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Charge Assisted Hydrophobic Binding of Ethanol Into the Cavity of Calix[4]arene receptors in Aqueous Solution.

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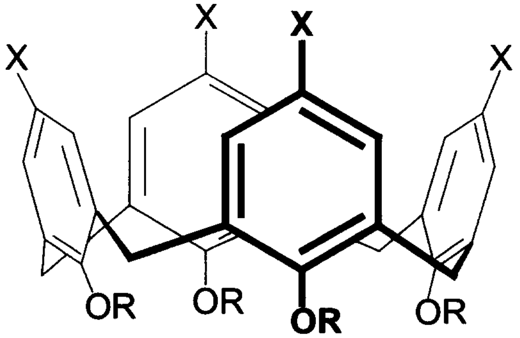
Abstract. Ethanol is included into the hydrophobic cavity of the water soluble calixarenes **1** and **2** in aqueous solution, with the alkyl residue pointing towards the cavity and the hydroxyl group facing the bulk of the solvent. No inclusion is detected for **3**, and this suggests that the sulphonate groups serve as anchoring points. © 1997 Elsevier Science Ltd.

In the last few years a number of water-soluble calixarenes have been reported[1-5] which form inclusion complexes with organic cations in solution[6] and a variety of organic compounds in the solid state[7,8]. However very little is known on the inclusion of small polar neutral organic guests by calixarene receptors in aqueous solution

We have now evidence that ethanol is included into the cavity of the water soluble calix[4]arene derivative, **1** and **2**. To the best of our knowledge this is the first example of inclusion of ethanol by calixarene receptors in aqueous solution ever reported in the literature.[9] We had previously shown[10] that **1** adopts a rigid *cone* conformation and possesses a preorganized apolar cavity in water and thus is potentially able to accomodate organic species of suitable size and characteristics.



1, X = SO_3^-, R = $-CH_2-COO^-$; **2**, X = SO_3^-, R = H; **3**, X = H, R = CH_2-COO^-.

The ^1H NMR spectrum of the **1**-EtOH system (Figure 1) shows that the signals of both the methyl and methylene protons of ethanol are shifted upfield if compared with the chemical shift values obtained for the free guest (δ_{CH3} = 1.157, δ_{CH2} = 3.628, ppm) under the same experimental conditions (pD = 7.3, [EtOH] = 10^{-2} mol

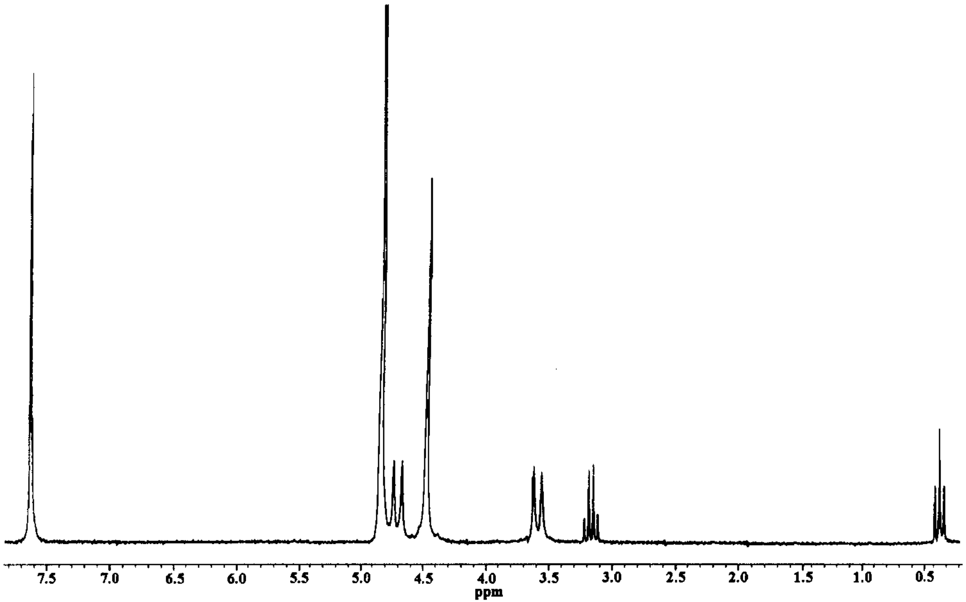


Figure 1. ^{1}H NMR spectrum of 1-EtOH complex. D_2O, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer), 25 °C, 200 MHz. [1] = [EtOH] = 1 x10^{-2} mol dm^{-3}.

dm^{-3}), whereas no change in the chemical shift values of 1 are detected. This indicates that EtOH is included in the cavity of 1 and undergoes the diamagnetic ring current effect of the aromatic calixarene moieties.[11]

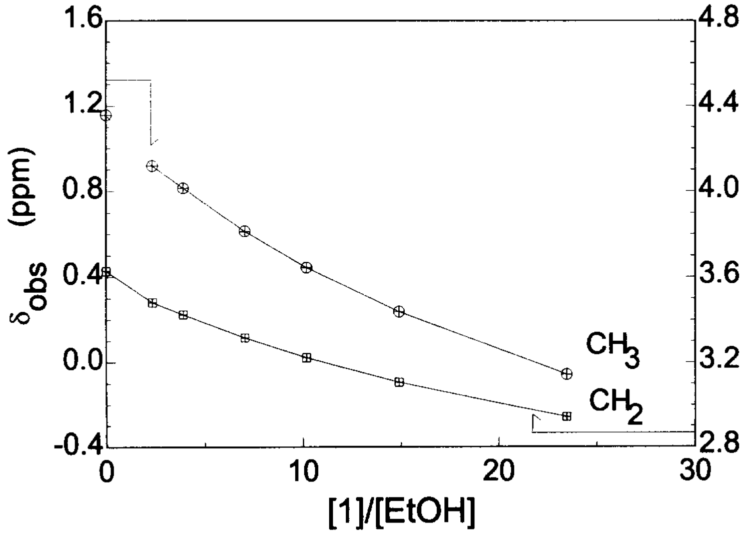


Figure 2. Plot of δ_{obs} *versus* [1]/[EtOH], in D_2O, 25 °C, [EtOH] = 8 x10^{-4} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer).

Figure 2 shows the chemical shifts of the methyl and methylene protons of EtOH as a function of the [Host]/[Guest] ratio. The observed chemical shifts are the average resulting from the fast exchange between free and included guest. These data were used to evaluate the binding constant for the inclusion process of EtOH into **1** through a non linear least square analysis;[12] this equilibrium turned out to have a logK=1.8.[13] The ^{1}H NMR titration experiments were run by keeping the guest concentration fixed (8 x 10^{-4} mol dm^{-3}) and allowing the host concentration to vary. It is noteworthy that the shielding effect is significantly greater for the methyl than for the methylene protons. This indicates that the aliphatic portion of ethanol is included into the cavity of **1** while the OH group faces the bulk of water molecules.

The analogous ^{1}HNMR experiments run for **2** and **3**[10] show that EtOH is not included by the calix[4]arene derivative **3**, while it is included by the *p*-sulphonatecalix[4]arene **2**. This supports the hypothesis that the EtOH inclusion is assisted by the presence of the sulphonate groups, which serve as anchoring points.[14] Also for ligand **2** we have carried out ^{1}HNMR titrations (Figure 3). Again the methyl protons are more shifted (although to a lesser extent) than the methylene protons, thus indicating that also in the **2**-EtOH system the alkyl residue is incorporated by the cavity whilst the hydroxyl group is exposed to the bulk of water molecules. The Table shows that in the **2**-EtOH system the $\Delta\delta_{max}$ value for the methylene protons is greater than that observed for **1**-EtOH. In principle this could be ascribed *i*) to the flexibility[15] of **2**, which tends to level off the difference or *ii*) to an equilibrium of inclusion in which the alkyl residue and the hydroxyl group are alternatively incorporated by the cavity. However, it seems unlikely that the polar OH group would prefer to interact with an apolar cavity

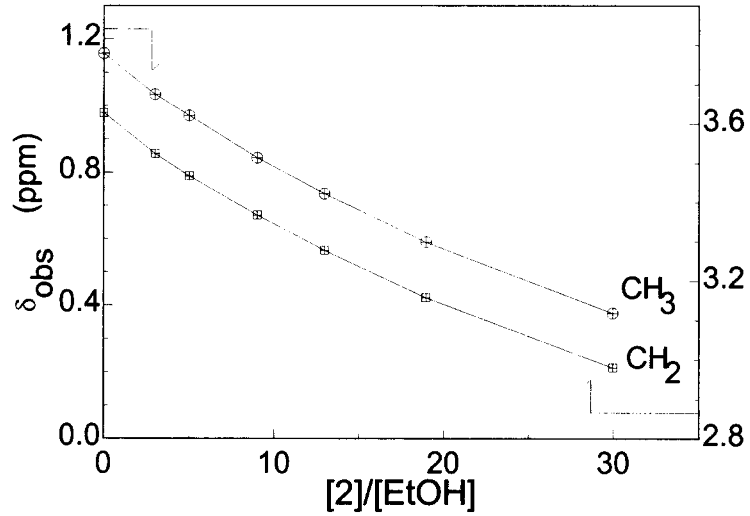


Figure 3. Plot of δ_{obs} *versus* [**2**]/[EtOH], in D_2O, 25 °C, [EtOH] = 8 x10^{-4} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer).

Table. Log K, $\delta_{complex}$ and $\Delta\delta_{max}$ ($\delta_{free\ guest}$ - $\delta_{complex}$) for **1**-EtOH and **2**-EtOH complexes.

	log K[a]	δ_{CH3}	$\Delta\delta_{CH3}$	δ_{CH2}	$\Delta\delta_{CH2}$
1-EtOH	1.80 (6)	-1.12	2.28	2.39	1.24
2-EtOH	1.47 (4)	-0.70	1.86	2.08	1.55

[a] Standard deviations are given in parentheses.

rather than with the dipoles of the solvent. Calorimetric work is in progress to clarify the forces driving the inclusion in these systems.

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REFERENCES AND NOTES.

1. Gutsche, C.D.; *Calixarenes*, J. F. Stoddart Ed., The Royal Society of Chemistry: Cambridge, 1989.
2. Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409..
3. Vicens, J., Böhmer, V. *Calixarenes: A versatile class of macrocyclic Compounds*. Kluver Academic Publishers, 1991.
4. Böhmer, V. *Angew. Chem., In Ed. Eng* **1995**, *34*, 713.
5. Pochini, A.; Ungaro, R. in *Comprehensive Supramolecular Chemistry*, Vol. 2; Vögtle, F. Ed., Pergamon Press, 1996; pp.135-138.
6. Shinkai, S. in Ref. 2, pp. 173-198.
7. Atwood, J.L., Bott, S.G. in reference 2, pp.199-210, and references therein.
8. Atwood, J.L.; Hamada, F.; Robinson, K.D.; Orr, G.W.; Vincent, R.L. *Nature* **1991**, *39*, 683-684.
9. Ethanol and other simple alcohols have been complexed in water by cyclotetrachromotropylene, a host with large hydrophobic surfaces: Poh, B. L.; Tan, C. M. *Tetrahedron* **1993**, *42*, 9581.
10. Casnati, A.; Ting, Y.; Berti, D.; Fabbi, M.; Pochini, A.; Ungaro, R.; Sciotto, D.; Lombardo, G.G. *Tetrahedron*, **1993**, *49*, 9815-9822.
11. Franke, J.; Vogtle, F.; *Complexation of Organic Molecules in Water Solution,* in *Topics in Current Chemistry,* Vogtle, F.; Weber, E. Eds.; Springer-Verlag: Berlin, Heidelberg, 1986, Vol. 132, pp. 135-170.
12. Legget, D.J. *J. Chem. Education* **1983**, *60*, 707-710.
13. The same logK value was obtained regardless of the shifts (methyl or methylene protons signals) taken into account in the refinement procedure.
14. Arena, G.; Casnati, A.; Contino, A.; Lombardo, G. G.; Sciotto, D.; Ungaro, R. *J. Am. Chem. Soc.*, submitted. This paper shows that the polar head of trimethylanilium faces the bulk of water molecules (with the aromatic residue included in the cavity) when sulphonate groups are attached at the upper rim.
15. Shinkai, S.; Araki, K.; Koreishi, H. *Chem. Lett.* **1986**, 1351.

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