



Complexation of small neutral organic molecules by water soluble calix[4]arenes

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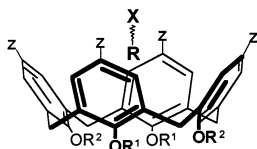
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Abstract

The inclusion of small neutral organic guests (alcohols, ketones and nitriles) by water-soluble calix[4]arene receptors was studied by ¹H NMR spectroscopy at neutral pH. The guests are included into the host hydrophobic cavity by their apolar aliphatic residues. The binding constants, determined by ¹H NMR titrations, confirm the importance of charge assistance in the apolar binding of guests inside calixarene cavities and highlight the role played by the conformational properties of the receptors in the recognition process. © 2000 Elsevier Science Ltd. All rights reserved.

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The recognition of neutral organic molecules by synthetic receptors is a topic of current interest in supramolecular¹ and analytical² chemistry. Recently, we have extensively investigated the complexation properties of water soluble calixarenes towards organic ions³ and amino acids⁴ in aqueous solution. We have also shown⁵ that ethanol can enter the hydrophobic cavity of calixarenes **1** and **2** in water, and that the inclusion is assisted by the presence of sulphonate groups at the upper rim. We have now extended these preliminary studies to several small neutral organic molecules, i.e. methanol (MeOH), ethanol (EtOH), *n*-propanol (PrOH), acetone (DMK), butanone (MEK) and acetonitrile (MeCN) as guests using compounds **1–5** as hosts.



X = CN, OH, COMe
R = Me, Et, *n*-Pr

- 1** Z = SO₃H, R¹=R² = H
2 Z = SO₃H, R¹=R² = CH₂COOH
3 Z = H, R¹=R² = CH₂COOH
4 Z = SO₃H, R¹ = H, R² = CH₂CH₂OEt
5 Z = SO₃H, R¹=R² = CH₂CH₂OEt

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The synthesis of the conformationally mobile compound **1**⁶ as well as compounds **2**, **3** and **5**⁷ blocked in the cone conformation, was previously reported, and that of compound **4** will be reported elsewhere. The inclusion of the above mentioned guests by hosts **1–5** was studied in D₂O by ¹H NMR at pD=7.3. The complexation of all guests takes place through insertion of the aliphatic moiety of the guest into the calixarene cavity. In most cases this results from a better host–guest complementarity, since the terminal polar groups of the guests are directed towards the polar sulphonate groups of the host and to the solvent, whereas the guest apolar chains face the host aromatic rings. As an example, we report the observed changes in chemical shifts of PrOH induced by the complexation with host **2** (Fig. 1).

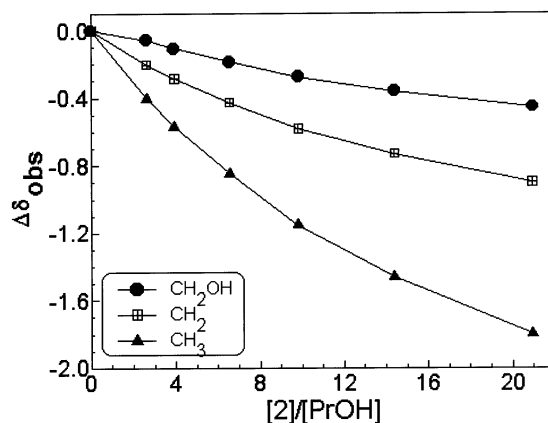


Figure 1. Plots of $\Delta\delta_{\text{obs}}$ (ppm) versus $[2]/[\text{PrOH}]$, in D₂O, 25°C, $[\text{PrOH}] = 9 \times 10^{-4} \text{ mol dm}^{-3}$, pD = 7.3 (0.1 mol dm⁻³ phosphate buffer)

Upon inclusion, the guest protons experience an upfield shift that follows the order CH₃>CH₂>CH₂–OH, thus indicating that the aliphatic moiety of the guest is selectively included into the cavity of **2** while the OH group faces the sulphonate groups and the water molecules, as previously observed for the complexes of EtOH with hosts **1** and **2**.⁵ The analogous plot for 2-butanone shows that both methyl and ethyl residues can be inserted into the host cavity (Fig. 2).

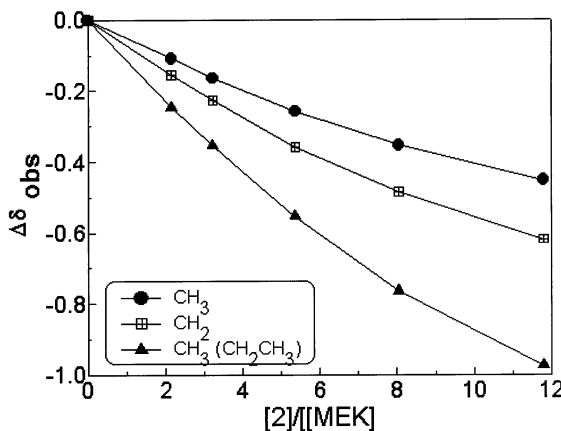


Figure 2. Plots of $\Delta\delta_{\text{obs}}$ (ppm) versus $[2]/[\text{MEK}]$, in D₂O, 25°C, $[\text{MEK}] = 1.1 \times 10^{-3} \text{ mol dm}^{-3}$, pD = 7.3 (0.1 mol dm⁻³ phosphate buffer)

The binding constants were obtained by analysing the ^1H NMR titration data using a non-linear least-squares fitting procedure;⁸ $\log K$ values are reported in Table 1.

Table 1
 $\log K$ values^a of complex formation of acetonitrile (MeCN), acetone (DMK), butanone (MEK), ethanol (EtOH) and propanol (PrOH) with **1**, **2**, **3** and **4** (pD=7.3; 25°C)^b

Reaction	$\log K$	Reaction	$\log K$
1 -MeCN	1.2(1)	3 -MeCN	1.6(1)
1 -DMK	1.7(1)	3 -DMK	NDI ^d
1 -MEK	1.8(1)	3 -MEK	NDI ^d
1 -EtOH	1.5 ^c	3 -EtOH	NDI ^d
1 -PrOH	1.5(1)	3 -PrOH	NDI ^d
2 -MeCN	1.4(1)	4 -MeCN	NDI ^d
2 -DMK	1.5(1)	4 -DMK	1.2(1)
2 -MEK	1.7(1)	4 -MEK	1.2(1)
2 -EtOH	1.8 ^c	4 -EtOH	1.0(1)
2 -PrOH	1.8(1)	4 -PrOH	1.0(1)

^a σ in parentheses; number of independent runs=4.

^b No complexation is observed for **5**.

^c Ref. 5.

^d NDI=no detectable inclusion.

To the best of our knowledge these are the first experimental values ever reported for the complexation of small neutral organic molecules by calixarene receptors in aqueous solution, with the exception of our preliminary results concerning ethanol.⁵ Interestingly MeOH is not complexed by hosts **1**–**5**. One possible explanation is that the complexation of MeOH is disfavoured because inclusion of the small methyl group inside the hydrophobic cavity would lead to a partial inclusion of the polar OH group, which would cause the polar hydroxyl group to be less exposed to the polar solvent.

The analysis of the data reported in Table 1 reveals some striking but interesting results. First of all, compound **5** does not include any of the guests. The same was observed for the inclusion of native L- α -amino acids⁴ and is due to the peculiar conformation of the host, which reduces the available space for complexation.⁴

Sulphonated calix[4]arenes **1** and **2** are able to complex the investigated guests, whereas compound **3**, which lacks the sulphonate groups at the upper rim, shows no complexation ability, with the exception of acetonitrile. This result confirms the importance of charge assistance in the apolar binding of guests inside calixarene cavities. The results obtained with acetonitrile and host **3** can be explained considering that this guest is probably less solvated in water and can undergo apolar complexation even without the assistance of the charge at the upper rim. Host **2**, fixed in the cone conformation, is more efficient for EtOH and PrOH, whereas the conformationally mobile compound **1** shows a better binding for acetone and 2-butanone. These data show that the inclusion capabilities of the investigated hosts are strictly correlated with their conformational properties.

Host **4** is the least efficient and selective among the receptors investigated here. In fact, owing to the lower rim difunctionalisation, this compound, is blocked in a C_{2v} conformation ('pinched cone') which renders the cavity less accessible.

In conclusion, we have shown for the first time that small polar organic molecules, such as alcohols, ketones and acetonitrile, which are usually found inside the apolar cavity of calix[4]arenes in the solid state,⁹ are complexed in aqueous solution, and that the inclusion process is controlled by subtle conformational and electrostatic effects.

Acknowledgements

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