Re-evaluation of the Acid Dissociation Constants of the Hydroxyl Groups in Tetrasodium 25,26,27,28-Tetrahydroxycalix[4]arene-5,11,17,23-tetrasulfonate

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The acid dissociation constants of the hydroxyl groups in tetrasodium 25,26,27,28-tetrahydroxycalix[4]arene-5,11,17,23-tetrasulfonate (CALX-S4) were determined at 25 °C by potentiometric and spectrophotometric titration methods. The first acid dissociation constant(pK_{a_1}) was found to be 3.26±0.02 (μ=0.1 with KNO_3), which demonstrated a remarkable pK_a shift due to intramolecular hydrogen-bonding interactions among the hydroxyl groups in CALX-S4. On the other hand, considerably weak acidities were observed on the residual three hydroxyl groups of CALX-S4 (pK_{a_2}=11.8±0.3 (μ=0.1 with KNO_3), 11.3±0.3 (μ=2.0 with KCl), pK_{a_3}=12.8±0.3 (μ=2.0 with KCl), and pK_{a_4}=ca. 14 (μ=2.0 with KCl)).

It is well known that the phenolic OH groups in calixarenes form strong intramolecular hydrogen bonds.[1—4] One can, thus, expect that the acid dissociation constants of the OH groups in calixarenes are quite different from those of the corresponding noncyclic analogs.[3—5]

Recently, one of the authors synthesized tetrasodium 25,26,27,28-tetrahydroxycalix[4]arene-5,11,17,23-tetrasulfonate, CALX-S4, the first water-soluble calixarene ever to be synthesized.[6] A potentiometric titration study concerning this new compound revealed that the titration curve obtained for CALX-S4 is very similar in shape to that for a strong protonic acid.[3] Therefore, it seemed to be difficult to analyze the curve in order to determine the correct values for the acid dissociation constants. One of the authors attempted an evaluation of their approximate values, and predicted the existence of very strong and very weak acidic OH groups in a CALX-S4 molecule.[3] This was supported by a computational study.[7] However, the strong acid dissociation of the OH groups, essentially, could not be distinguished from those of sulfonic acid groups attached to the parent molecule. Thus, we again carefully carried out the potentiometric and photometric titration of CALX-S4 in order to determine even more precise values for its acid dissociation constants. We believe that these values are of particular importance because calixarenes are gaining an ever more important position in the fields of coordination- and bio-chemistry as the characteristic ligand to some metal ions, as well as enzyme mimics.

Results and Discussion

It is important to know the number of acidic and basic groups of a CALX-S4 molecule prior to a titration study. The sodium salt of CALX-S4 (purchased from Sugai Kagaku Co.) was used as a sample in a titration study. Judging from the synthetic route of CALX-S4, one has to take the possibility into account that the sample contains barium ions in addition to sodium ions. Thus, before starting the titration study, the metal ion content for sodium and barium ions was first determined based on its aqueous solution using the AA and ICP-AES methods. The analytical results indicated that the sample contained 4 mole of sodium ion per 1 mole of CALX-S4, but no barium ions. Therefore, CALX-S4 can be expressed as Na_4LH_4. The molecular structure for L^{8-} is illustrated in Fig. 1. The result of a preliminary titration study indicated that a commercially-available sample of CALX-S4 is not sufficiently pure for a precise determination of the acid dissociation constants. We thus recrystallized CALX-S4 three times from methanol–water mixtures. A metal-ion analysis indicated that the purified sample had a composition of Na_4LH_4 within the experimental error.

The sample was then treated with a cation exchange resin in order to remove sodium ions. The CALX-S4 sample (4.774 mmol) was dissolved in 100 ml of water, and the solution then passed through a column (23 cm

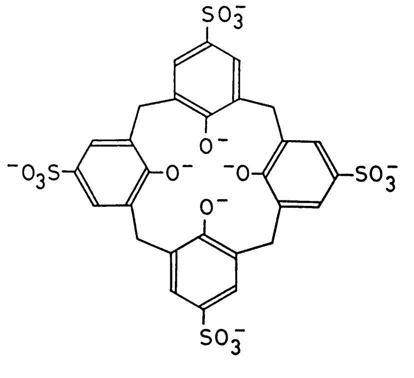

Fig. 1. Molecular structure for completely deprotonated 25,26,27,28-tetrahydroxycalix[4]arene-5,11,17,23-tetrasulfonate, L^{8-}.

long) containing 50 g of an H-type cation exchanger (Amberlite IR-120B). An additional 100 ml of water was passed through the column in order to recover the sample completely. The quantitative recovery of the sample in the combined eluate was confirmed by spectrophtometry. A p[H] (p[H]=$-\log[H^+]$) measurement and titration of the eluate revealed that it contained 14.16 mmol of hydrogen ions. It was also confirmed from an AA analysis that it contained 5.03 mmol of sodium ions. Therefore, it was clear that 3 mole of sodium ion was replaced with hydrogen ions by the cation exchanger, giving the sample in a form of $NaLH_7$.

This result shows that even a treatment with a strongly acidic cation exchanger could not give completely protonated CALX-S4 (i.e., LH_8). It is now necessary to specify whether a residual sodium ion attaches to the sulfonate group or the phenolate group. In order to clarify this point, a UV absorption spectrophotometric study was carried out. The UV absorption spectrum of $NaLH_7$ in the ion-exchange eluate (p[H]=1.995) was similar to that in a 4 M (1 M=1 mol dm^{-3}) hydrochloric acid solution. This indicated that the acidic groups of $NaLH_7$ is in the form of 4 mole for -OH, 3 mole for $-SO_3H$ and 1 mole for SO_3Na. The UV absorption spectrum of Na_4LH_4 in water was also identical to that in a 4 M hydrochrolic acid solution, and these spectra were also similar to those of $NaLH_7$. The results indicate that the deprotonation of CALX-S4 in a fairly acidic region occurs on the sulfonic acid side, but not on the phenol side, and that the formula of Na_4LH_4 exactly represents the tetrasodium sulfonate structure of CALX-S4.

The titration curve for purified CALX-S4, denoted as (a), is given in Fig. 2, where p[H] is plotted as the ordinate and the values for *a* (*a*=molar ratio of added KOH to CALX-S4) are plotted as the abscissa. A steep rise in p[H] takes place at $a=1$, and a very gradual increase of p[H] occurs from $a=1$ to $a=4$. The titration curve is very similar to those of strong protonic acids. As an example, the titration curve for hydrochloric acid, denoted as (b), is also shown in Fig. 2. It can be seen from Fig. 2 that the value of p[H] at $a=0.5$ is about 3.3, which corresponds to that of the first dissociation constant (pK_{a_1}). Therefore, the other three dissociations are likely to occur in the region $a>1$.

Based on these preliminary results, we analyzed the titration data using a computer program (PKAS[8]) to obtain the following dissociation constants: $pK_{a_1}=3.26\pm0.02$, $pK_{a_2}=12.3$, $pK_{a_3}=12.9$, and $pK_{a_4}=13.6$. These values were obtained from calculations on the five repeated titration data. The difference between the observed and calculated p[H] by PKAS was so small ($\sigma_{\text{fitt}}=0.0076$) that the values for pK_{a_1} can be considered to be quite reliable. However, the values for pK_{a_3} and pK_{a_4} are not sufficiently reliable, since their acidities were too weak to measure the precise p[H]. Thus, a computation was carried out again on the same titration data, but while assuming that CALX-S4 is a diprotonic,

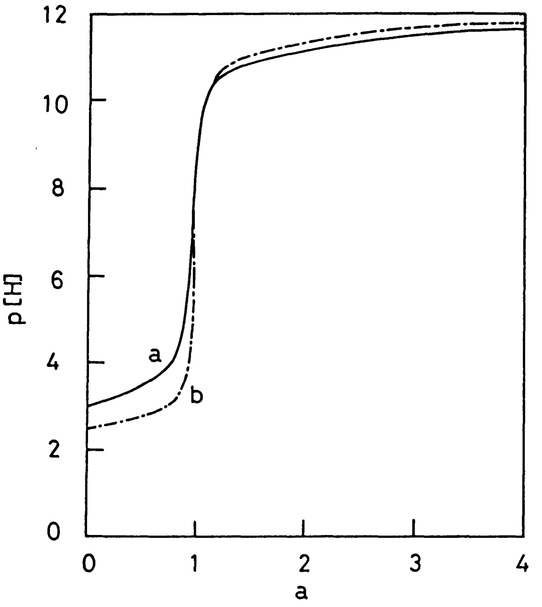

Fig. 2. Titration curves for CALX-S4(a) and for hydrochloric acid(b) with 0.09961 M KOH at 25 °C. $\mu=0.1$ with KNO_3, CALX-S4=0.1101 mmol, HCl=0.1101 mmol, Initial volume of the sample solution=35.0 ml.

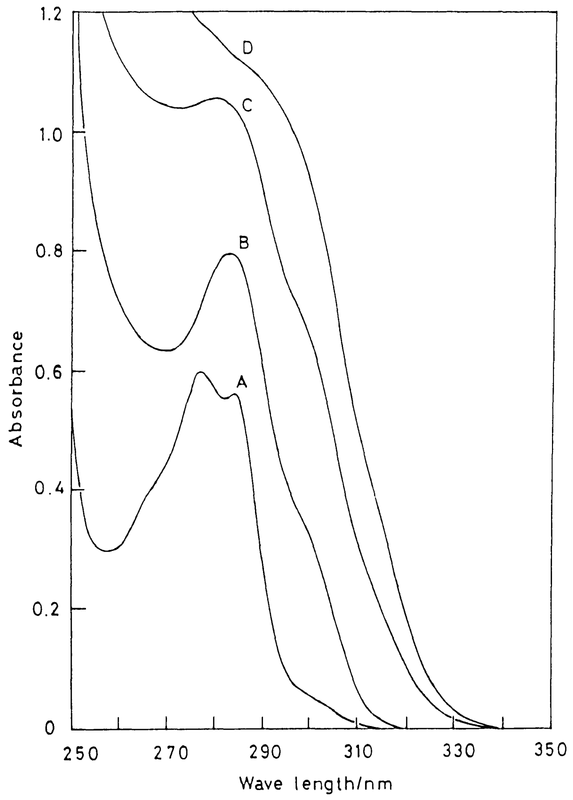

Fig. 3. UV absorption spectra of CALX-S4 at 25 °C. A: p[H]=2.46, B: p[H]=4.20, C: p[H]=12.54, D: p[H]=13.30, [CALX-S4]=1.00×10^{-4} M, light-pass length=1 cm.

instead of tetraprotonic acid. The values for pK_{a_1} and pK_{a_2}, thus obtained, were 3.26±0.02, and 11.8±0.3 ($\sigma_{\text{fitt}}=0.0086$), respectively.

The UV absorption spectrum of CALX-S4 showed two absorption peaks at 276 and 284 nm in an acidic solution, as illustrated in Fig. 3. With an increase in the p[H] of the solution, the absorptivity increased over the entire wavelength region; further, the absorption peak at 276 nm first disappeared at p[H]=4.2, and then the peak at 284 nm disappeared at p[H]=12.8. Such changes in the UV absorption are attributed to proton dissociations from the phenol groups to phenolate ions. The change in the absorbance at 300 nm as a function of p[H] is given in Fig. 4. At p[H]<2, the absorbance is small and constant. Then, a symmetrical sigmoidal increase of the absorbance is observed in the region 2<p[H]<5. The A-diagram (diagram of absorbances at λ_1 against those at λ_2 at various p[H]) and the AD-diagram (diagram of absorbance differences at λ_1 against those at λ_2 at various p[H])[9] over a wavelength range of 250 to 300 nm for this p[H] region were all found to give straight lines, showing that an isolated single-step acid dissociation takes place in an acidic solution. A plot of p[H] vs. $\log\{(A-A_{LH_4}/(A_{LH_3}-A)\}$, where A_{LH_4} and A_{LH_3} are the absorbances at the acid and neutral sides, also resulted in a good straight line. This shows, again, that acid dissociation in this p[H] range is an isolated single step. From the p[H] value at the intercept of the line with the abscissa, the first acid dissociation constant, $pK_{a_1}=3.26$, having exactly the same value in a potentiometric study, was obtained. It can thus be concluded that pK_{a_1} corresponds to the "first" acid dissociation constant of the phenol group.

At p[H]>10.0, the absorbance increases markedly with an increase in the p[H]. Therefore, a second acid dissociation due to the -OH group is likely to occur at about p[H]=10.0+1.5=11.5. Moreover at p[H]>14, the absorbance still increases appreciably, showing that at least one other acid dissociation still takes place near p[H]=14. None of the A-, AD-, and the ADQ- (absorbance difference quotient diagram)[9] diagrams applied for the absorbances at 10.0<p[H]<14.2 gave a straight line, showing the overlapping of more than three acid dissociation steps in this p[H] region. It is therefore concluded that there exist three acid dissociation steps for LH_3^{5-} in an alkaline solution, as was suggested by the potentiometric titration study.

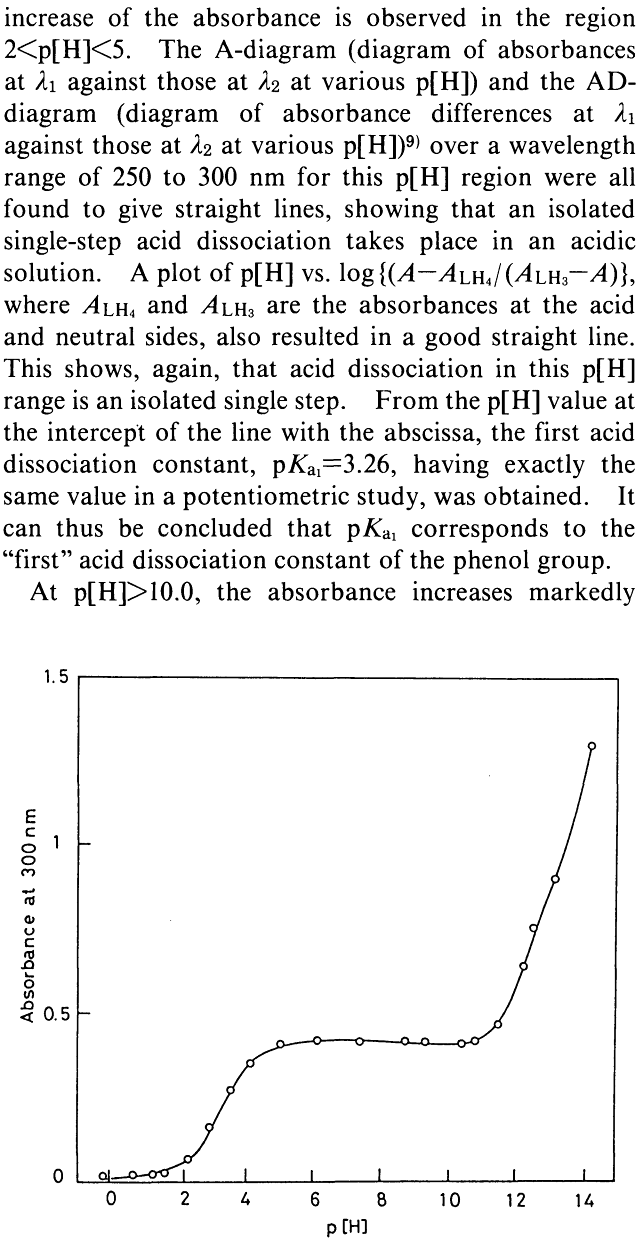

Fig. 4. Variation of the absorbance at 300 nm as a function of the p[H] at 25 °C.
$\mu=0.1$ with KCl for a solution of 2<p[H]<10, [CALX-S4]=1.00×10^{-4} M, light-pass length=1 cm.

In order to determine the exact pK_a values corresponding to these dissociation steps, a complementary experiment was carried out on the photometric titration of CALX-S4 in 2.0 M KCl at 25 °C, the absorbances being measured at 8 wavelengths between 300 and 260 nm. After an analysis of the titration data using a computer program (TIFIT[9]) we obtained $pK_{a_2}=11.3\pm0.3$, $pK_{a_3}=12.8\pm0.3$ and pK_{a_4}=ca. 14. These results are in accord with the pK_a values determined by potentiometric titration.

We and Reinhoudt et al. collaboratively determined the pK_a values for 5,11,17,23-tetranitro-25,26,27,28-tetrahydroxylcalix[4]arene in 85.4% EtOH/H_2O at 25 °C: $pK_{a_1}=2.9$, $pK_{a_2}=10.9$, $pK_{a_3}=12.3$, and $pK_{a_4}=14$.[7,10] The results indicate, along with the present study, that the first acid dissociation occurs in a very acidic pH region whereas, the second to fourth acid dissociations occur in a rather basic pH region. As a result, one can observe the mono-dissociated species at a wide pH range (from pH 3 to 9). Since the pK_a for 4-hydroxybenzenesulfonate is 8.9,[3] the first acid dissociation of CALX-S4 shifts to the acidic region by more than 5 pK units. The unusually large pK_a shift can be ascribed to a strong intramolecular repulsion among -OH groups and/or to stabilization of the dissociated $-O^-$ through intramolecular hydrogen bonds. On the contrary, the pK_{a_2} (11.8) is higher by more than 3 pK units than for 4-hydroxybenzenesulfonate.[3] This implies that deprotonation from the mono-anionic species is suppressed by the strengthened intramolecular hydrogen-bonding interactions. The interactions would be further strenghtened in the third and fourth acid dissociation steps.

In conclusion, the present study conclusively established that in CALX-S4 (and probably in calix[4]arene-25,26,27,28-tetrol derivatives in general), the first acid dissociation occurs in a very acidic pH region, whereas the residual acid dissociations occur in a basic pH region. The unusually large pK_a split is ascribed to the characteristic framework of calix[4]arene, which provides a structure that is exactly suitable to the formation of an intramolecular hydrogen bond. This result is of particular importance to an understanding of the behaviors of calix[4]arene-25,26,27,28-tetrol derivatives as ligand, catalysts, and host molecules.[1,4]

Experimental

Into a 50 ml water-jacket cell, 5 ml of the sample solution containing about 0.1 mmol of purified CALX-S4 was pipetted. After 0.35 g of potassium nitrate was added to adjust the ionic strength to 0.1, 30 ml of water was added to make up the solution to 35 ml. The resulting solution was stirred gently with a magnetic stirrer. Under a nitrogen stream, the solution was titrated with 0.1 M carbonate free potassium hydroxide using a piston burett (Metrohm AG CH-9100) at 25 °C. The p[H] of the sample solution was measured using a glass electrode (Horiba 1026-06T) and a reference electrode (Horiba 2535A-06T) with a IOC-10 (Denkikagaku Keiki) pH meter. The pH meter reading was calibrated for the p[H] using 0.1 M standard hydrochloric acid and potassium hydroxide solutions at 25 °C according to a method proposed by A. E. Martell and his co-workers.8) The photometric titration was carried out using the batchwise method in 0.1 and 2.0 M potassium chloride solutions at 25 °C for the acidic and basic pH regions, respectively. p[H] values higher than 12 were calculated according to the hydroxide ion concentration and $pK_w = 13.96$.11)

The UV spectrum of CALX-S4 was recorded with a Shimadzu UV-180 spectrophotometer. A blank solution with no CALX-S4, but containing potassium chloride and potassium hydroxide at the same concentration as those for sample solution, was used as a reference solution. A Hitachi 180-30 atomic absorption spectrophotometer and a Seiko Denshi SPS-1200 ICP spectrophotometer were used for the determination of the metal ion concentrations.

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