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Acid–base properties of sulfur-bridged calix[4]arenes†

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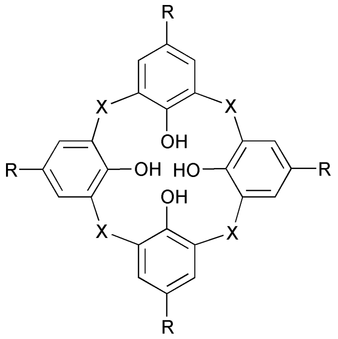
Received (in Cambridge, UK) 8th January 2002, Accepted 15th April 2002
First published as an Advance Article on the web 9th May 2002

The acid–base properties of sulfur-bridged calixarenes, thiacalix[4]arenetetrasulfonate (**4**) and its sulfonyl analogue (**5**), have been investigated *via* potentio- and spectrophoto-metric studies, comparing them with the conventional methylene-bridged calix[4]arenetetrasulfonate (**3**). The titration curves revealed the acidity of the phenolic OH groups in the calix[4]arenes **3**–**5** to be in the order: $\mathbf{3} < \mathbf{4} \ll \mathbf{5}$. In particular, the oxidation of the bridging sulfur to sulfone strongly enhanced the acidity of the sulfur-bridged calix[4]arene; the $pK_{a,n}$ values ($n = 2$–4) of the sulfone-bridged **5** were lower by 7 pK units than those of the sulfide-bridged **4**. The effects of the linkage groups on the acidity of the calix[4]arenes are discussed from the structural and electronic viewpoints, such as the macrocyclic ring size, the hydrogen bonding manner, and the resonance of the linkage moiety.

Introduction

Calixarenes (*e.g.* **1**, Scheme 1) are a class of macrocycles, generally made up of phenol units linked *via* methylene bridges.[1] During the last two decades, calixarenes have attracted much interest because of their unique molecular structure, and have been extensively investigated in various fields such as analytical,[2,3] separation,[3] and supramolecular[4] chemistry. To investigate and develop their functions, a great number of attempts have been made at the modification of their lower rim (phenolic OH groups) and/or upper rim (the *p*-position).[1–4] Although the replacement of the bridging methylene groups of calixarenes with heteroatoms, such as O, N, and S, is an alternative approach for the development of their functions, the exploration into such heteroatom-bridged calixarenes has emerged only recently because of their synthetic difficulty.[5]



	X	R
1	CH_2	Bu^t
2	S	Bu^t
3	CH_2	SO_3^-
4	S	SO_3^-
5	SO_2	SO_3^-

Scheme 1 Structures of calix[4]arenes.

The synthesis of the sulfur-bridged calixarene, *p-tert*-butylthiacalix[4]arene (**2**), was first achieved by Sone *et al. via* stepwise linking of phenol units followed by cyclization, but resulted in poor yield (4%).[6] In 1997, we reported a facile single-step procedure for the synthesis of **2** with satisfactory yield (54%) by simply heating *p-tert*-butylphenol with elemental sulfur in the presence of a base.[7] Since this finding, we have been engaged in a study to investigate its functions, particularly those which could not be achieved by the conventional methylene-bridged calixarenes.[8] As one of the remarkable results, we have demonstrated the modification of the bridging moieties to be highly effective in metal-ion recognition; sulfur-bridged calixarenes have high binding ability toward many kinds of metal ions owing to the coordination of not only their phenolates O^- but also bridging groups (X).[9] Furthermore, the metal-ion selectivity can be controlled by the oxidation state of the bridging sulfur, *i.e.* sulfide (S), sulfoxide (SO), or sulfone (SO_2).[9b] Attracted by the structure, properties, and reactivity, other research groups have also started studies on the chemistry of sulfur-bridged calixarenes.[10]

The acid dissociation of the phenolic OH groups in calixarenes, which induces the change of electron density in the aromatic π-system, plays one of the key roles in the inclusion process of guest molecules into the calixarene cavity.[11] Furthermore, as mentioned above, sulfur-bridged calixarenes act as ligands for Lewis acids. Therefore, knowledge of the acid–base properties of the calixarenes is essential to investigate and apply them, for example, to synthetic receptors. On the conventional methylene-bridged calixarenes, well-known are their unique acid–base properties resulting from their having a super-acidic proton as well as a super-basic oxy-anion within one molecule.[12] For instance, the first and second pK_a values for the phenolic OH groups of calix[4]arenetetrasulfonate (**3**) were reported to be 3.26 and 11.8, respectively, which significantly deviate from the pK_a value (8.9) of the corresponding monomer, *p*-hydroxybenzenesulfonate.[13] Because the replacement of the linkage methylene groups with sulfide or sulfonyl groups would cause substantial changes in structural and electronic features, it is intriguing to know how the replacement of the linkage groups affects the acid–base properties of calix[4]arenes. However, the study on the acid–base properties of sulfur-bridged calixarenes has been limited by their extremely low solubility in aqueous solutions. Recently, we succeeded in the preparation of the water-soluble analogues, thia- (**4**) and sulfonylcalix[4]arenetetrasulfonate (**5**),[14] which allowed us to investigate the acid–base properties of sulfur-bridged calixarenes in aqueous solutions. Herein, we disclose the results of potentio- and spectrophoto-metric study on sulfur-bridged calix[4]arenes **4** and **5**, comparing them with the conventional methylene **3** to reveal the effect of the bridging groups.

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† Electronic supplementary information (ESI) available: raw data and determined experimental parameters for the potentio- and photometric titrations; A–, AD–, ADQ–diagrams of **3**. See http://www.rsc.org/suppdata/p2/b2/b200228k/

DOI: 10.1039/b200228k

Results

Potentiometric titration

Calix[4]arenes **3**–**5** have four phenolic OH groups within one molecule. Therefore, four-step acid dissociations of the phenolic OH groups will occur in aqueous solution. The first to fourth acid dissociation constants, $K_{a,n}$ (n = 1–4), are then defined by eqns. (1)–(4),[15] where L^{8-} denotes the completely deprotonated form of the calix[4]arene (here, **3**, **4**, or **5**). It should be noted that the acid dissociation constants are given in terms of concentrations, not activities, throughout this paper.

$$H_4L^{4-} \rightleftharpoons H^+ + H_3L^{5-}; \qquad K_{a1} = \frac{[H^+][H_3L^{5-}]}{[H_4L^{4-}]} \qquad (1)$$

$$H_3L^{5-} \rightleftharpoons H^+ + H_2L^{6-}; \qquad K_{a2} = \frac{[H^+][H_2L^{6-}]}{[H_3L^{5-}]} \qquad (2)$$

$$H_2L^{6-} \rightleftharpoons H^+ + HL^{7-}; \qquad K_{a3} = \frac{[H^+][HL^{7-}]}{H_2L^{6-}} \qquad (3)$$

$$HL^{7-} \rightleftharpoons H^+ + L^{8-}; \qquad K_{a4} = \frac{[H^+][L^{8-}]}{[HL^{7-}]} \qquad (4)$$

In order to evaluate the acidity of the calix[4]arenes, potentiometric titrations of **3**, **4**, and **5** were carried out under the conditions of 298 K and I = 0.2 M with NaCl, where I is the ionic strength of the solutions.[16] For **5**, a 1 mol equivalent of strong acid HCl was added to the titrated solution because a pentasodium salt of **5** was used, in which one hydroxy group deprotonates. The titration curves are illustrated in Fig. 1 with those of HCl solutions (as blanks). The titration fraction, F, is given by eqn. (5), where C is the total concentration at a given titration point.

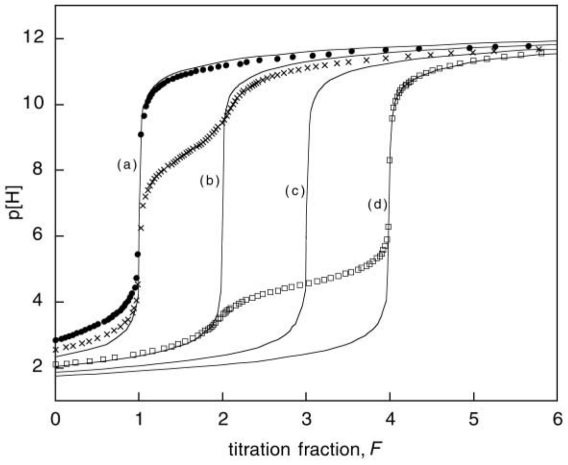

Fig. 1 Potentiometric titration curves for calix[4]arenes at 298 K and I = 0.2 mol dm^{-3} (NaCl): (●) 0.221 mmol of compound **3**; (×) 0.205 mmol of compound **4**; (□) 0.256 mmol of compound **5** together with 0.250 mmol of HCl. Solid lines, the titration curves for HCl solutions; the amounts of HCl (in mmol): 0.248 for (a), 0.503 for (b), 0.752 for (c), and 0.976 for (d). Initial volumes of the sample solutions were 55.0 cm^3. The sample solutions were titrated by 0.104 mol dm^{-3} NaOH solution.

$$F = C_{NaOH}/C_{calixarene} \qquad (5)$$

It can be seen from Fig. 1 that the acidity of calix[4]arenes **3**–**5** is roughly in the order: the methylene-bridged **3** < the sulfide-bridged **4** ≪ the sulfone-bridged **5**. In particular, it is interesting to note that the titration curve for **5** is quite different from those of either **3** and **4**.

In the case of the sulfone-bridged **5**, the titration curve at $F < 2$ was almost the same as that for 2 mol equivalent of HCl. This implies that **5** has two strongly acidic protons within one molecule. Above $F > 2$, the solution p[H] (= −log [H]) was gradually increased from 4 to 5, then steeply jumped at $F = 4$. This indicates that 2 mol equivalents of hydroxide ion were consumed for neutralization of the last two OH groups, which corresponds to the third and fourth acid dissociations of **5**.

By contrast with **5**, the titration curves for either methylene-bridged **3** or sulfide-bridged **4** could be clearly separated from that for 1 mol equivalent of HCl at $F < 1$, and gave a steep rise in the solution p[H] at $F = 1$. These results indicate that the first acid dissociation of **3** and **4** also occurs in an acidic p[H] region, but that their acidity is weaker than that of **5**. At $F > 1$, the titration curve for **3** could be scarcely distinguished from that for 1 mol equivalent of HCl. Therefore, the further acid dissociations of **3** are likely to occur in a highly alkaline p[H] region. In the case of the sulfide-bridged **4**, a buffer region at 8 < p[H] < 9 was observed in the region of $1 < F < 2$, which corresponds to the second acid dissociation. The further acid dissociations of **4** were barely observed in a highly alkaline p[H] region, the same as in the case of **3**.

Based on these preliminary results, the pK_a values of the calix[4]arenes **3**–**5** were determined by the Bjerrum–Schwarzenbach method[17] (for details, see the Experimental Section). For the determination of the first pK_a values of **3** and **4**, eqn. (6) was used, where $\bar{n}_H$ means the average number of protons bound to the base (here, L^{8-}).

$$\log\left(\frac{3-\bar{n}_H}{\bar{n}_H-4}\right) = pK_{a1} - p[H] \qquad (6)$$

The left term of eqn. (6) can be calculated because $\bar{n}_H$ is a function consisting of the experimental data ($C_{calixarene}$, C_{NaOH}, and [H]) as given by eqn. (7), where K_W (= [H][OH]) is the autoprotolysis constant of water.[18]

$$\bar{n}_H = \frac{4C_{calixarene} - C_{NaOH} + K_w[H]^{-1} - [H]}{C_{calixarene}} \qquad (7)$$

For the determination of the second pK_a values of **4**, eqn. (8) was used similarly.

$$\log\left(\frac{2-\bar{n}_H}{\bar{n}_H-3}\right) = pK_{a2} - p[H] \qquad (8)$$

The left terms of eqns. (6) and (8) were plotted as a function of p[H]. Every plot gave straight lines with a slope of −1, and the pK_a values were obtained as the intercept with the p[H] axis (for raw data and plotting, refer to the supplementary material).

Since the third and fourth acid dissociations of **5** cannot be dealt with as an isolated single-step acid dissociation, a set of eqns. (9) and (10) were used to determine the pK_{a3} and pK_{a4} values of **5**. As described above, the $\bar{n}_H$ values were calculated by introducing the titration data into eqn. (10).

$$\frac{(2-\bar{n}_H)[H]}{(\bar{n}_H-1)} = K_{a3} + \frac{\bar{n}_H}{(\bar{n}_H-1)[H]}K_{a3}K_{a4} \qquad (9)$$

$$\bar{n}_H = \frac{3C_{calixarene} + C_{HCl} - C_{NaOH} + K_w[H]^{-1} - [H]}{C_{calixarene}} \qquad (10)$$

The $\{(2 - \bar{n}_H)[H](\bar{n}_H - 1)^{-1}\}$ *versus* $\{\bar{n}_H(\bar{n}_H - 1)^{-1}[H]^{-1}\}$ plot of eqn. (9) gave a straight line, and the K_{a3} value was obtained

Table 1 pK_a values determined from the potentio- and spectrophoto-metric titration curves for calix[4]arenes at 298 K and I = 0.2 mol dm^{-3} [(Na,H)(OH,Cl)][a]

Compound	Method[b]	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}
3	A	3.10 ± 0.05	[c]	[c]	[c]
3	B	3.08 ± 0.03	12.02 ± 0.02	[d]	[d]
4	A	2.17 ± 0.05	8.41 ± 0.04	[c]	[c]
4	B	2.18 ± 0.04	8.45 ± 0.10	11.99 ± 0.15	11.62 ± 0.12
5	A	[c]	[c]	4.81 ± 0.18	4.43 ± 0.09
5	B	[e]	1.28 ± 0.09	4.60 ± 0.11	4.42 ± 0.13

[a] The errors are given as the standard deviation in 3 repeated experiments. [b] Methods A and B denote potentiometric and spectrophotometric titrations, respectively. [c] Reliable pK_a values could not be obtained from the potentiometric data. See text for details. [d] The pK_{a3} and pK_{a4} values are not measurable, estimated to be > 13. [e] The pK_{a1} value is not measurable, roughly estimated to be in the range of −2–0.

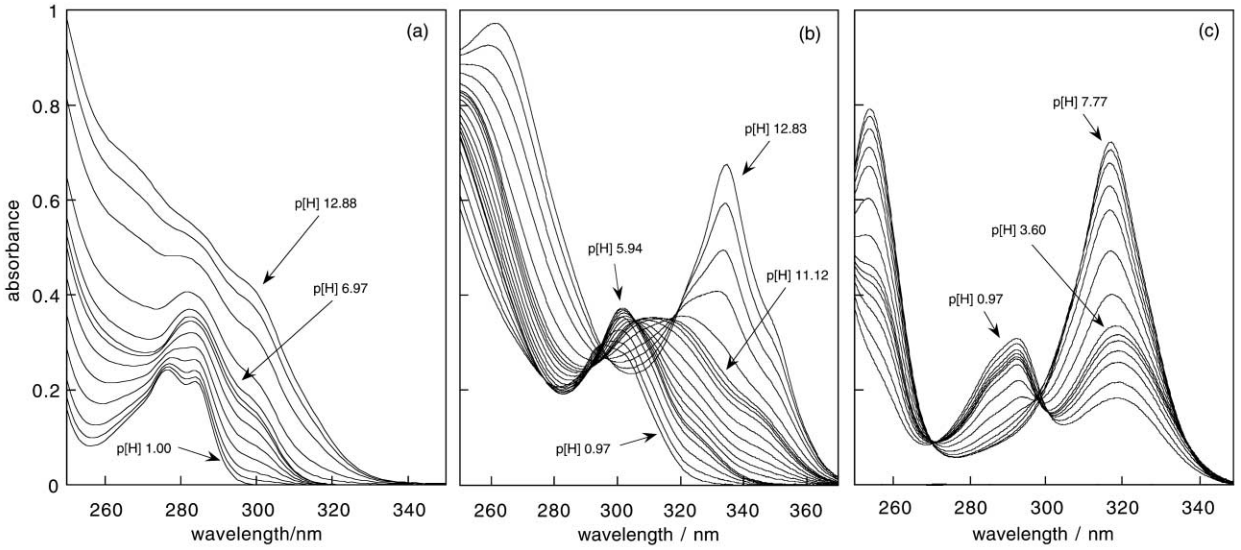

Fig. 2 UV absorption spectra of calix[4]arenes as a function of the solution p[H] at 298 K and I = 0.2 mol dm^{-3} [(Na,H)(OH,Cl)]: (a) 44.2 µmol dm^{-3} of compound **3** (p[H] values of the single spectrum: 1.00, 1.91, 2.36, 2.79, 3.14, 3.56, 4.20, 6.97, 10.90, 11.50, 12.10, 12.51, and 12.88); (b) 20.5 µmol dm^{-3} of compound **4** (p[H] values of the single spectrum: 0.97, 1.79, 2.34, 2.93, 3.73, 5.94, 7.73, 8.09, 8.37, 8.66, 8.99, 9.54, 10.13, 10.71, 11.12, 11.57, 11.91, 12.13, 12.39, and 12.83); (c) 20.5 µmol dm^{-3} of compound **5** (p[H] values of the single spectrum: 0.97, 1.30, 1.72, 2.03, 2.51, 3.03, 3.60, 4.08, 4.39, 4.67, 4.98, 5.61, 5.79, 7.77). The optical path length of the sample solution was 1 cm.

as the intercept with the $\{(2 - \bar{n}_H)[H](\bar{n}_H - 1)^{-1}\}$ axis. Also, the K_{a4} value was calculated by dividing the slope with the intercept, K_{a3}.

The results are collected in Table 1, where all the missing pK_a values are too high or low to determine the pK_a values by potentiometric titration. Therefore, we decided to carry out a spectrophotometric study under the same conditions in order to evaluate the missing pK_a values.

Spectrophotometric titration

The UV absorption spectra of the calix[4]arenes **3**–**5** at various p[H] conditions are shown in Fig. 2. For **4** and **5**, the absorption band around 340 nm rose with increase in the solution p[H]. Such spectral change in the UV absorption is attributed to the acid dissociation of phenolic OH in the calix[4]arene to form phenolate O$^-$. In the case of **3**, the absorptivity over the entire wavelength region increased with the acid dissociations of the phenolic OH, as previously reported by Yoshida *et al.*[13]

The photometric titration curves for the calix[4]arenes **3**–**5** are shown in Fig. 3, where absorbance at a typical wavelength is plotted as a function of the solution p[H]. Judging from the results of the above-described potentiometric study, the symmetrical sigmoidal increase of the absorbance for the methylene-bridged **3** and the sulfide-bridged **4** at 1 < p[H] < 4 is undoubtedly ascribed to the first acid dissociation of their phenolic OH groups. As expected from the potentiometric study, the second acid dissociation of **4** was observed at 6.0 < p[H] < 9.4 as the spectral change with isosbestic points at 296 and 306 nm, showing that the isolated single-step acid dissociation occurred in this p[H] region. However, the isosbestic points in the spectral change of **4** disappeared at pH > 9.4. This indicates the overlapping of the third and fourth acid dissociations, which cause the steep absorbance change in the highly alkaline region (pH > 11).

For the methylene-bridged **3**, the symmetrical sigmoidal increase of the absorbance was observed at p[H] > 10. The A-diagram (diagram of absorbance at λ_1 against those at λ_2 at various p[H]), AD-diagram (diagram of absorbance differences at λ_1 against those at λ_2 at various p[H]), and ADQ-diagram (diagram of absorbance difference quotients at λ_1 against those at λ_2 at various p[H])[19] were found to give straight lines at 10 < p[H] < 12.8. This establishes that the isolated single-step acid dissociation occurred in this p[H] region, which corresponds to the second acid dissociation of **3**. In other words, the third and fourth acid dissociations of **3** could not be observed at least in the region of p[H] < 12.8.

In the case of the sulfone-bridged **5**, on the basis of the potentiometric study, the increase of the absorbance at 4 < p[H] < 6 is ascribed to the third and fourth acid dissociations of the phenolic OH groups. At p[H] < 2.3, the spectral change of **5** showed the isosbestic points at 280 and 322 nm, indicating that the isolated single-step acid dissociation occurred. Further increasing the acidity of the solution by adding from 1 M to 6 M of HCl, the absorption band around 345 nm steeply decreased with disappearance of the isosbestic points, as shown in Fig. 4. Therefore, it should be concluded that the first acid dissociation of the phenolic OH groups of **5** occurred in the extremely acidic conditions, such as > 1 M of HCl, and that the

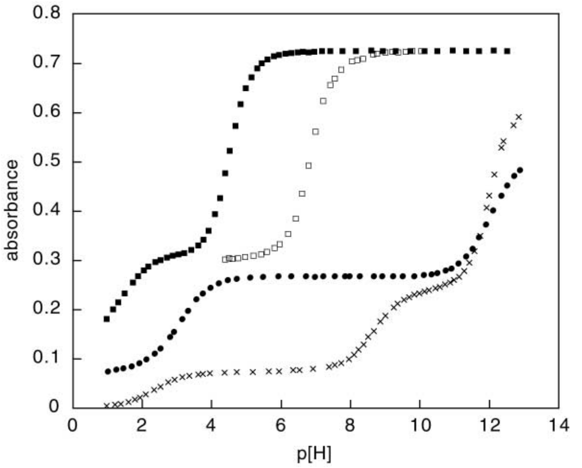

Fig. 3 Photometric titration curves for calix[4]arenes at 298 K: (●) 44.2 μmol dm^{-3} of compound **3** at $I = 0.2$ mol dm^{-3} [(Na,H)(OH,Cl)]; (×) 20.5 μmol dm^{-3} of compound **4** at $I = 0.2$ mol dm^{-3} [(Na,H)(OH,Cl)]; (■) 20.5 μmol dm^{-3} of compound **5** at $I = 0.2$ mol dm^{-3} [(Na,H)(OH,Cl)]; (□) 20.5 μmol dm^{-3} of compound **5** in the absence of supporting electrolyte. The wavelength (in nm): compound **3**, 290; compound **4**, 330; compound **5**, 345. The optical path length of the sample solution was 1 cm.

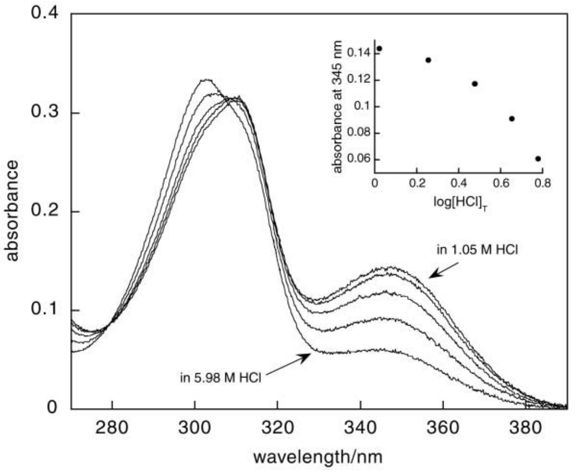

Fig. 4 UV absorption spectra of compound **5** (20.5 μmol dm^{-3}) in aqueous HCl solution at 298 K. Concentrations of HCl at the single spectrum (in mol dm^{-3}): 1.05, 1.79, 3.00, 4.49, and 5.98. *Inset*: Variation of the absorbance at 345 nm as a function of the log [HCl]$_{\mathrm{Total}}$ values.

spectral change around p[H] 1 was caused by the second acid dissociation.

Based on these results, the pK_a values of the calix[4]arenes **3**–**5** were determined from the photometric titration data (for details, see the Experimental Section). The first and second pK_a values of **3**, **4** and **5** (except for the pK_{a1} of **5**) were determined by the conventional Hildebrand–Reilly method,[20] as given by eqns. (11) and (12), where A denotes the absorbance of the sample solution at a given wavelength. Subscripts H_4L, H_3L, and H_2L mean the absorbance assigned to the species H_4L^{4-}, H_3L^{5-}, and H_2L^{6-}, respectively.

$$\log \frac{A_{\mathrm{H_4L}} - A}{A - A_{\mathrm{H_3L}}} = -\mathrm{p}K_{\mathrm{a1}} + \mathrm{p[H]} \qquad (11)$$

$$\log \frac{A_{\mathrm{H_3L}} - A}{A - A_{\mathrm{H_2L}}} = -\mathrm{p}K_{\mathrm{a2}} + \mathrm{p[H]} \qquad (12)$$

The left terms of eqns. (11) and (12) were plotted as a function of p[H]. Every plot gave good straight lines with a slope of 1, and the pK_a values were obtained as the intercept with the p[H] axis.

Since the Hildebrand–Reilly method cannot be applied to simultaneous reactions, the pK_{a3} and pK_{a4} values of **4** and **5** were calculated by applying a curve-fitting program to eqn. (13), setting K_{a3}, K_{a4}, A_{HL}, and A_{L} as unknown parameters (in the case of **5**, A_{L} is known).

$$A = \left\{ \frac{A_{\mathrm{H_2L}}[\mathrm{H}]^2}{K_{\mathrm{a3}}K_{\mathrm{a4}}} + \frac{A_{\mathrm{HL}}[\mathrm{H}]}{K_{\mathrm{a4}}} + A_{\mathrm{L}} \right\} \Bigg/ \left\{ \frac{[\mathrm{H}]^2}{K_{\mathrm{a3}}K_{\mathrm{a4}}} + \frac{[\mathrm{H}]}{K_{\mathrm{a4}}} + 1 \right\} \qquad (13)$$

The obtained pK_a values are summarized in Table 1.‡ The pK_a values of **3** obtained here are reasonable in comparison with the previously reported values at 298 K: pK_{a1} = 3.26 ± 0.02 [I = 0.1 M (KNO$_3$)], pK_{a2} = 11.8 ± 0.3 [I = 0.1 M (KNO$_3$)], pK_{a3} = 12.8 ± 0.3 [I = 2.0 M (KCl)], and pK_{a4} = *ca.* 14 [I = 2.0 M (KCl)].[13] The difference between the values obtained here and those reported previously may arise from the differences in ionic strength and/or supporting electrolytes. Based on the isolated single-step acid dissociation behaviour of **3** at 10 < p[H] < 12.8, the pK_{a3} and pK_{a4} of **3** should be high, at least higher than 13, under the experimental conditions, I = 0.2 M. Also, the pK_{a1} of **5** should be low; the pK_{a1} value may be roughly estimated to be in the range of −2–0 from the spectral change of **5** in 1–6 M of HCl solutions (needless to say, the ionic strength is extremely high under these conditions). In any case, those values seem to be over the limits of accurate pK_a determination in aqueous solution.

Discussion

For the methylene-bridged **3** and sulfide-bridged **4**, the first pK_a values are far lower than the subsequent pK_a values. This indicates that the first acid dissociation of the phenolic OH groups occurs quite easily, whereas the further acid dissociations are strongly suppressed. As suggested by several researchers,[21] these can be ascribed chiefly to the stabilization of the monophenolate species through the strong intramolecular hydrogen bonding between the phenolate O$^-$ and its flanking OH groups, which are in turn stabilized by a bifurcated hydrogen bonding with the fourth OH group (see Scheme 2(a)). Computational studies on the methylene-bridged **1** by Grootenhuis *et al.* also indicate that the hydrogen bonding effects still contribute to suppress the further acid dissociations although unfavorable intramolecular electrostatic repulsion seems to become the dominant factor with further acid dissociations.[21a]

It is noteworthy that the replacement of the methylene linkage groups of **3** with sulfide strengthens the acidity of the calix[4]arene by more than 1 pK unit. This may be related to the presence of the vacant 3d-orbital of the sulfide linkages,[22] which allows a resonance-like interaction with the π-orbital of adjacent aromatic rings to delocalize anionic charges, resulting in the enhancement of the acid dissociation. Another noticeable feature in the acid dissociation behaviour is that the difference

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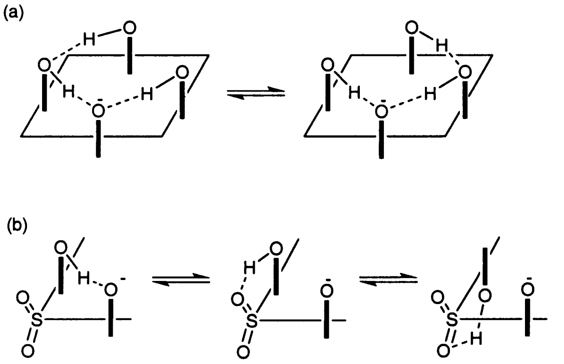
‡ In the case of either **4** or **5**, it may seem unusual that the third pK_a values are larger than the fourth ones. A possible reason may be ascribed to the difference of the ionic behaviour of highly charged species, such as H_2L^{6-}, HL^{7-}, and L^{8-}, under the experimental conditions (I = 0.2 M) from that in an ideal dilute solution, which is caused by ionic atmosphere as expected from the Debye–Hückel theory. Furthermore, this departure from ideality in ionic solutions expands with increases in the charge of the species. This may be responsible for the unusual order of the third and fourth pK_a values under the condition of I = 0.2 M. Actually, the pK_{a3} of 6.75 ± 0.20 and pK_{a4} of 6.75 ± 0.13 were determined for **5** by spectrophotometric titration in the absence of supporting electrolyte, where the measured pH values were directly used without correction because the ionic strength was kept extremely low, I < 0.0008. Concerning the Debye–Hückel theory, refer to *e.g.* P. W. Atkins, *Physical Chemistry, 4th Edn.*, Oxford University Press, Oxford, 1990, Chapter 10.



Scheme 2 Schematic representation of possible intramolecular hydrogen bonding modes in (a) calix[4]arenes **3**, **4**, and (b) **5** (part of calix[4]arene is drawn for clarity).

between the first and second pK_a values of the sulfide-bridged **4** (6.3 pK units) is less than that of the methylene-bridged **3** (9.0 pK units). A possible reason may be ascribed to the difference in the strength of the above-mentioned intramolecular interactions such as hydrogen bonding and electrostatic repulsion. On the basis of the X-ray crystallography on **3**[23] and **4**,[24] the replacement of the methylene linkages by sulfide groups enlarges the calixarene ring by *ca.* 15% in terms of the bond length between the benzene ring and the linkage group (Ar–X): av. 1.53 Å for the methylene-bridged **3** and av. 1.78 Å for the sulfide-bridged **4**. Therefore, it may be reasonable to presume that the above-mentioned intramolecular interactions in the sulfide-bridged **4** are weaker than those of the methylene-bridged **3**,[25] resulting in less stabilization of the mono-phenolate species.

On the other hand, the oxidation of the bridging sulfur of **4** to sulfone remarkably enhances the acidity; the p$K_{a,n}$ (n = 2–4) values of sulfone-bridged **5** are lower by 7 pK units than those of sulfide-bridged **4**. In other words, all the four phenolic OH groups of **5** completely deprotonate to form phenolate O^- even in a neutral pH region, whereas the last two phenolic OH groups of the other calix[4]arenes **3** and **4** hardly deprotonate even in extremely alkaline conditions. To the best of our knowledge, the sulfone-bridged **5** seems to be the most acidic calix[4]arene so far. The "super-acidic" behaviour of **5** may be rationalized in terms of not only the inductive effect but also the resonance effect of the sulfonyl groups[26] to delocalize anionic charges in the whole calixarene ring through the linkage moiety. Interestingly, whereas the calixarene ring size of the sulfone-bridged **5** (Ar–X = av. 1.77 Å)[14] is almost the same as that of the sulfide-bridged **4**, the difference between the first and second pK_a values of **5**, estimated to be at most 3 pK_a units, becomes much less than that of **4**. Based on the X-ray structure of **5**,[27] even in the cone conformation, the phenolic OH groups are able to form intramolecular hydrogen bonds with not only the adjacent OH groups (and most probably phenolate O^-) but also the sulfonyl oxygens,[28] which is likely to interrupt the hydrogen bonding between the phenol units stabilizing the mono-phenolate species (see Scheme 2(b)). This may explain, at least in part, why the difference between the first and second pK_a values of the sulfone-bridged **5** is far less than that of the other calix[4]arenes.

Conclusions

In this paper, the effects on the acidity of the calix[4]arenes by replacing their linkage groups have been studied *via* potentio- and spectrophoto-metric titration. The titration curves revealed the acidity of the calix[4]arenes **3**–**5** to be in the order: the methylene-bridged **3** < the sulfide-bridged **4** ≪ the sulfone-bridged **5**. In particular, the sulfone-bridged **5** is quite remarkable for its super acidic nature having extremely low pK_a values for a calix[4]arene class compound. The effects of the bridging groups on the acidity of the calix[4]arenes may be rationalized in the terms of the variation in their structural and electronic properties, such as the macrocyclic ring size, the hydrogen bonding manner, and the resonance of the linkage moiety. The findings presented here will be highly helpful in further exploration of calixarene chemistry, such as metal ion- and organic molecular-recognition.

Experimental

Apparatus

A TOA IM-40S ion meter equipped with a TOA GS-5015C combined glass/Ag–AgCl electrode was used for the solution pH measurements. The electrode was calibrated by using the standard pH buffers as an a_H probe before use. All the solution pH (= $-\log a_H$) data in this work were corrected to p[H] (= $-\log$ [H]) by introducing the activity coefficient,[29] γ_H = 0.83, into eqn. (14), unless otherwise noted.

$$a_H = \gamma_H[H] \quad (14)$$

The absorption spectra measurements were made on a JASCO V-570 UV/VIS/NIR spectrophotometer with a 1-cm quartz cell. All measurements were made at 298 K using a NESLAB Exacal EX-300 water-circulating bath.

Materials

Tetrasodium 25,26,27,28-tetrahydroxycalix[4]arene-5,11,17,23-tetrasulfonate (**3**) was purchased from Sugai Chemie Inc. (Wakayama, Japan). Tetrasodium 25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiacalix[4]arene-5,11,17,23-tetrasulfonate (**4**) and pentasodium 25,26,27-trihydroxy-28-oxido-2,8,14,20-tetrasulfonylcalix[4]arene-5,11,17,23-tetrasulfonate (**5**) were synthesized as described in the literature.[14] All the calix[4]arenes **3**, **4**, and **5** were purified by recrystallization from water–acetone mixture and their purity checked by HPLC and ^{1}H NMR before use. Sodium hydroxide (guaranteed reagent grade, min. 99.9%) from Cica-Merck Japan (Tokyo, Japan) was used. Doubly distilled water was used throughout this study.

Procedure

Potentiometric titration. The titrations were carried out at 298 K and I = 0.2 M. The solution pH was measured for 55.0 cm^3 of nitrogen-flushed aqueous solution containing *ca.* 0.22 mmol of the compound and 11 mmol of NaCl as a supporting electrolyte, titrating with 0.1 M NaOH solution.

Spectrophotometric titration. The conditions of temperature and ionic strength were the same as for potentiometric titration, except where otherwise noted. The UV absorption spectra were recorded for 250 cm^3 of aqueous solution containing the compound, 0.10 M of HCl, and 0.10 M of NaCl at appropriate pH intervals, adjusted by adding saturated NaOH solution or the pellets. The UV absorption spectra were also recorded for 250 cm^3 of aqueous solution containing **5** at appropriate pH intervals in the same fashion. The concentrations of **4** and **5** were adjusted to be 20.5 µM, and that of **3** was adjusted to be 44.2 µM. The absorption spectra were also recorded for the solution of **5** at various HCl concentrations.

Calculation of acid dissociation constants §

Potentiometric method. The pK_a determinations from potentiometric data were made by the Bjerrum–Schwarzenbach method.[17] The average number of protons bound to the base (here, L^{8-}), $\bar{n}_H$ is defined by eqn. (15).

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§ The linear and curve-fitting regression analyses were carried out by using Kaleida Graph™ software (Synergy Software) on a Macintosh computer. For the raw data, refer to the supplementary material.

$$\bar{n}_H = \frac{4[H_4L] + 3[H_3L] + 2[H_2L] + [HL]}{C_{calixarene}} \quad (15)$$

The mass balance equation is given by eqn. (16). The proton-balance equations are given by eqns. (17) and (18).

$$C_{calixarene} = [H_4L] + [H_3L] + [H_2L] + [HL] + [L] \quad (16)$$

$$4C_{calixarene} - C_{NaOH} + [OH] = [H] + 4[H_4L] + 3[H_3L] + 2[H_2L] + [HL]; \text{ for } \mathbf{3} \text{ and } \mathbf{4} \quad (17)$$

$$3C_{calixarene} + C_{HCl} - C_{NaOH} + [OH] = [H] + 4[H_4L] + 3[H_3L] + 2[H_2L] + [HL]; \text{ for } \mathbf{5} \quad (18)$$

The $\bar{n}_H$ equation [eqn. (15)] was converted to eqns. (7) and (10) by introducing eqns. (17) and (18), respectively, into eqn. (15).

When the first pK_a values of **3** and **4** were determined, the isolated single-step behavior of the first acid dissociation of **3** and **4** allowed us to neglect the species H_2L^{6-}, HL^{7-}, and L^{8-}. Therefore, the $\bar{n}_H$ equation [eqn. (15)] could also be converted to eqn. (19) by introducing eqns. (1) and (16) into eqn. (15). Finally, eqn. (19) was rearranged to eqn. (6) to obtain the pK_{a1} values.

$$\bar{n}_H = \left\{\frac{4[H]}{K_{a1}} + 3\right\} \Big/ \left\{\frac{[H]}{K_{a1}} + 1\right\} \quad (19)$$

When the second pK_a value of **4** was determined, a similar argument explains why eqn. (8) could be deduced to obtain the pK_{a2} value from the $\bar{n}_H$ equation [eqn. (15)] *via* eqn. (20).

$$\bar{n}_H = \left\{\frac{3[H]}{K_{a2}} + 2\right\} \Big/ \left\{\frac{[H]}{K_{a2}} + 1\right\} \quad (20)$$

In the case of the determination of the third and fourth pK_a values of **5**, these acid dissociations should be dealt with as a simultaneous reaction. However those could be isolated from the first and second acid dissociations at p[H] > 4. Therefore, the species H_4L^{4-} and H_3L^{5-} could be neglected, and the $\bar{n}_H$ equation [eqn. (15)] could be converted to eqn. (21) by introducing eqns. (3), (4), and (16) into eqn. (15).

$$\bar{n}_H = \left\{\frac{2[H]^2}{K_{a3}K_{a4}} + \frac{[H]}{K_{a4}}\right\} \Big/ \left\{\frac{[H]^2}{K_{a3}K_{a4}} + \frac{[H]}{K_{a4}} + 1\right\} \quad (21)$$

Finally, eqn. (21) was rearranged to eqn. (9) to obtain the K_{a3} and K_{a4} values.

Spectrophotometric method. The calculation of the acid dissociation constants was carried out at 3 different wavelengths. The standard deviations of the difference in the results between the chosen wavelengths were less than 0.1 for all the cases.

For the determination of the first and second pK_a values of **3**, **4**, and **5** (except for the pK_{a1} of **5**), the spectrophotometric titration data were applied to the Hildebrand–Reilly method.[20] The absorbance of sample solution, A, at a given wavelength is expressed by eqn. (22), where ε and l denote the molar absorption coefficient and the optical path length of sample solution (1 cm), respectively.

$$A = \varepsilon_{H_4L}l[H_4L] + \varepsilon_{H_3L}l[H_3L] + \varepsilon_{H_2L}l[H_2L] + \varepsilon_{HL}l[HL] + \varepsilon_{L}l[L] \quad (22)$$

When the first pK_a values of **3** and **4** were determined, the species H_2L^{6-}, HL^{7-}, and L^{8-} could be neglected due to the isolated single-step behavior of the first acid dissociation. Therefore, eqn. (25) is deduced from eqns. (16), (22), (23) and (24), where subscripts H_4L and H_3L mean the absorbance at the p[H] conditions where only one species, H_4L^{4-} and H_3L^{5-} respectively, presents in the solution.

$$A_{H_4L} = \varepsilon_{H_4L}lC_{calixarene} \quad (23)$$

$$A_{H_3L} = \varepsilon_{H_3L}lC_{calixarene} \quad (24)$$

$$\frac{[H_3L]}{[H_4L]} = \frac{A_{H_4L} - A}{A - A_{H_3L}} \quad (25)$$

Finally, eqn. (11) was deduced to obtain the pK_{a1} values by introducing eqn. (25) into eqn. (1). The A_{H_4L} and A_{H_3L} values were easily measured at p[H] $\ll$ pK_{a1} and pK_{a1} $\ll$ p[H] $\ll$ pK_{a2}, respectively.

When the second pK_a values of **3**, **4**, and **5** were determined, a similar argument explains why eqn. (12) could be deduced to obtain the pK_{a2} values from eqns. (2), (16) and (22) *via* eqn. (26).

$$\frac{[H_2L]}{[H_3L]} = \frac{A_{H_3L} - A}{A - A_{H_2L}} \quad (26)$$

The A_{H_2L} values of **3** and **4** could not be measured because the second acid dissociation overlaps with the third acid dissociation or their A_{H_2L} values exist in the extremely alkaline region. Therefore, A_{H_2L} values were obtained as the intercept of the $\{(A_{H_3L} - A)[H]\}$ axis in the A *versus* $\{(A_{H_3L} - A)[H]\}$ plots of eqn. (27), which were deduced from eqns. (2) and (26).

$$A = A_{H_2L} + \frac{(A_{H_3L} - A)[H]}{K_{a2}} \quad (27)$$

Similarly, for the determination of the second pK_a value of **5**, the A_{H_2L} value was obtained by using the A *versus* $\{(A_{H_2L} - A)/[H]\}$ plots of eqn. (28), which were deduced from eqns. (2) and (26). The A_{H_3L} value measured at p[H] 4.4 in the solution with no supporting electrolyte was used for the determination of the pK_a values of **5**.

$$A = A_{H_3L} + \frac{(A_{H_2L} - A)K_{a2}}{[H]} \quad (28)$$

For the determination of the third and fourth pK_a values of **4** and **5**, the Hildebrand–Reilly method could not be applied because the second to fourth acid dissociations simultaneously occurred. However, those could be isolated from the first acid dissociations at p[H] > 10.6 and p[H] > 3.4 for **4** and **5**, respectively. Therefore, the species H_4L^{4-} and H_3L^{5-} could be neglected, and eqn. (13) was deduced from eqns. (3), (4), (16), and (22) to obtain the pK_{a3} and pK_{a4} values.

Acknowledgements

This work was supported by the Proposal-Based New Industry Creative Type Technology R&D Promotion Program from the New Energy and Industrial Technology Development Organization (NEDO) of Japan. We also thank Professor I. Yoshida for providing useful information.

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