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A New Water-Soluble Calix[4]arene Ditopic Receptor Rigidified by Microsolvation: Acid-Base and Inclusion Properties

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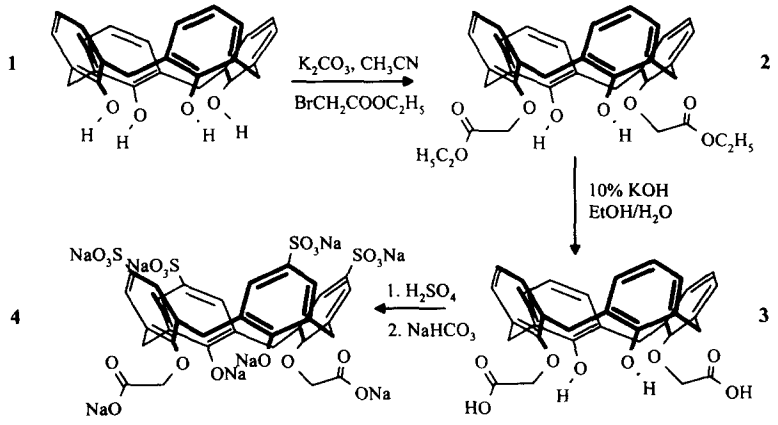
Abstract: The coordination of a water molecule, bridging two distal phenolate anions of the tetrasulphonated calix[4]arene 1,3-dicarboxylic acid, has a remarkable influence on the acid base and inclusion properties of the ditopic receptor. © 1997 Elsevier Science Ltd. All rights reserved.

In the last few years evidence has been accumulated showing that preorganization plays a fundamental role in *molecular recognition* by synthetic receptors.[1] Preorganization and rigidity of host molecules are usually obtained by covalently linking binding groups or rigid spacers to suitable templates.[2]

Calix[4]arenes are very interesting host molecules and their conformational properties have been widely exploited to induce selectivity in the recognition of ions and neutral molecules.[3] Recently the acid-base and molecular inclusion properties of the conformationally mobile water soluble calix[4]arene tetrasulphonate[4] and its tetracarboxylated derivative fixed in the *cone* conformation[5], have been studied. It has been found that these two compounds behave differently. Calix[4]arene tetrasulphonate binds unselectively both the ammoniummethyl and the phenyl moieties of trimethylanilinium (TMA), whilst its tetracarboxylate derivative binds the phenyl moiety selectively[5a, 5c].

In this paper we report the synthesis of a new water soluble dicarboxylic acid derivative, **4**, together with a combined spectroscopic and thermodynamic (including direct calorimetry) study, which shows that rigidification of the calix conformation in solution is attained through a water molecule bridging two opposite distal phenolate anions of the host. Microsolvation effects often play an important role in chemical and biological processes[6], although they are difficult to detect. In fact only few examples have been reported in literature[7, 8].

Compound **4** was synthesized[9] from **1**, according to the following Scheme. **4** is highly water soluble and exists in solution in the *cone* conformation as indicated by *i)* the presence of a single AX system for the Ar-CH_2-Ar protons and *ii)* the remarkable difference between the chemical shifts of the equatorial and axial



methylene protons ($\Delta\delta$= 0.73 ppm). The molecular inclusion properties of host **4** towards TMA were investigated. ^{1}HNMR spectrum of the **4**-TMA system (Figure 1), measured at pD = 7.3 clearly shows that TMA is included in the cavity of **4** in the way depicted in the same Figure. In fact, upon complexation, all the aromatic protons of the guest are shifted to higher fields if compared with the free guest ($\Delta\delta$ (ppm), H_{ortho} = 0.88; H_{meta} = 1.36; H_{para} = 1.88, [Host] = [Guest]= 10^{-3} mol dm^{-3}), whereas an almost negligible ($\Delta\delta$ = 0.15 ppm) upfield shift is detected for the -N(CH$_3$)$_3$ protons. Although small, the diamagnetic shift ($\Delta\delta$ = 0.18 ppm) (Figure 1) detected for the two pairs of *ortho* aromatic protons of **4**, that resonate at δ (ppm) = 7.32 in the uncomplexed host[9], provides further support to the inclusion of TMA into the calixarene cavity. On the other hand the δ values of Ar-CH$_2$-Ar host protons do not change upon TMA inclusion showing that the free host **4** is preorganized (Figure 1) since its symmetry is not modified upon the complexation of the guest.

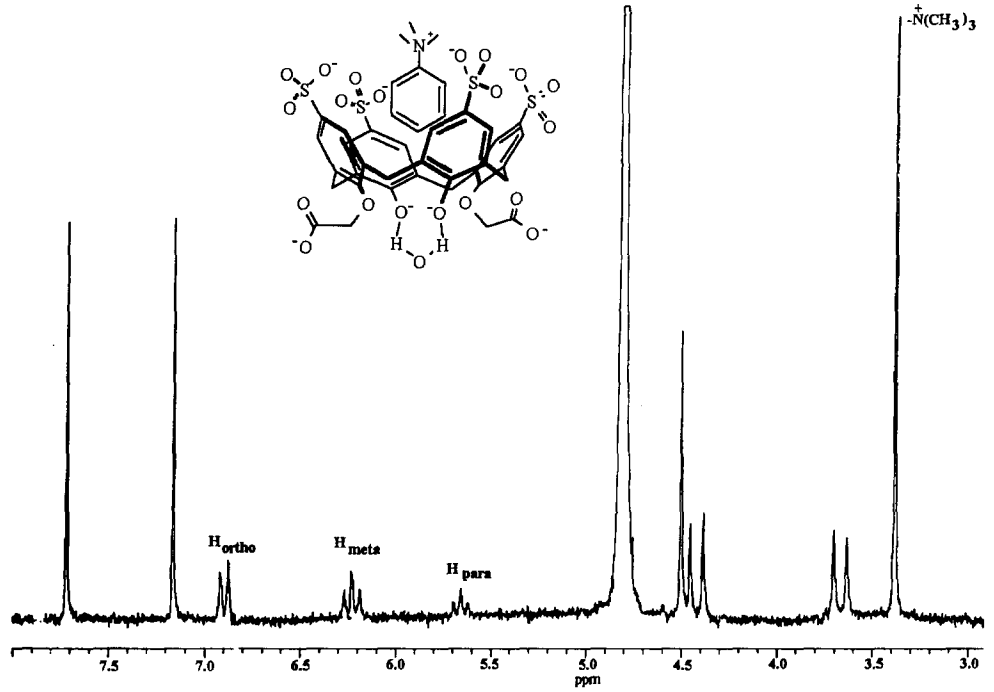


Figure 1. ^{1}H NMR spectrum of the **4**-TMA system (D_2O, [**4**] = [TMA] = 1 x 10^{-3} mol dm^{-3}, pD = 7.3, 25° C, 200 MHz). δ values (ppm) of free TMA (D_2O, pD = 7.3, [TMA]=1 x 10^{-3} mol dm^{-3}) H_{ortho} = 7.83, H_{meta} =7.65 , H_{para} = 7.61, N(CH$_3$)$_3$ = 3.64.

The binding constant value (log K = 3.38) has been obtained by measuring the chemical shift values of the *ortho, meta* and *para* aromatic protons of the guest as a function of the [Host]/[Guest] ratio; complexation induced shift data (CIS) (Figure 2) were refined by using a non linear least-squares fitting procedure[10]; at 100% complexation, CIS values ($\Delta\delta$, ppm) from the fit are: H_{para} = 3.51, H_{mata} = 2.62, H_{ortho} = 1.57. The selective inclusion of TMA aromatic moiety into the calixarene apolar cavity is different from that reported[4] at neutral pH for the inclusion of TMA into the conformationally mobile *p*-tetrasulphonatedcalix[4]arene, where complexation of TMA occurs unselectively *via* both the aromatic and the aliphatic moieties, but closely resembles the binding mode of the conformationally rigid terasulphonated-tetracarboxylated derivative.[5c] The selective inclusion of the aromatic moiety is due to the rigidification of the calixarene cavity, that is in turn to be ascribed to a "clip" active over the entire protonation range of the

two hydroxyl groups. This clip can only result from solvent effect and/or hydrogen bonding. For clarity, in the discussion that follows, only the charges of the protonation site (*i.e.* lower rim) are taken into consideration.

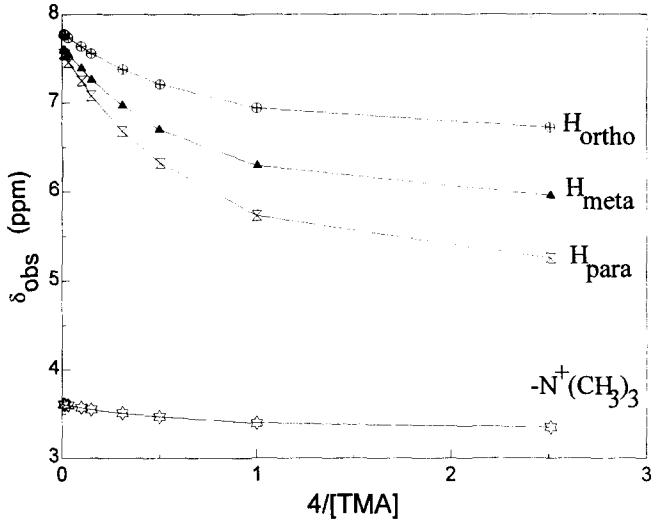


Figure 2. Plot of chemical shifts of TMA protons (δ ,ppm) *vs* [**4**]/TMA in D_2O, 25 °C, [**4**]=1 x 10^{-3} mol dm^{-3}, pD = 7.3.

The log K_1 of protonation (see Table) shows that the first proton is going onto an anionic system (4 -) that is quite stabilized; in fact $logK_1$ is some 2 logK units lower than the logK of *p*-hydroxybenzenesulphonate (logK = 8.62).[11]

Table . Log K Values and Thermodynamic Parameters for the Protonation of the Phenolate Groups of **4** (L) and *p*-Hydroxybenzenesulphonate (L')[c] at 25°C and I = 0.1 mol dm^{-3} ($NaNO_3$).[a]

Reaction				log K	ΔG°[b]	ΔH°	ΔS°
L	+ H	⇄	HL	6.86(1)	-9.35(1)	-6.8(5)	9(2)
HL	+ H	⇄	H_2L	6.58(1)	-8.97(1)	1.0(3)	33(1)
L'	+ H	⇄	HL'	8.62	-11.75	-3.5	27.6

[a] Standard deviations are given in parentheses. [b] ΔG° and ΔH° in kcal mol^{-1}, ΔS° in cal mol^{-1} deg^{-1}. [c] Ref. 11.

The $logK_2$ value is also lower than the logK of the monomer and indicates that the proton is entering a markedly stabilized system also at this stage. $LogK_3$ and $logK_4$ are typical of the protonation of carboxylate groups and their thermodynamic values will not be discussed here. Interestingly, a comparison with the thermodynamic values of the monomer shows that the lowering of $logK_1$ and $logK_2$ results from different thermodynamic factors, namely the lowering of $logK_1$ is mainly due to a less favourable entropic contribution (9 *vs* 27.6 cal mol^{-1} deg^{-1}) whilst the lowering of $logK_2$ results from a significantly unfavourable enthalpic contribution (1.0 *vs* -3.5 kcal mol^{-1}). This is quite peculiar for a hard-hard interaction[12] for which

the first protonation step is usually associated with a large entropic change, resulting from the release of water molecules into the bulk of the solvent and by an enthalpic change value that is almost close to zero. In the present case, the entropic contribution value associated with the first protonation step indicates that the entering of the first proton causes neither the release of a considerable number of molecules into the bulk of the solvent (which should result in a $\Delta S >> 0$[12]) nor a significant order-disorder change; the enthalpic contribution value (-6.8 kcal mol^{-1}), unusually large for a typical *hard-hard* interaction, shows that *i)* no ion-dipole bonds are destroyed and *ii*) a "strong" stabilizing interaction is taking place at this stage. On the other hand the extra-stabilization of the lower rim system, that has formally four negative charges, cannot result from hydrogen bonding due to protons, since, at this pH, the system is fully deprotonated. This, together with the observation that the title ligand behaves as a preorganized structure, leads to the conclusion that the lowering of $\log K_1$ is to be ascribed to hydrogen bonding resulting from a water molecule bridging the distal phenolate oxygens. The thermodynamic changes associated with the second protonation step provide further support to this conclusion. The entering of the second proton onto the second phenolate oxygen destroys the favourable hydrogen bond network ($\Delta H > 0$) and confers to the system a somewhat greater flexibility ($\Delta S > 0$). Thus, the fully deprotonated system is preorganized thanks to a water molecule that acts as a clip; in the monoprotonated system such a clip (O---H-O-H---O) is replaced by a more efficient one (O---H^+---O) that is lost as the second proton enters the O---H^+---O system.

These results show that subtle microsolvation effects can play an important role not only on the acid-base but also on the molecular inclusion properties of macrocyclic receptors.

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9. All new compounds synthesized **2-4** show satisfactory elemental analyses. NMR patterns are consistent with a 1,3 position of the carboxylic groups.

Compound **2**: m.p.=174-6°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.35 (6H, t, OCH_2CH_3, J = 7.1Hz), 3.40 (4H, d, $ArCH_2Ar$, H_{eq}, J =13.2 Hz), 4.33 (4H, q, OCH_2CH_3), 4.49 (4H, d, $ArCH_2Ar$, H_{ax}), 4.73 (4H, s, OCH_2CO), 6.66 and 6.69 (2H, t, ArH_{para}, J =7.3 Hz), 6.89 and 7.07 (4H, d, ArH_{meta}),7.55 (2H, s, OH); MS (DCI): *m/z 566.6 (M*$^+$calcd. 566.2).

Compound **3**: m.p.= 310-2°C (dec.); δ (ppm) ^{1}HNMR ($CDCl_3/CD_3OD$ = 10/1, 300 MHz): 3.27 (4H, d, $ArCH_2Ar$, H_{eq}, J=13.2 Hz), 4.12 (4H, d, $ArCH_2Ar$, H_{ax}), 4.48 (4H, s, OCH_2CO), 6.53 and 6.60 (2H, t, ArH_{para}, J=7.2 Hz), 6.73 and 6.91 (4H, d, ArH_{meta}); MS (DCI): *m/z* 540.5 (M^+ calcd. 540.2).

Compound **4**: m.p.=250-2°C (dec.); δ (ppm) ^{1}HNMR (D_2O, 200 MHz) : (ppm) 3.67 (4H, d, Ar-CH_2-Ar, H_{eq}, J=13.8 Hz), 4.40 (4H, d, Ar-CH_2-Ar, H_{ax}), 4.53 (4H, s, O-CH_2-CO), 7.32 (4H, s, ArH), 7.69 (4H, s, ArH).

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