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On the Acidity of the Hydroxyl Groups in Calix[4]arenes and the Dissociation-dependent Conformational Change

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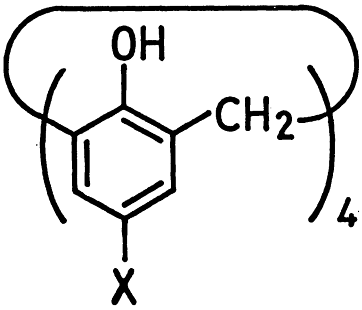
By using a water-soluble calix[4]arene derivative and a p-nitro-substituted calix[4]arene the pK_a values of the OH groups were determined for the first time. The first dissociation occurred at $pH < 1$ while the dissociation of the last proton occurred at $pH > 11$, indicating that these molecules have a super-acidic proton as well as a super-basic oxy-anion within a molecule. We also found that the calixarene conformation changes as a function of medium pH. These novel findings are rationalized in terms of strong intramolecular hydrogen bonding among the OH groups.

The chemistry of cyclodextrins has occupied a central interest in host-guest chemistry for last two decades, and many functionalized cyclodextrins which can partly mimic the action of enzymes have been exploited.1-3) Recently, Gutsche and co-workers4) have reported on a series of new cyclic molecules called "calixarenes": they are cyclic oligomers made up of benzene units like cyclodextrins made up of glucose units. Thus, they are expected to be useful to design enzyme mimics in totally synthetic systems. However, one has to estimate the pK_a's of the OH groups in calixarenes before he enjoys molecular design of calixarene-based enzyme mimics, because they are profoundly associated with the calixarene conformations. It is known that the OH groups form very strong intramolecular hydrogen bonding.5) Therefore, the pK_a's should be quite different from those of the corresponding noncyclic analogs. Determination of the pK_a's has been attempted repeatedly,6,7) but to the best of our knowledge there exist no reliable reported data. Conceivably, this is due to the difficulty to synthesize calixarene derivatives usable for titration: for example, water-soluble calixarenes for potentiometric titration or chromophoric calixarenes for phototitration. Recently, we synthesized calix[4]arene derivatives of water-soluble 18) and nitro-substituted 2.9) These are ideal molecules to estimate the pK_a's of the OH groups. We here address the first example for pK_a determination of calixarenes and evidence that the calixarene conformation is profoundly related to the dissociation of the OH groups.



$1H_4$: X = SO_3Na
$2H_4$: X = NO_2

The potentiometric titration of tetrasodium calix[4]arene-p-tetrasulfonate (1) is illustrated in Fig. 1. Computer analysis of the titration curve established that (i) the first dissociation ($1H_4 \rightleftharpoons 1H_3^-$) occurs in very acidic pH region, the pK_{a1} being lower than 1, (ii) the second and the third dissociation ($1H_3^- \rightleftharpoons 1H_2^{2-} \rightleftharpoons 1H^{3-}$) give pK_{a2} = 3.0 and pK_{a3} = 4.0, and (iii) the dissociation of the last proton ($1H^{3-} \rightleftharpoons 1^{4-}$) occurs in very basic pH region, the pK_{a4} being higher than 11. This pK_a estimation was further supported by phototitration.[10] As compared with p-hydroxybenzenesulfonate, $1H_4$ is an acid stronger by more than seven log units while 1^{4-} is a base stronger by more than two log units (Table 1). The remarkable pK_a separation is attributed to intramolecular hydrogen bonding in calix[4]arene.[5]

As p-nitrocalix[4]arene (2) was not so soluble in water, the titration

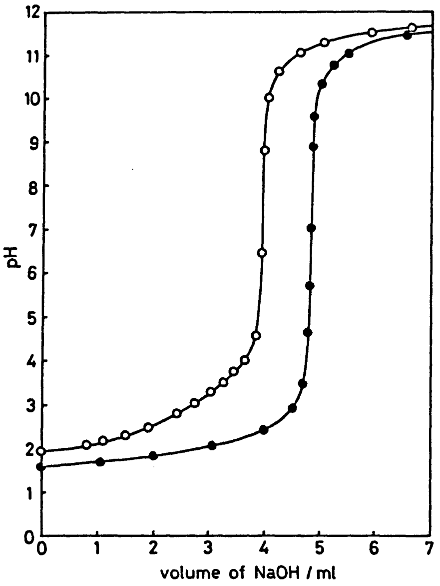


Fig. 1. Potentiometric titration of 1 by 0.1 mol dm^{-3} NaOH at 30 °C. ● blank (20 ml of 26.6 mmol dm^{-3} HCl), ○ 7.38 mmol dm^{-3} of Na_31H plus 26.6 mmol dm^{-3} HCl in 20 ml of water.

Table 1. pK_a values for 1, 2, and the noncyclic analogs[a)]

Compound	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}
1	<1	3.0±0.4	4.0±0.4	>11
p-Hydroxybenzenesulfonate	8.9±0.1			
2[b)]	<0	10.3±0.3	13±1	>14
p-nitrophenol[b)]	7.1±0.1			

a) 30 °C.
b) Water:tetrahydrofuran = 70:30 (v/v). The pK_a values are not corrected.

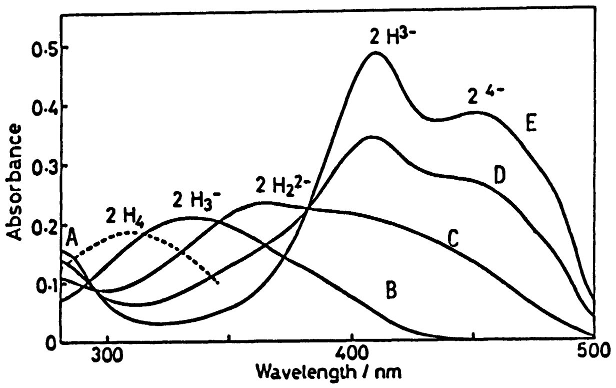


Fig. 2. pH-Dependent spectral change in 2 (8.90×10^{-6} mol dm^{-3}) in water:THF = 70:30 (v/v) at 30 °C. The spectra were recorded at 12% $HClO_4$ (A), pH 3.5-8.5 (B), pH 11.5 (C), pH 13.5 (D), and pH 14 (E).

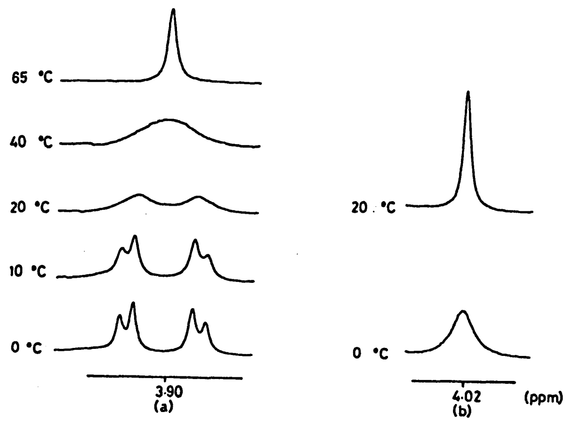


Fig. 3. ^{1}H-NMR spectra of the $ArCH_2Ar$ methylene protons of 1 in D_2O: Me_2SO-d_6 (2:1 v/v). (a) pH 9.0 with borate buffer, (b) 0.04 mol dm^{-3} H_2SO_4.

experiments were carried out in water:tetrahydrofuran = 7:3 (v/v). As shown in Fig. 2, 2 gave pH-dependent five different absorption maxima at 315, 332, 365, 410, and 450 nm which could be attributed to five species of 2, that is, $2H_4$, $2H_3^-$, $2H_2^{2-}$, $2H^{3-}$, and 2^{4-}. Under the identical conditions the absorption maxima of p-nitrophenol and p-nitrophenolate appeared at 318 and 406 nm, respectively. It is worth mentioning that the absorption maximum of 2^{4-} shifts to longer wavelength by 44 nm as compared with that of p-nitrophenolate.[11] 2 was photo-titrated by using these absorption maxima. The results, together with the potentiometric titration data (not shown here), gave the pK_a values recorded in Table 1. As has been shown about 1, the first dissociation occurred at strongly acidic pH region. In fact, the absorption band (315 nm) for $2H_4$ could be seen only in the presence of strong acids (H_2SO_4, $HClO_4$, CF_3COOH, etc.). Similarly, the dissociation of the last proton occurred at strongly basic pH region and the absorption band for $2H^{3-}$ (410 nm) was still observable in 10% KOH solution.

The foregoing results indicate that calix[4]arenes are very novel molecules having a super-acidic proton as well as a super-basic oxy-anion within a molecule. Presumably, intramolecular hydrogen bonding in a calix[4]arene family is so strong as has never been attained in other systems.

Here, we assessed how the "cone" conformation is stabilized in an aqueous system. The "cone" conformers can be conveniently discriminated from others by ^{1}H-NMR[4]: observing the resonances arising from the $ArCH_2Ar$ methylene protons of calixarenes, the pattern of "cone" calixarenes gives a pair of doublets below room temperature. When the ^{1}H-NMR spectrum of 1 was taken in D_2O-Me_2SO-d_6 (2:1 v/v), the $ArCH_2Ar$ methylene protons gave a pair of doublets at pH 9.0 and a singlet at 0.04 mol dm^{-3} H_2SO_4 (Fig. 3). The difference suggests that the "cone" conformation is favofably adopted by dissociated 1 (e.g., $1H^{3-}$) rather than by undissociated 1 (e.g., $1H_4$): that is, in an aqueous system the oxy-anions can form stronger intramolecular hydrogen bonding leading to fixation of the calixarene conformation to "cone".

In conclusion, this paper describes two basic findings in the calixarene chemistry, the pK_a values and the relation between the OH-dissociation and the conformation. These would serve as very important knowledges when the calixarene-based synthetic enzyme mimics are designed in near future.

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10) 1 gave the absorption maximum at 283 nm in water. The absorbance increased with the dissociation of the OH groups, but the absorption maximum did not shift appreciably.
11) We now believe that the unusual red shift is related to the "alternate" conformation of 2^{4-}.

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