3480 © 1990 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 63, 3480—3485 (1990) [Vol. 63, No. 12

"pK_a" of Calixarenes and Analogs in Nonaqueous Solvents

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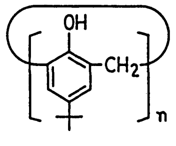
(Received July 2, 1990)

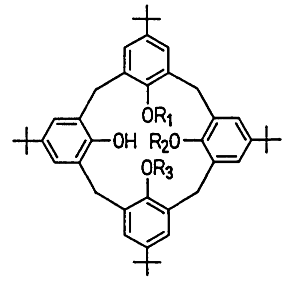
The acid dissociation constants (K_{app}) of *p*-*t*-butylcalix[*n*]arenes (**1**$_n$: n=4, 6, and 8), *O*-methylated *p*-*t*-butylcalix[4]arene (**2**Me$_n$), and their noncyclic analogs (**3**$_n$) were estimated in THF at 25 °C. As pH indicators, Et_4N^+ salts of *p*-nitrophenolate, 2,4-dinitrophenolate, and picrate were employed. The pK_{app} values for **1**$_n$ were lowered by at least four pK units from that of *p*-*t*-butylphenol because of strong intramolecular hydrogen-bonding interactions. Compounds **2**$_n$ involved both the strong and weak hydrogen bonds: the proton in the strong hydrogen bond showed the acidity comparable with that of **1**$_n$ whereas that in the weak hydrogen bond showed the relatively high pK_{app}. These properties were discussed in relation to δ_{OH} (chemical shift in ^{1}H NMR) and ν_{OH} (OH vibration band in IR). This is the first systematic discussion on "pK_a" of *p*-*t*-butylcalix[*n*]arenes.

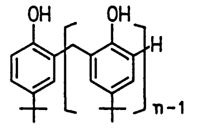
Calixarenes are cyclic oligomers made up of phenol units. Phenolic hydroxyl groups appended on the lower rim form strong intramolecular hydrogen bonds, which serve as a main driving force for stabilizing a "cone" conformation.[1,2] Because of the intramolecular hydrogen-bonding interactions,[1-3] they are expected to have the pK_a values which are quite different from those of the corresponding monomeric units such as phenol and *p*-*t*-butylphenol. Through our previous studies on calixarenes,[4,5] we noticed that to know the pK_a values is indispensable to understand conformational and host-guest properties of calixarenes. They frequently play decisive roles in the stabilization of a cone conformation and in the guest selectivity.[6,7] The studies on pK_a determination have been very limited, however. Böhmer et al.[8] synthesized a few calix[4]arenes containing a *p*-nitrophenol unit and estimated the pK_a by a spectroscopic method. They concluded that the *p*-nitrophenol unit in calix[4]arenes shows nearly the same dissociation behavior as the linear analog. On the other hand, we synthesized *p*-sulfonatocalix[4]arene and *p*-nitrocalix[4]arene and found out that the dissociation of the first proton occurs at very acidic pH region (pK_{a1}=1—2.9).[9,10] The surprisingly large pK_a shift was also observed for *p*-phenylazocalix[4]arenes.[11] The presence of such a "super-acidic" proton is also supported by X-ray crystallographic studies by Atwood et al.[12] The unusual pK_{a1} value (pK_a for the dissociation of the first proton) is attributed to the formation of a strong, circular hydrogen-bonding belt on the lower edge of the calix[4]arene cavity.

The pK_a values of calix[4]arenes mentioned above could be determined because they were water-soluble (at least partially). Then, how can we estimate the "pK_a" of conventional *p*-*t*-butylcalix[*n*]arenes? They are soluble only in organic solvents. We have employed spectroscopic titration in nonaqueous solvents. We selected *p*-nitrophenolate (NP^-), 2,4-dinitrophenolate (DNP^-), and picrate (P^-) as pH indicators because (i) indicators having a phenolic hydroxyl group as a dissociation group are recommended for titration of the phenolic hydroxyl groups in **1**$_n$, (ii) they have strong absorption bands at visible region, (iii) they have different pK_a values covering from pH 1 to 7, and (iv) they are commercially available. In this paper, we estimate not only "pK_a" values of *p*-*t*-butylcalix[*n*]arenes (**1**$_n$: n=4, 6, and 8) but also those of partially methylated **1**$_4$ (**2**Me$_n$) and their acyclic analogs (**3**$_n$).



1$_n$





3$_n$

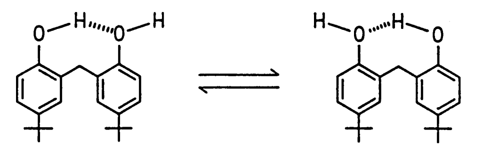
2Me$_1$: R_1=Me, R_2=R_3=H
2Me$_2$: R_1=R_3=Me, R_2=H
2Me$_3$: R_1=R_2=R_3=Me

Results and Discussion

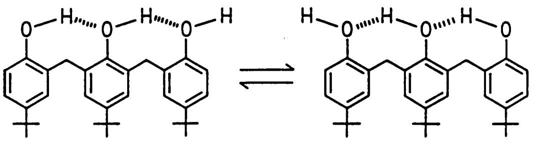
IR and ^{1}H NMR Spectra. As a prelude to pK_a determination, we measured IR and ^{1}H NMR spectra of **1**$_n$, **2**Me$_{1-3}$, and their acyclic analogs **3**$_n$. The results are summarized in Table 1. It has been noticed that in **1**$_n$, ν_{OH} bands in IR appear at around 3100 cm^{-1} and δ_{OH} in ^{1}H NMR appear at around 10 ppm.[1-3] These shifts are attributed to intramolecular hydrogen-bonding interactions. In ^{1}H NMR, the OH protons in the dimer (**3**$_2$), which has the smallest unit to form an intramolecular hydrogen bond, give a single peak at δ_{OH}=7.23 ppm. This chemical shift corresponds to a "half" hydrogen-bonded proton (Eq.

Table 1. ν_{OH} in IR Spectra (Nujol, Room Temperature) and δ_{OH} in ^{1}H NMR (CDCl$_3$, 25 °C, Internal Standard TMS)

Compound	ν_{OH}/cm^{-1}	δ_{OH}/ppm (Integral Intensity)
1$_4$	3170	10.34(4H)
1$_6$	3120	10.50(6H)
1$_8$	3190	9.60(8H)
2Me$_1$	3150, 3280	9.54(2H), 10.13(1H)
2Me$_2$	3450	7.19(2H)
2Me$_3$	3470	6.20(1H)
3$_2$	3280	7.23(2H)
3$_3$	3240	8.51(2H), 9.17(1H)
3$_4$	3200	8.32(2H), 9.46(2H)


(1)

3$_2$


(2)

3$_3$

1). The trimer (**3**$_3$) gives two peaks at 8.51 and 9.17 ppm. The integral intensity tells us that the peak at lower magnetic field (integral intensity 1H) is assigned to the proton of the inner phenol unit and that at the higher magnetic field (integral intensity 2H) is assigned to the protons of external phenol units (Eq. 2): that is, the proton of the inner phenol unit always participates in hydrogen-bonding interactions whereas those of external phenol units are "half" hydrogen-bonded. These results suggest that the chemical shift of the phenolic protons reflects the degree of intramolecular hydrogen-bonding interactions. The δ_{OH} for the "fully" hydrogen-bonded proton appears at the magnetic field lower by 0.66 ppm than that for the "half" hydrogen-bonded protons: thus, the stronger the hydrogen bond, the greater the down-field shift.[13)]

The δ_{OH} values for the "half" hydrogen-bonded protons in **3**$_3$ and **3**$_4$ shift to the lower magnetic field (by 1.09—1.28 ppm) from that for the "half" hydrogen-bonded proton in **3**$_2$. In **3**$_3$ and **3**$_4$, the OH groups in inner phenol units are polarized through hydrogen-bonding interactions ($O(\delta-)$-$H(\delta+)\cdots OH$). Hence, the hydrogen bond with the polarized OH group ($OH\cdots O(\delta-)$-$H(\delta+)\cdots OH$) is more strengthened.

The δ_{OH} values for **1**$_n$ further shift to the lower magnetic field. In particular, the shifts observed for

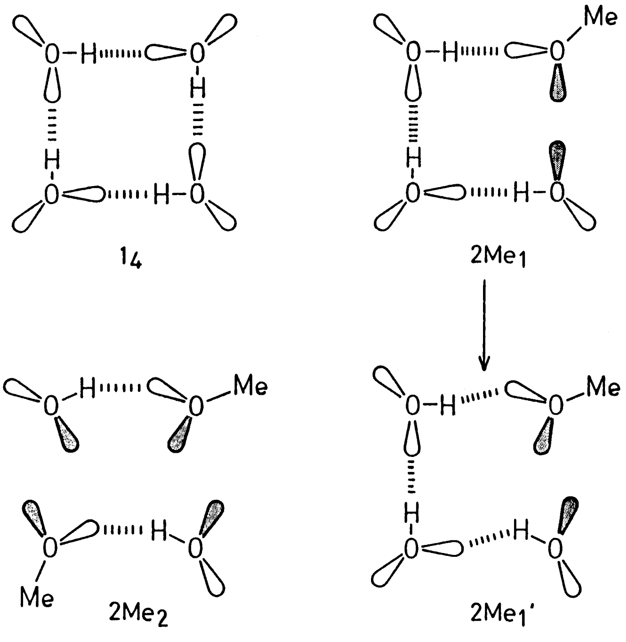


Fig. 1. Intramolecular hydrogen-bonding interactions in **1**$_4$, **2**Me$_1$, and **2**Me$_2$. The filled lone pairs denote the occurrence of electrostatic repulsion.

1$_4$ and **1**$_6$ are surprisingly large. The finding indicates that a strong, hydrogen-bonding belt is formed on the lower rim of the calixarene cavity. This serves as the origin of the stabilization of a "cone" conformation.[1,2,6,7)] In **1**$_4$, for example, all protons are chelated through hydrogen bonds and the resultant structure features high C_{4v} symmetry (Fig. 1).[14)] In contrast, the relatively small shift in **1**$_8$ implied that the hydrogen-bonding belt is somewhat destabilized, presumably, by the flexible nature of the calix[8]arene ring.[1,2)] Among **1**$_n$, the δ_{OH} for **1**$_6$ appears at the lowest magnetic field and that for **1**$_4$ is the next, indicating that the strength of the intramolecular hydrogen-bonding interactions is in the order of **1**$_6$>**1**$_4$>**1**$_8$.

In contrast, monomethylated **2**Me$_1$ gives two peaks at 9.54 (integral intensity 2H) and 10.13 (integral intensity 1H) ppm. This shows that the hydrogen bonds are destabilized by introduction of a methyl group. In **1**$_4$ four protons can interact with each other through four lone electron pairs in oxygens to form a circular hydrogen-bonding belt (Fig. 1). This is due to high symmetry of **1**$_4$.[14)] In **2**Me$_1$, on the other hand, the methyl group should be placed outside the ring when it adopts a cone conformation (Fig. 1) because the lower rim of the ring is too small to accept the methyl group. The examination of Corey-Pauling-Koltun molecular models also supports the "outside-methyl." The ^{1}H NMR supports that **2**Me$_1$ is present in a cone conformation: at 30 °C in CDCl$_3$, the ArCH$_2$Ar protons give two pairs of doublets (3.43 and 4.27 ppm for one pair and 3.43 and 4.36 ppm for the other pair). Under this situation, two lone electron pairs are enforced to be confronted with each other (Fig. 1). This orientation would induce serious electrostatic repulsion, so that the arrangement of lone electron pairs would be distorted from C_{4v} symmetry (for example, as in $\mathbf{2Me_1'}$). This explains why the two hydrogen bonds in $\mathbf{2Me_1}$ are specifically weakened: as shown in $\mathbf{2Me_1'}$, the distortion results in two weak hydrogen bonds. In $\mathbf{2Me_2}$, the electrostatic repulsion between lone electron pairs can take place at two positions (Fig. 1).[15] In fact, it gives a single peak at $\delta_{OH}=7.19$ ppm for the phenolic protons, which shifts by 3.15 ppm to the higher magnetic field from that of $\mathbf{1}_4$. The δ_{OH} value for $\mathbf{2Me_3}$ further shifts to the higher magnetic field (6.20 ppm), indicating the formation of a very weak hydrogen bond.

It has been noticed that in IR, the ν_{OH} vibration band of $\mathbf{1}_n$ appears at around 3100 cm^{-1}.[1-3] This is also attributed to the strong, intramolecular hydrogen-bonding interactions.[1-3] Examination of Table 1 reveals that the shift width of the ν_{OH} band to the lower frequency is in the order of $\mathbf{1}_6>\mathbf{1}_4>\mathbf{1}_8$. This order is in good accord with that of the δ_{OH} in ^1H NMR. This suggests that the strength of the hydrogen bond is also reflected by the ν_{OH}: the stronger the hydrogen bond, the greater the shift to the lower frequency. In fact, $\mathbf{2Me}_n$ and $\mathbf{3}_n$, the hydrogen bonds of which are relatively weakened, give the ν_{OH} at higher frequency region. In Fig. 2, we illustrate a plot of δ_{OH} vs. ν_{OH}. Clearly, the ν_{OH} value correlatively increases with increase in the δ_{OH} value.

Interestingly, $\mathbf{2Me_1}$, which gave two δ_{OH} values in ^1H NMR, results in two ν_{OH} bands in IR. This supports again that $\mathbf{2Me_1}$ includes two different hydrogen bonds, one is strong and the other is weak. It is clear from the foregoing discussion that ν_{OH} 3150 and 3280 cm^{-1} bands correspond to δ_{OH} 10.13 (strong bond) and 9.54 (weak bond) ppm peaks, respectively. The ^1H NMR data suggest that $\mathbf{3}_3$ and $\mathbf{3}_4$ may also give two ν_{OH} bands. In fact, however, the ν_{OH} band for these compounds appeared as a single, broad peak.

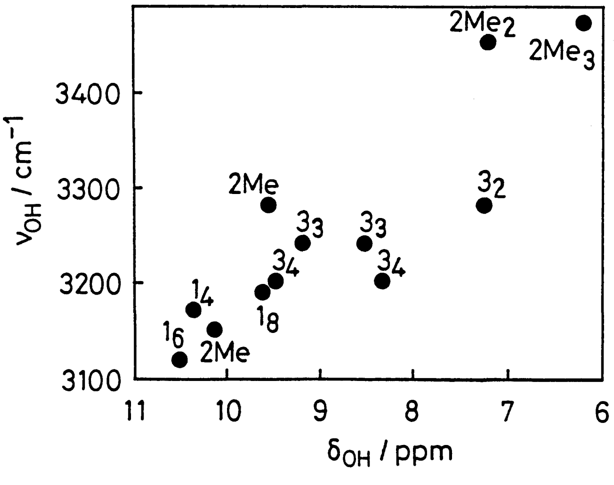


Fig. 2. Plots of ν_{OH} vs. δ_{OH}.

The foregoing results consistently demonstrate the presence of the strong hydrogen-bonding interactions in $\mathbf{1}_n$ and the relatively weakened interactions in $\mathbf{2Me}_n$ and their acyclic analogs. Hereafter, we discuss how the strength of the hydrogen bonds is reflected by their pK_a values.

pK_{app} Determination. We have used NEt_4^+ salts of NP^-, DNP^-, and P^- as pH indicators (Table 2). Their pK_a values in water at 25 °C are 0.71, 4.11, and 7.15, respectively. Taking the titration of $\mathbf{1}_4H_4$ (undissociated species of $\mathbf{1}_4$) by P^-, for instance, the following equilibrium will be attained in solution (THF, 25 °C).

$$\mathbf{1}_1H_4+P^- \underset{}{\overset{K_e}{\rightleftarrows}} \mathbf{1}_4H_3^- + PH \tag{3}$$

The decrease in $[P^-]$ is readily measured by a spectroscopic method and the equilibrium constant (K_e) can be determined. Thus, the apparent acid dissociation (dissociation of the first proton) constant (K_{app}) for $\mathbf{1}_4H_4$ is defined by Eq. 4.

$$K_{app}=K_e\cdot K_a \tag{4}$$

To test the reliability of this method, we titrated four *p*-substituted phenols *p*-X-C_6H_4OH (X=OMe, H, Br, and CN) by NP^-. The results in Table 3 show that one can obtain reasonable pK_{app} values by this method. We thus applied this method to the determination of pK_{app} values for $\mathbf{1}_n$, $\mathbf{2Me}_n$, and $\mathbf{3}_n$. The results are summarized in Table 4. The most compounds resulted in reasonable titration curves which could be analyzed according to the theoretical equation (Fig. 3). In contrast, the titration curves for $\mathbf{3}_3$ and $\mathbf{3}_4$ significantly deviated from the theoretical

Table 2. Absorption Spectra of Tetramethylammonium Salts of *p*-Nitrophenolate (NP^-), 2,4-Dinitrophenolate (DNP^-), and Picrate (P^-) at 25 °C in THF

Indicator	λ_{max}	ε_{max}
	nm	$dm^3\,mol^{-1}\,cm^{-1}$
NP^-	422	8470
DNP^-	372 422	9820 9090
P^-	371	11800

Table 3. pK_a (water, 25 °C) and pK_{app} (THF, 25 °C) of *p*-Substituted Phenols

p-X-C_6H_4OH	pK_a	pK_{app}[a]	$pK_{app}-pK_a$
X=OMe	10.21	10.91	0.70
X=H	9.99	10.68	0.69
X=Br	9.34	9.67	0.33
X=CN	7.95	7.83 (7.76)[b]	−0.12 (−0.19)

a) Estimated with NP^-. b) Estimated with DNP^-.

Table 4. pK_{app} of **1**$_n$, **2Me**$_n$, and **3**$_n$ (THF, 25 °C)

Compound	pK_{app} Determined by		
	NP$^-$	DNP$^-$	P$^-$
1$_4$	a)	a)	4.11
1$_6$	a)	a)	3.62
1$_8$	a)	a)	4.05
2Me$_1$	6.95	7.10	3.98
2Me$_2$	12.2	b)	b)
2Me$_3$	12.5	b)	b)
3$_1$	10.9	b)	b)
3$_2$	7.92	—	—
3$_3$	6.9	7.0	—
3$_4$	5.3	5.5	—

a) The dissociation of 2—4 protons occurred simultaneously. b) The spectral change is too small to estimated the pK_{app}: that is, the basicity of DMP$^-$ and P$^-$ is too weak to abstract a proton from **2Me**$_n$.

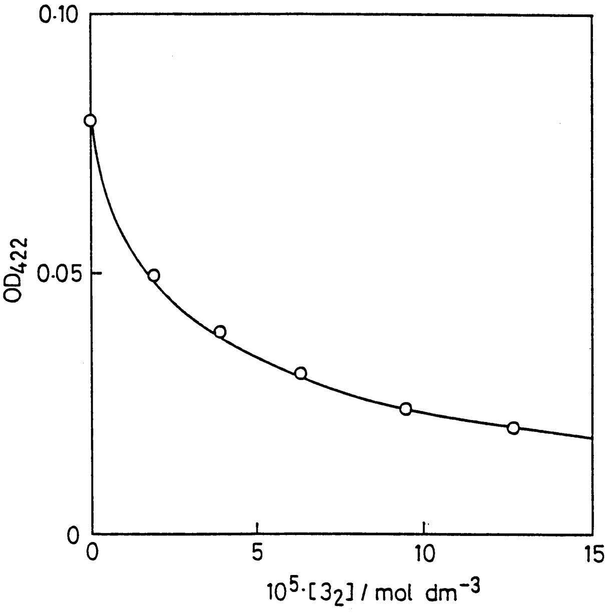


Fig. 3. Titration of **3**$_2$ with NP$^-$ (9.31×10^{-6} mol dm^{-3}) in THF at 25 °C. The solid curve indicates the theoretical line for the titration.

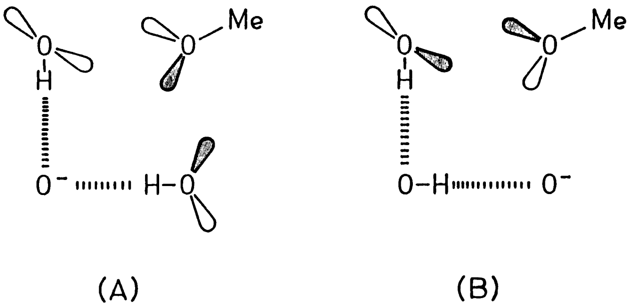


Fig. 4. (A) Dissociation from a strong hydrogen bond (the oxide anion can form two hydrogen bonds). (B) Dissociation from a weak hydrogen bond (the oxide anion can form only one hydrogen bond).

equation: at the initial stage of the titration the dissociation of the first proton occurs easily whereas at the last stage of the titration the dissociation is rather suppressed. Presumably, the deviation is caused by intermolecular hydrogen-bonding interactions between partially dissociated species of **3**$_3$ and **3**$_4$. In **1**$_n$ and **2Me**$_n$, intramolecular hydrogen-bonding interactions occur in preference to intermolecular ones. Thus, the titration curves obey the theoretical equation. For **3**$_3$ and **3**$_4$, we picked up the data at around pK_{app} (half-dissociated) and estimated the pK_{app} values.

The pK_{app} values for **1**$_n$, determined with P$^-$, are in the order of **1**$_6$>**1**$_8$>**1**$_4$. This is not quite in accord with the order of δ_{OH} (**1**$_6$>**1**$_4$>**1**$_8$). In **1**$_n$, the dissociation of the proton involved in a strong hydrogen bond would be suppressed. Once it is dissociated, the oxide anion would be strongly stabilized by the hydrogen bond. The pK_{app} reflects the difference between these two energy states and therefore does not give the same order as δ_{OH}. Anyhow, the result suggests that **1**$_6$ possesses the strongest hydrogen bond and the most acidic proton. Compound **2Me**$_1$, which has one strong hydrogen bond and two weak hydrogen bonds, affords the low pK_{app} comparable with those for **1**$_n$. Which proton is dissociated first? The fact that **2Me**$_2$, which has only two weak hydrogen bonds, affords the high pK_{app} value supports the dissociation from a strong hydrogen bond. This is also understandable from Fig. 4: if a strongly hydrogen-bonded proton is dissociated, the oxide anion can be stabilized by two hydrogen bonds. If a weakly hydrogen-bonded proton is dissociated, the oxide anion can be stabilized only by one hydrogen bond. The difference argues for the dissociation of the strongly hydrogen-bonded proton.

When NP$^-$ and DNP$^-$ were used for the determination of pK_{app} for **1**$_n$, the dissociation of 2—4 protons occurred simultaneously. Thus, we could not estimate the pK_{app}. For **2Me**$_1$, in contrast, the dissociation of the first proton could be determined with NP$^-$ and DNP$^-$. The difference indicates that in **1**$_n$ the dissociation of plural protons occurs successively, whereas in **2Me**$_1$ the dissociation of the first proton occurs at very acidic region but that of the second proton occurs at considerably basic region. We here noticed a serious problem about the present titration method. The pK_{app} values for **2Me**$_1$ determined with NP$^-$ and DNP$^-$ are similar each other but are largely different from that determined with P$^-$: pK_{app} determined with P$^-$ is lower by about 3 pK units. This implies that in THF P$^-$ apparently acts as a relatively stronger base. Although this reason is not understood well, we consider that in $Et_4N^+P^-$, the ion pair is more loosened because of steric crowding of 2,6-dinitro moieties. Anyhow, we cannot directly compare $\mathrm{p}K_{\mathrm{app}}$ values determined with NP$^-$ and DNP$^-$ with those determined with P$^-$. As described above, the $\mathrm{p}K_{\mathrm{app}}$ values for **1**$_n$ are comparable with that for **2**Me$_1$. We thus considered that if they could be determined with NP$^-$ and DNP$^-$, then their $\mathrm{p}K_{\mathrm{app}}$ values should be about 7.

As shown in Table 4, the $\mathrm{p}K_{\mathrm{app}}$ for **3**$_1$ (i.e., *p*-*t*-butylphenol) is 10.9. One can thus consider that the $\mathrm{p}K_{\mathrm{app}}$ values for **1**$_n$ and **2**Me$_1$ are lowered by about four p*K* units. Very recently, Grootenhuis et al.[16] reported computational studies of calix[4]arenes. They predicted that the difference in acidity between calix[4]arenes and its acyclic analogs would be 9—11 p*K* units. The remarkably large $\mathrm{p}K_{\mathrm{a}}$ difference was actually observed for *p*-sulfonatocalix[4]arene and *p*-nitrocalix[4]arene.[9,10] The *p*-substituents in these calix[4]arenes are strongly electron-withdrawing. Hence, the dissociation of the first proton from a phenol unit is facilitated not only by the conventional hydrogen-bonding interactions but also by the electron-withdrawing nature of neighboring phenol units. Of course, the latter effect is primarily transduced through the hydrogen bonds, but the contribution of through-space interactions must be also taken into account. In the present system, the difference in acidity between **1**$_n$ and *p*-*t*-butylphenol is estimated to be about four p*K* units. We consider that the relatively small $\mathrm{p}K_{\mathrm{app}}$ shift is attributed to the absence of the latter effect: in other words, introduction of electron-withdrawing substituents into *p*-position acceleratively lowers the $\mathrm{p}K_{\mathrm{app}}$.

2Me$_2$ and **2**Me$_3$, which only possess weak hydrogen bonds, afford the $\mathrm{p}K_{\mathrm{app}}$ values higher by more than five p*K* units than that for **2**Me$_1$. This implies that weak hydrogen bonds are not capable of stabilizing the oxide anion efficiently. The $\mathrm{p}K_{\mathrm{app}}$ values for **2**Me$_2$ and **2**Me$_3$ are even higher than that for **3**$_1$. In contrast, the $\mathrm{p}K_{\mathrm{app}}$ values for noncyclic trimer **3**$_3$ and tetramer **3**$_4$ are unusually low. We consider that this $\mathrm{p}K_{\mathrm{app}}$ shift is brought forth by the stabilization through intermolecular hydrogen-bonding interactions.[17]

Conclusion. This paper describes the first systematic estimation of acid dissociation constants for **1**$_n$ and their analogs. The $\mathrm{p}K_{\mathrm{app}}$ values for **1**$_n$ are lowered at least by four p*K* units because of strong intramolecular hydrogen-bonding interactions. This conclusion is of great significance in understanding characteristic properties of **1**$_n$ such as conformational isomerism,[1,2,13] autoaccelerative substituion,[18] ring invertsion rates,[1,2,19] etc.

Experimental

Materials. Compounds **1**$_n$ were prepared according to Gutsche's method.[20] Compounds **3**$_n$ were prepared according to the literatures.[21,22] Compound **2**Me$_2$ was kindly supplied by Professor D. N. Reinhoudt(University of Twente).

25-Methoxy-*p*-*t*-butylcalix[4]arene (2Me$_1$).† Compound **1**$_4$ (500 mg, 0.77 mmol), methyl iodide (0.48 ml, 7.7 mmol), and K_2CO_3 (106 mg, 0.77 mmol) were added to 25 ml of acetone and the mixture was stirred at room temperature for 23 h. The progress of the reaction was followed by an HPLC method. After filtration the filtrate was concentrated in vacuo. The residue was taken in water-chloroform. The chloroform solution was separated and subjected to a column purification (silica gel, chloroform : hexane=1 : 1 vol/vol). The eluent was evaporated to dryness and the residue was crystallized from chloroform-methanol; white powder, mp 186—188 °C, yield 15%; IR (Nujol) ν_{OH} 3150, 3250 cm^{-1}; 400 MHz ^{1}H NMR ($CDCl_3$, 25 °C) δ=1.20, 1.21, 1.22 (9H, 18H, 9H, respectively, *t*-Bu), 3.44 (4H, H$_{\mathrm{exo}}$ in $ArCH_2Ar$), 4.12 (3H, OMe), 4.27, 4.36 (2H each, H$_{\mathrm{endo}}$ in $ArCH_2Ar$) 6.99, 7.04, 7.05, 7.09 (2H each, ArH), 9.54, 10.13 (2H, 1H, respectively, OH). Two pairs of doublets for the $ArCH_2Ar$ protons indicate that **2**Me$_1$ adopts a cone conformation.

Found: C, 80.74; H, 8.66%. Calcd for $C_{45}H_{58}O_4\cdot0.5CH_3OH$: C, 80.45; H, 8.91%.

25,26,27-Trimethoxy-*p*-*t*-butylcalix[4]arene (2Me$_3$). 25,26,27-Trimethoxycalix[4]arene has been synthesized by Gutsche et al.[22] According to this method, we here employed $Ba(OH)_2$ as base for the trisubstitution reaction. Compounds **1**$_4$H (1.0 g, 1.5 mmol), BaO (1.5 g, 10.4 mmol), $Ba(OH)_2\cdot8H_2O$ (1.7 g, 5.4 mmol) were added in 25 ml of DMF. To this mixture (stirred at room temperature) methyl iodide (2.88 ml, 4.62 mmol) was added dropwise. After 30 min, the solution was diluted with water and extracted with chloroform. The chloroform layer was separated and evaporated to dryness. The residue was recrystallized from chloroform-methanol; white powder, mp 213—214 °C, yield 58%; IR (Nujol) ν_{OH} 3470 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$, 25 °C) δ=0.83, 1.33, 1.34 (18H, 9H, 9H, respectively, *t*-Bu), 3.21, 3.28 (2H each, H$_{\mathrm{exo}}$ in $ArCH_2Ar$), 3.84, 3.95 (6H, 3H, respectively, OMe), 4.29, 4.32 (2H each, H$_{\mathrm{endo}}$ in $ArCH_2Ar$), 6.20 (1N, OH), 6.54, 6.57, 7.07, 7.14 (2H each, ArH). Two pairs of doublets for the $ArCH_2Ar$ protons indicate that we selectively recovered a cone isomer.

Found: C, 81.46; H, 9.03%. Calcd for $C_{47}H_{62}O_4$: C, 81.70; H, 9.04%.

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† For numbering of calix[4]arenes see Refs.1 and 2.

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9) S. Shinkai, K. Araki, H. Koreoshi, T. Tsubaki, and O. Manabe, *Chem. Lett.*, **1986**, 1351.

10) The pK_a values for *p*-nitrocalix[4]arene were determined in 85.4 wt% EtOH–H_2O at 25 °C by potentiometric titration: pK_{a1} 2.9, pK_{a2} 10.9, pK_{a3} 12.3, pK_{a4}>13: P. D. J. Grootenhuis, D. N. Reinhoudt, and S. Shinkai, to be submitted.

11) S. Shinkai, K. Araki, J. Shibata, D. Tsugawa, and O. Manabe, *Chem. Lett.*, **1989**, 931.

12) S. G. Bott, A. W. Coleman, and J. L. Atwood, *J. Am. Chem. Soc.*, **110**, 610 (1988).

13) It is known that in phenol derivatives the δ_{OH} is linearly correlated with Hammett's σ with ρ=1.53—1.65, indicating that the δ_{OH} shifts to lower magnetic field with increasing σ value: N. Inamoto, "Hammett Rule," Maruzen, Tokyo (1983), p. 90. In the present system calixarenes having acidic protons tend to give the δ_{OH} at lower magnetic field (see Tables 1 and 4). One may thus regard that the δ_{OH} values reflect the acidity of the OH groups which is profoundly affected by intramolecular hydrogen-bonding interactions.

14) X-Ray studies of *p*-*t*-octylcalix[4]arene and some clathrates of $\mathbf{1}_4$ show the calixarene moiety to be present in a cone conformation with C_{2v} symmetry: G. D. Andreetti, R. Ungaro, and A. Pochini , *J. Chem. Soc., Chem. Commun.*, **1979**, 1005; G. D. Andreetti, A. Pochini, and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2*, **1983**, 1773; R. Ungaro, A. Pochini, G. D. Andreetti, and G. D. Domiani, *J. Chem. Soc., Perkin Trans. 2*, **1985**, 197. However, ^{1}H NMR studies support the view that $\mathbf{1}_4$ adopt a cone conformation with C_{4v} symmetry: C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, **107**, 6052 (1985). The discrepancy is rationalized as such that $\mathbf{1}_4$ in solution is subject to a rapid interconversion $C_{2v} \rightleftarrows C_{2v}'$, resulting in apparent C_{4v} symmetry.

15) According to the recent X-ray crystallographic studies by Grootenhuis et al.,[16] $\mathbf{2}Me_2$ has C_{2v} symmetry: the two anisole moieties are more or less parallel to each other, with the methoxy groups pointing outwards while the two phenol units are flattened. This conformation may also weaken the hydrogen-bonds.

16) P. D. J. Grootenhuis, P. A. Kollman, L. C. Groenen, D. N. Reinhouldt, G. J. van Hummel, F. Ugozzoli , and G. D. Andreetti, *J. Am. Chem. Soc.*, **112**, 4165 (1990).

17) The spectral studies of $\mathbf{1}_4$ and related acyclic compounds have been reported by T. Cairns and G. Eglinton (*Nature*, **196**, 535 (1962)). However, the synthetic method used therein (Zinke's method) later turned out to be doubtful: that is, the sample might be a mixture of $\mathbf{1}_4$ and $\mathbf{1}_8$. In this paper they proposed the association of acyclic compounds through intermolecular hydrogen-bonding interactions.

18) S. Shinkai, K. Araki, J. Shibata, and O. Manabe, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 195.

19) K. Araki, S. Shinkai, and T. Matsuda, *Chem. Lett.*, **1989**, 581.

20) C. D. Gutsche and M. Iqbal, *Org. Synth.*, **68**, 234, 238, 243 (1989).

21) H. Kämmerer and K. Haberer, *Monatsh. Chem.*, **95**, 1589 (1964).

22) B. Dhawan and C. D. Gutsche, *J. Org. Chem.*, **48**, 1536 (1983).

23) C. D. Gutsche, B. Dhawan, and J. A. Levine, *Tetrahedron*, **39**, 409 (1983).