conductance and potentiometric measurements), thermodynamic (titration calorimetry) and structural (^{13}C NMR) study on the interactions of *p-tert*-butylcalix[8]arene (Calix 8) and cryptands 22 **2**† and 222 **3** in benzonitrile at 298.15 K; the results are reported here. Benzonitrile was selected because, unlike acetonitrile (the solvent mostly used), a phase separation between water and benzonitrile can be achieved. Therefore, direct partitioning of amines in this solvent system is feasible.

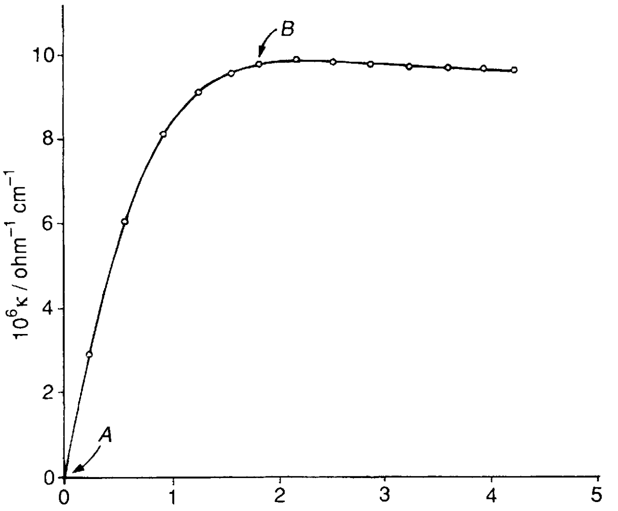


Fig. 1 Conductimetric titration of calix[8]arene and cryptand 222 in benzonitrile at 298.15 K

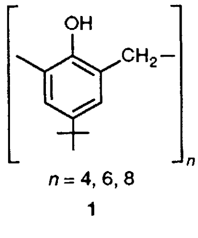
Conductance measurements have provided the basis for our present knowledge of the nature of electrolyte solutions and it is surprising that such studies have not hitherto been undertaken on these systems. Fig. 1 shows the conductimetric curve for the titration of Calix 8 (non-electrolyte, κ 0) and cryptand 222 in benzonitrile. These results unambiguously demonstrate that (*i*) as the reaction proceeds (A–B), proton transfer from Calix 8 to Cry 222 occurs, since the increase in conductivity can only be attributed to an increase of ion formation in solution; (*ii*) a 1 : 1 Calix 8–Cry 222 adduct is formed. Comparison of conductance data of Calix 8 with cryptands (222 and 22) with those for triethylamine (where only one proton is involved) showed that in the interaction of Calix 8 with Cry in benzonitrile only one proton is transferred. From conductance measurements quantitative data were obtained on the extent of (*a*) interaction between Calix 8 and Cry 222 [eqn. (1)] and (*b*) dissociation of the resulting electrolyte [eqn. (2)]. Combination of eqns. (1) and (2) yields log K'_s values for the process in eqn. (3). This was further corroborated by potentiometric studies carried out on these systems, where the titration curve for Calix 8 + Cry 222 showed only one inflection point. This result is in agreement with our recent studies on the dissociation constants (expressed as pK_a = −log K_a on a pS scale = 34.3) in benzonitrile at 298.15 K for Calix 8 [eqns. (4)–(7)], and for cryptand 222 [eqns. (8) and (9)].

$$\text{Calix 8} + \text{Cry 222} \xrightarrow[3.70]{\log K_s} [\text{Calix 8}^- \text{ Cry 222 H}^+] \qquad (1)$$

$$[\text{Calix 8}^- \text{ Cry 222 H}^+] \xrightarrow[-\,2.52]{\log K_a} \text{Calix 8}^- + \text{Cry 222 H}^+ \qquad (2)$$

$$\text{Calix 8} + \text{Cry 222} \xrightarrow[1.18]{\log K'_s} \text{Calix 8}^- + \text{Cry 222 H}^+ \qquad (3)$$

$$\begin{aligned}
&\text{Calix 8} \longrightarrow \text{Calix 8}^- + \text{H}^+ && \text{p}K_{a_1} = 17.42 && (4)\\
&\text{Calix 8}^- \longrightarrow \text{Calix 8}^{2-} + \text{H}^+ && \text{p}K_{a_2} = 20.01 && (5)\\
&\text{Calix 8}^{2-} \longrightarrow \text{Calix 8}^{3-} + \text{H}^+ && \text{p}K_{a_3} = 26.99 && (6)\\
&\text{Calix 8}^{-3} \longrightarrow \text{Calix 8}^{4-} + \text{H}^+ && \text{p}K_{a_4} = 30.42 && (7)\\
&\text{Cry 222 H}^{2+} \longrightarrow \text{Cry 222 H}^+ + \text{H}^+ && \text{p}K_{a_1} = 15.18 && (8)\\
&\text{Cry 222 H}^+ \longrightarrow \text{Cry 222} + \text{H}^+ && \text{p}K_{a_2} = 18.40 && (9)
\end{aligned}$$



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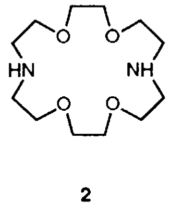

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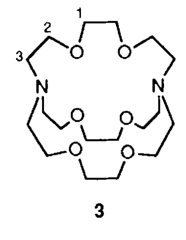

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† In this communication, for ease of comparison between the monocyclic and bicyclic compounds, the monocycle 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane **2** is denoted as cryptand 22 (Cry 22).

Table 1 Thermodynamic data for the interaction of *p-tert*-butylcalix[8]arene and amines (cryptand 222, cryptand 22 and triethylamine) in benzonitrile at 298.15 K

Amine	$\log K_s$	$\Delta_c G°$ /kJ mol^{-1}	$\Delta_c H°$ /kJ mol^{-1}	$\Delta_c S°$ /K^{-1} mol^{-1}
Cry 222	3.84 ± 0.06	−21.92	−57.29 ± 0.67	−118.6
Cry 22	3.15 ± 0.04	−17.98	−37.34 ± 0.81	−65.0
Et_3N	3.97 ± 0.24	−22.66	−34.50 ± 2.20	−39.7

Therefore, for the process illustrated by eqn. (3), a $\log K'_s$ value of 0.98 is calculated. Considering that two independent methods have been used to derive these data, the agreement between this value and that of 1.18 (conductimetry) is considered to be excellent.

A reflection of the lack of enthalpy and entropy data in the field of calixarene chemistry is found in the latest review by Izatt *et al.*[8] It may be correctly argued that thermodynamics do not provide structural information about the processes taking place. Nevertheless, provided suitable methods are used to derive highly accurate thermodynamic data, any model proposed must fit the thermodynamic experimental data.[9,10] Table 1 shows the first results obtained calorimetrically in the area of calixarene chemistry for processes involving neutral molecules. These data are referred to the process represented by eqn. (1) (where Cry = 222 or 22). For comparison purposes, $\Delta_c G°$, $\Delta_c H°$ and $\Delta_c S°$ values for Calix 8 and Et_3N are also included. Again, an excellent agreement is found between $\log K_s$ for cryptand 222 (conductimetry) and the value obtained by titration calorimetry.

The free-energy term reveals that, as far as the cryptands are concerned, the tendency for charge transfer complex formation is selective. In all cases, the process is enthalpically controlled and takes place with a considerable loss of entropy, which may be partly associated with the interaction of two components to give a single unit (*i.e.* ion pair). However, the most striking feature of these results is the enthalpy data; in particular for cryptand 222 (its value is almost twice that for triethylamine). These results strongly suggest that, as far as the cryptands are concerned, the process is not limited solely to protonation of the nitrogen atom of the ligand (as in triethylamine). Indeed, the proton in a poor solvating medium like benzonitrile and with the possibility of being hosted in a hydrophilic environment (cavity of 222) is more likely to choose this medium and therefore, interact with all electronegative atoms of the molecule. For cryptand 22 the electronegative sites are reduced (relative to 222) to the circular array of nitrogen and oxygen atoms and, therefore, interactions between the proton and this ligand are weaker as reflected in the enthalpy data. This interpretation is supported by ^{13}C NMR studies. The spectrum of cryptand 222 **3** consists of three lines corresponding to the C-1, C-2 and C-3. Upon complexation with calix[8]arene, the resonances move to higher frequency. To a lesser extent, this is also observed for cryptand 22. In both cases, the symmetry of the molecule is maintained after complexation with the proton. Results will be reported shortly.

Finally, we wish to stress that the interaction between calix[8]arene and cryptands may be regarded as a double 'pH switching mechanism' by which, as a result, the inherent binding properties of both the calix[8]arene and the cryptands are altered. Studies involving other calixarenes and various amines in several media are now in progress. The emphasis is directed towards electrochemical[11] and thermodynamic characterisation of these processes, a relevant aspect of chemistry which as far as calixarenes are concerned has not been developed.

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