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Deprotonation of Calixarenes in Acetonitrile

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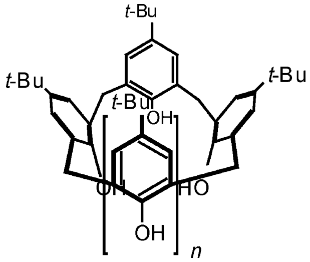

The pK_a values for calixarenes in MeCN have been determined by selective titration with bases using a spectroscopic method. These values are as follows: calix[4]arene p$K_a(1) = 19.06 \pm 0.22$, p$K_a(2) > 33$; calix[6]arene p$K_a(1) = 15.59 \pm 0.06$, p$K_a(2) = 23.85 \pm 0.35$, p$K_a(3) > 33$; calix[8]arene p$K_a(1) = 17.20 \pm 0.20$, p$K_a(2) = 20.32 \pm 0.31$, p$K_a(3) > 33$. The trends in acidity are rationalized using structures generated by a DFT model. For mono-deprotonation, the degree and nature of hydrogen bonding in the anion is the dominant factor; for di-deprotonation, spatial separation of the anionic charges becomes important.

Introduction

Calixarenes (e.g., **1**) continue to excite interest at the forefront of chemistry.[1] However, although the phenolic hydroxy groups are responsible for many calixarene properties, it is surprising to find no comprehensive, systematic, and reliable pK_a data for these intriguing compounds. The most recent update of calixarene chemistry by Gutsche devotes only two pages to this topic (he quotes "the accurate measurement of their pK_a values has posed some difficulties");[2] the original monograph in 1989 could manage only one page.[3] Why are these pK_a data important? Apart from the academic incongruity of science's ignorance of a fundamental property of such extensively studied compounds, there are further reasons. Selective lower-rim (i.e., hydroxy) modification is increasingly important in modifying calixarene function,[4] and this usually involves initial deprotonation; however, much current design is empirical. Comprehensive pK_a data would allow improved rationalization of modification methodology. In calixarene host−guest interactions,[5] many guests are potential bases toward the calixarene; pK_a data would allow better assessment of the extent of ionic (e.g., ion-pair) vs dipolar (e.g., hydrogen-bonded) complexation. Calixarenes are increasingly being used as selective hosts for neutral and cationic guests, and the strength of binding is dependent on the protonation of the calixarene;[6] reliable pK_a data will allow better design of such systems. Calixarenes show a complex and varied conformational chemistry;[7] examination of pK_a data can provide information about conformational effects. Calixarene salts have been proposed as novel surfactants, and

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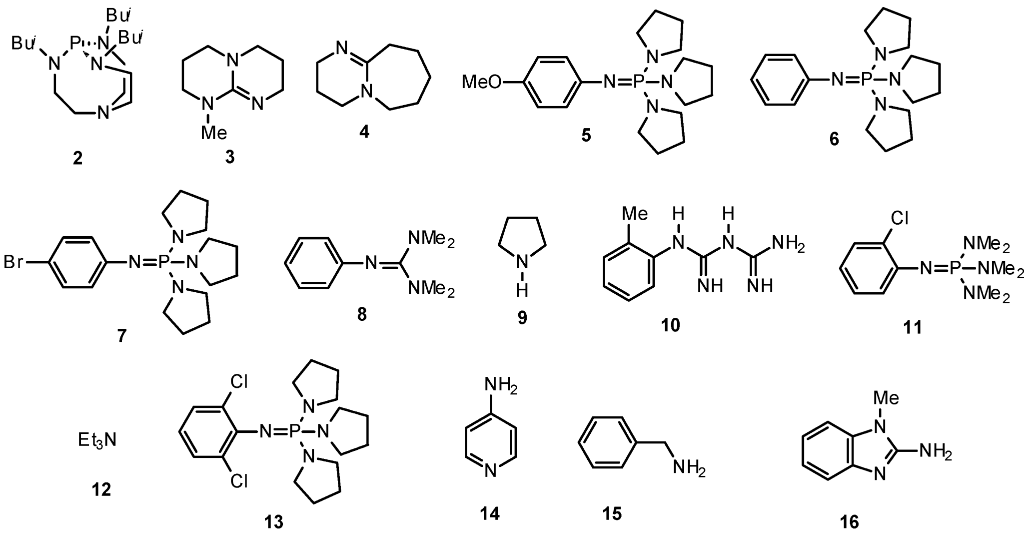
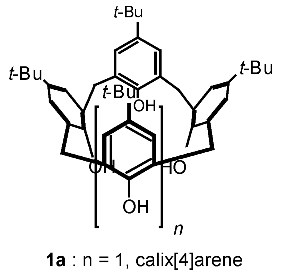
CHART 1. Structures for Organic Bases 2−16



better pK_a data would remove uncertainty over the degree of neutralization.[8] Finally, calixarenes are ideally constructed to facilitate hydrogen bonding, both intramolecularly and as a directing force in supramolecular structural motifs.[9] As one of the most important factors in acidity is hydrogen-bonding stabilization of an anion,[10] a study of calixarene acidity would give insight into the wider aspects of hydrogen bonding.

Some pK_a values have been determined for nitro or sulfonic acid modified calixarenes.[11] These groups facilitate pK_a determination by increasing solubility and reducing the pK_a values, so for example, values of 4−6 are quoted for mono-nitrated calix[4]arenes.[12] However, data for the parent calixarenes are far more limited. Shinkai has estimated p$K_a(1)^{\mathrm{water}}$ [13] values for **1a**, **1b**, and **1c** as 4.11, 3.62, and 4.05, respectively, from titrations with nitrophenoxide bases in THF,[14] and potentiometric titrations have yielded some values in benzonitrile (PhCN).[15] However, the Shinkai approach was indirect, and the potentiometric method is limited to solvents in which calixarene solubility is high (>1 mM), and so excludes many of the most common solvents used in organic chemistry, including water, MeCN, THF, MeOH, EtOH, hexane, etc.



1a : n = 1, calix[4]arene
1b : n = 3, calix[6]arene
1c : n = 5, calix[8]arene

In this work, pK_a values for *tert*-butylcalix[n]arenes (*n* = 4, 6, 8) **1a**, **1b**, and **1c** have been determined in MeCN using a spectroscopic method. Organic bases **2**−**16** (see Chart 1) of known pK_a,[16−18] many with accessible UV−vis spectroscopic characteristics, were used to selectively deprotonate the calixarenes. Selective deprotonation by a base whose pK_a is closely tuned to that of the acid in question, e.g., H_4A, H_3A^-, etc., is essential. Calixarenes are multibasic acids, so if titrated with a strong base, the various forms will exist together to an extent determined by the relative pK_a(1), pK_a(2), etc., values. Examination of the UV−vis spectra at different titration stages might be expected to allow for calculation of the relative pK_a values.[19] However, this approach depends very much on there being clean, well-defined, and distinct UV−vis spectra for the various acidic species, and this is unlikely to be the case for the calixarenes, which tend not to show clear trends in UV−vis properties.[2,3] In summary, it is not safe to rely on the spectroscopic changes to the calixarene alone to provide reliable data for pK_a calculation, hence the inclusion of UV-active bases. Also, the spectroscopic method is the one of choice in situations, as here, in which substrate solubility is very low and high dilution is required to minimize the potential for ion-

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[19] For example, see the method used by: Leito, I.; Rodima, T.; Koppel, I. A.; Schwesinger, R.; Vlasov, V. M. *J. Org. Chem.* **1997**, *62*, 8479.

TABLE 1. Basicity Scale of Bases in MeCN

base	pK_a[a]	base	pK_a
2	33.53[b]	**10**	19.66
3	25.49	**11**	19.07
4	24.34	**12**	18.82
5	23.12	**13**	18.56
6	22.34	**14**	17.62
7	21.19	**15**	16.91
8	20.84	**16**	16.31
9	19.56		

[a] Most values are taken from ref 16. These are slightly revised values of those found in refs 17 and 18. [b] Value taken from ref 23.

pairing, ion–neutral molecule interaction, and calixarene di- and trimerization.[20] Furthermore, the dilute solutions (μM) associated with the spectroscopic method allow for the use of simple concentrations rather than activities.

Results

Bases. This work makes use of a large number of organic bases **2**–**16** whose pK_a values lie in the estimated range of calixarene acidity (i.e.,15–33) in MeCN. These bases have been chosen because a self-consistent basicity scale in the 3.8–32 range for these materials (ca. 89 bases) in MeCN is available.[16–18] Furthermore, many of the bases give UV–vis spectra distinct from the calixarenes, and show significant spectral changes on protonation to complement those of the calixarene. The bases used in this work are illustrated, and pK_a values (for conjugate acids) are collected in Table 1. Slightly different values are found throughout the literature for the same bases.[21–30] The main source (ref 16) is the most recent, and the values are part of a self-consistent scale. Bases **2**–**4**, **9**, **10**, **12**, and **14**–**16** are commercially available, whereas the remainder, **5**–**8**, **11**, and **13**, were synthesized according to literature procedures. The conjugate acids were prepared and isolated as PF_6^-, BPh_4^-, or Cl^- salts, or in situ by addition of HCl to a solution of base in MeCN.

Calix[4]arene. Addition of 1 equiv of the strong base DBU **4**, invisible above 265 nm, to a solution of calix[4]arene in MeCN at 25 °C led to the spectral change shown in Figure 1.

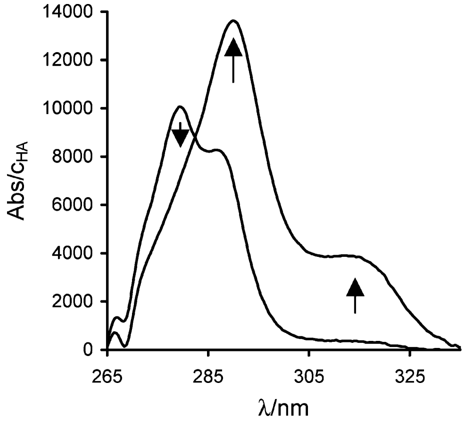

FIGURE 1. UV–vis spectral change on addition of 1 equiv of DBU **4** to calix[4]arene in MeCN.

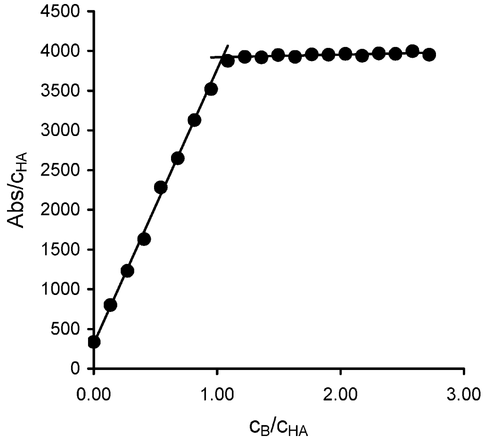

FIGURE 2. Titration of calix[4]arene with DBU **4** at 315 nm.

This change is attributed to the conversion of the calixarene to its anion, and the literature reports similar changes for the addition of a base to *p*-allylcalix[4]arene.[31] Importantly, no further change occurred after the addition of the first equivalent, as shown in the titration plot (at 315 nm) of Abs/c_{HA} vs c_B/c_{HA} (Figure 2).

Further examination of Figure 1 reveals isosbestic points at 282 and 265 nm, and because neither DBU **4** nor its conjugate acid absorbs at these wavelengths, these mark the wavelengths where $\epsilon(H_4A) = \epsilon(H_3A^-)$. Similar plots were obtained for **2** and **3**.

Changes due to a mono-deprotonation are also seen on addition of a strong visible base **6**. Figure 3 shows the titration of calix[4]arene **1a** by **6** at 265 nm (the isosbestic point of H_4A/H_3A^-). The lack of absorbance is due to protonation of the added base by the calixarene ($\epsilon(BH^+)_{265} \approx 0$), and absorbance at 265 nm is seen only after 1 equiv ($\epsilon(B)_{265} = 17\,000$).

Titration with the bases **8**–**14** spanning the pK_a range 20.84–17.62 located the pK_a of calix[4]arene within this range, and titration with bases **11**, **12**, and **13** yielded solutions with measurable amounts of all components B, BH^+, H_4A, and H_3A^- at equilibrium. The values of the extinction coefficients for use in the calculations (see Experimental Section) are readily determined for B, BH^+, and H_4A. The important value for H_3A^- was determined from titrations resulting in complete mono-deprotonation using strong bases transparent in the UV–vis region of interest (**2**, **3**, and **4**, along with their conjugate acids, are transparent at 290 nm, where H_3A^- absorbs strongly; see Figure 1). Alternatively, direct use of $\epsilon(H_3A^-)$ was

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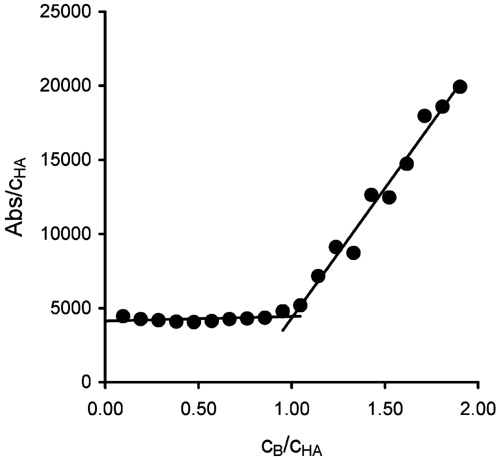

FIGURE 3. Titration of calix[4]arene with (phenylimino)-tripyrrolidinophosphorane **6** at 265 nm.

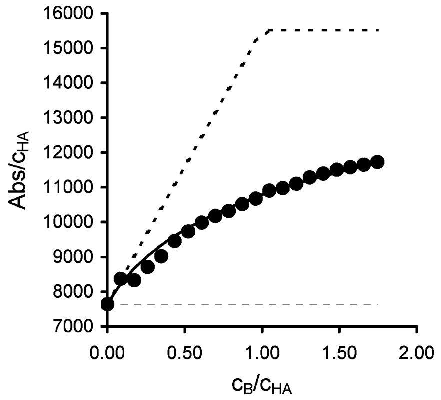

FIGURE 4. Titration of calix[4]arene with **12** at 290 nm. The upper and lower broken lines represent calculated plots for complete mono-deprotonation and complete non-deprotonation, respectively. The solid line represents the calculated plot based on the measured value of K.

TABLE 2. Determination of pK_a for Mono-Deprotonation of Calix[4]arene 1a in MeCN at 25 °C

base	pK_a (BH$^+$)	λ (nm)	K	pK_a (H$_4$A/H$_3$A$^-$)
11	19.07	290	0.53 ± 0.09	19.36 ± 0.08
12	18.82	290	0.57 ± 0.14	19.09 ± 0.10
13	18.56	265	0.53 ± 0.11	18.84 ± 0.09
		282	0.53 ± 0.06	18.84 ± 0.05
		290	0.78 ± 0.22	19.15 ± 0.09
mean				19.06 ± 0.22

avoided by selection of a wavelength corresponding to an isosbestic point between H$_4$A and H$_3$A$^-$. This approach was most useful for those bases (i.e., **6**, **8**, **10**, **11**, **13**, and **14**) showing significant spectral changes on protonation in the UV−vis region of interest. Titrations with bases **11**, **12**, and **13** (a typical plot is shown in Figure 4) yielded the data of Table 2, and gave a pK_a value for H$_4$A of 19.06 ± 0.22.

Since K is derived from the reaction between the bases and calixarene, the possibility of an association between the protonated base and deprotonated acid must be considered, as per eq 1.

$$H_4A + B \overset{K_1}{\rightleftharpoons} H_3A^- + BH^+ \overset{K_2}{\rightleftharpoons} BH^+H_3A^- \qquad (1)$$

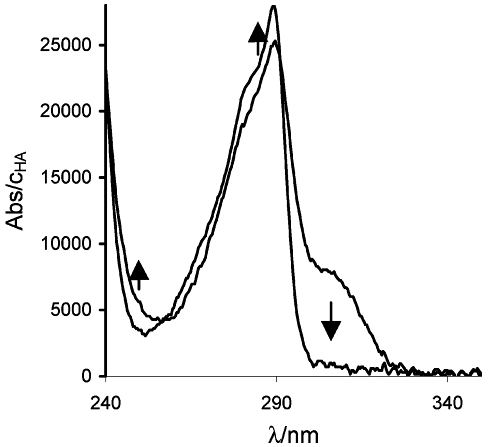

FIGURE 5. UV−vis change on addition of excess triflic acid to calix[8]arene in MeCN.

Evidence for such an association, the formation of an endo complex, was found by Gutsche for neutralization of *p*-allylcalix[4]arene by the primary amine neopentylamine in MeCN.[31] However, we believe such a contribution here to be minimal; in particular, we point to the fact that a similar pK_a value was obtained using triethylamine **12** and the highly hindered bases **11** and **13**. Although the K_1 term (eq 1) is dependent only on the relative acidities of HA and BH$^+$, the K_2 term would also be dependent on the structure of the base, so an overall $K = K_1K_2$ that has a significant contribution from K_2 would differ greatly for different bases, as would the pK_a value derived from it.

It is of interest that no evidence of further deprotonation was found, even when the stronger (relative to DBU) base **3** (pK_a = 25.49) or Verkade's superbase **2** (pK_a = 33.53) was used. The pK_a of the latter is close to the accepted autoprotolysis constant of MeCN ($pK_{autoprotolysis}^{MeCN} > 33$), so it appears that only a monoanion of calix[4]arene is possible in this solvent.

Calix[8]arene. Dissolution of calix[8]arene **1c** in MeCN at 25 °C gave the spectrum shown in Figure 5. It is noteworthy that there is a shoulder above 300 nm similar to that seen for the mono-deprotonated calix[4]-arene anion. A similar shoulder was also noted but not explained by Gutsche for *p*-allylcalix[4]arene in EtOH or MeCN/water.[31]

Titration with triflic acid (a strong acid compared to the calixarenes, even in MeCN) led to loss of this shoulder, and a spectrum of the form seen for calix[4]-arene (Figure 1) and for calix[8]arene in chloroform or dioxane.[32] The shoulder at $\lambda > 300$ nm, therefore, we attribute to some preexisting mono-deprotonated calix-[8]arene in the base-free MeCN.[33] This titration shows the isosbestic points for H$_8$A/H$_7$A$^-$ to be at 291 and 257 nm.

Titration of calix[8]arene with DBU **4** monitored at 305 nm gave a shallow increase in absorbance up to 1 equiv, followed by a steeper increase up to 2 equiv, and then no

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(32) Gutsche, C. D. In *Calixarenes Revisited*, *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1998; p 79.

(33) We are grateful to a reviewer for the suggestion that this species might be an *endo*-calixarene zwitterion, wherein a H$^+$ has left its hydroxy group to reside within the cavity, stabilized by hydrogen bonding to the remaining hydroxy groups.

TABLE 3. Determination of pK_a for the Second Deprotonation of Calix[8]arene 1c in MeCN at 25 °C

base	pK_a (BH$^+$)	λ (nm)	K	pK_a (H$_7$A$^-$/H$_6$A^{2-})
8	20.84	305	3.7 ± 2.0	20.36 ± 0.22
	20.84	285	1.9 ± 0.5	20.60 ± 0.15
9	19.56	305	0.37 ± 0.03	19.99 ± 0.04
mean				20.32 ± 0.31

TABLE 4. Determination of pK_a for the First Deprotonation of Calix[8]arene 1c in MeCN at 25 °C

base	pK_a (BH$^+$)	λ (nm)	K	pK_a (H$_8$A/H$_7$A$^-$)
11	19.07	305/260	52 ± 19	17.4 ± 0.2
13	18.56	305/260	39 ± 16	17.0 ± 0.2
14	17.62	305/260	3.0 ± 1.5	17.2 ± 0.25
mean				17.20 ± 0.20

further change. These changes are attributed to mono-followed by di-deprotonation of the calixarene. Since neither the base **4** nor its conjugate acid absorbs above 260 nm, the experiments yield extinction coefficients for H_7A^- and H_6A^{2-} (e.g., $\epsilon_{305}(H_7A^-) = 9382$, $\epsilon_{305}(H_6A^{2-}) = 17\,964$), and isosbestic points for H_7A^-/H_6A^{2-} are observed at 265 and 284 nm, slightly different than those for mono-deprotonation. The existence of two calixarene pK_a values well below that of DBU (24.34) is supported by titrations with UV-active bases **5** (pK_a = 23.12) and **6** (pK_a = 22.34) monitored at the calixarene isosbestic point, 265 nm. These show no absorbance due to base until 2 equiv has been added.

Titration with the guanidine base **8** and pyrrolidine **9** gave a linear increase in absorbance at 305 nm up to 1 equiv of base, followed by a curved increase beyond this. This reflects the presence of measurable amounts of H_7A^-, H_6A^{2-}, B, and BH$^+$, and allowed for calculation of the second pK_a as 20.11 ± 0.35 (Table 3). Guanidine **8** shows some absorbance at the 285 nm isosbestic point for calixarene deprotonation, and a value determined at this wavelength is included in Table 3.

Determination of the first pK_a of calix[8]arene is complicated by the high level of preexisting mono-deprotonated calixarene in the MeCN solution. Titration with bases **11**, **13**, and **14** each showed a small further increase in deprotonation, indicating that the first pK_a for calix[8]arene is close to those for these bases. The equation for K is still valid, except that the simplification of $[A^-] = [BH^+]$ no longer holds. This requires independent measurement of [BH$^+$] (or [B]) and [A$^-$]. This is possible for these three bases, since they have significant absorption at 260 nm near the H_8A/H_7A^- isosbestic point. A value for the first pK_a of calix[8]arene is found to be 17.20 ± 0.20 (Table 4).

Titration with the strong base **2** (pK_a = 33.53) showed some curvature, but the final product, even after titration with more than 3 equiv of base, was not different from the dianion obtained using the much weaker base **4** (pK_a = 24.13). For calix[8]arene, a second deprotonation is the maximum possible in MeCN.

Calix[6]arene. Dissolution of calix[6]arene in MeCN at 25 °C gave a spectrum showing, as with calix[8]arene, a shoulder attributed to the presence of some preexisting mono-deprotonated calix[6]arene.[33] This disappeared on titration with triflic acid (Figure 6), and isosbestic points are observed at 262 and 283 nm.

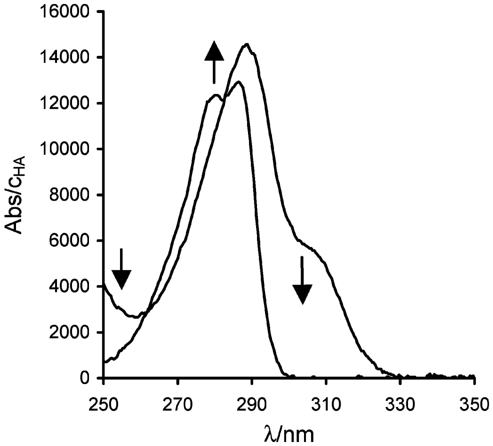

FIGURE 6. UV–vis change on addition of excess triflic acid to calix[6]arene in MeCN.

Titration at the H_6A/H_5A^- isosbestic points of 262 and 283 nm with the large hindered base **7** (pK_a = 21.19) showed complete mono-deprotonation of the calixarene up to 1 equiv, followed by an increase in absorbance due to the (strongly absorbing) base **7**. Clearly, mono-deprotonation occurs with a pK_a below 21.19. Titration with triethylamine (**12**) (pK_a = 18.82) at 305 nm, where only H_5A^- absorbs, also showed a change only up to 1 equiv, with no further change after this. This yielded extinction coefficients for H_5A^- ($\epsilon_{305}(H_5A^-) = 5478$), confirmed the isosbestic points for H_6A/H_5A^- at 262 and 283 nm, and located the first pK_a for calix[6]arene at well below 18.82. Titration with the more compact base pyrrolidine (**9**) (pK_a = 19.56) gave a result broadly similar to that for triethylamine (**12**), except that a slight linear rise in absorbance was observed after the addition of 1 equiv; furthermore, there was a slight shift in the isosbestic point (ca. 2 nm). This may be indicative of some interaction between the calix[6]arene monoanion and pyrrolidine and/or its conjugate acid.

As with calix[8]arene, precise determination of the first pK_a of calix[6]arene is complicated by the high level of preexisting mono-deprotonated calixarene in the MeCN solution. Titration at >300 nm with bases **15** and **16** each showed a small curved increase in absorbance due to further mono-deprotonation of calix[6]arene, indicating that its first pK_a is in this region. However, for these titrations, although determination of [A$^-$] was facile at wavelengths >300 nm, independent measurement of [BH$^+$] (or [B]) was not possible because of a lack of appropriate absorbance for **15** and **16** at the calixarene isosbestic points. A modified equation for K in which [BH$^+$] was estimated was used,[34] and pK_a values for H_6A/H_5A^- are shown in Table 5.

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(34) In this case eq 9 (see Experimental Section) for K is used. If the interfering base is called X, then $[BH^+] = [A^-] - [XH^+]$. At $c_B = 0$, the existing A$^-$ is from the deprotonation of HA by X, so $K_X = [XH^+][A^-]/\{(c_X - [XH^+])[HA]\}$. However, if it is assumed that $c_X \gg [XH^+]$ (i.e., that $[X] \approx c_X$), then $[XH^+] = (K_Xc_X)[HA]/[A^-]$. Since [XH$^+$] is likely to decrease as c_B is added, this approximation will hold throughout the titration. The term K_Xc_X can be calculated from the $c_B = 0$ reading where $[XH^+] = [A^-]$, and so $K_Xc_X = [A^-]^2/[HA]$ or $K_Xc_X = [A^-]^2/(c_{HA} - [A^-])$. Therefore, [XH$^+$] can then be calculated at any titration point using $[XH^+] = (K_Xc_X)[HA]/[A^-]$, and from this, [BH$^+$] can be calculated using $[BH^+] = [A^-] - [XH^+]$. This requires a direct measurement of [A$^-$].

TABLE 5. Determination of pK_a for the First Deprotonation of Calix[6]arene 1b in MeCN at 25 °C

base	pK_a (BH^+)	λ (nm)	K	pK_a (H_8A/H_7A^-)
15	16.91	305	19 ± 4	15.64 ± 0.08
16	16.31	310	5.98 ± 0.75	15.54 ± 0.05
mean				15.59 ± 0.06

TABLE 6. Determination of pK_a for the Second Deprotonation of Calix[6]arene 1b in MeCN at 25 °C

base	pK_a (BH^+)	λ (nm)	K	pK_a (H_8A/H_7A^-)
3	25.49	310/315	71 ± 34	23.6 ± 0.2
4	24.34	315	32 ± 10	24.10 ± 0.13
mean				23.85 ± 0.35

TABLE 7. pK_a Values for Calixarenes in MeCN at 25 °C and Calculated Gas-Phase Acidities

calixarene	experimental pK_a values	ΔE^a (kJ mol^{-1})	G^b (kJ mol^{-1})
1b pK_a(1)	15.59 ± 0.06	1363	1337
1c pK_a(1)	17.20 ± 0.20	1361	1335
1a pK_a(1)	19.06 ± 0.22	1396	1370
1c pK_a(2)	20.32 ± 0.31	1561	1535
1b pK_a(2)	23.85 ± 0.35	1621	1595
1a pK_a(2)	>33	1779	1753
all pK_a(3)	≫33	>1916	>1890
phenol	26.6	1524	1498

[a] Difference in total energy between acid and conjugate base, $E(H_{n-1}A^{(m+1)-}) - E(H_nA^{m-})$; e.g., for the H-calix[6]arene pK_a(2), $\Delta E = E(H_4A^{2-}) - E(H_5A^-)$ in kJ mol^{-1}. [b] Gas-phase acidity here is defined following Chipman (Chipman, D. M. *J. Phys. Chem. A* **2002**, *106*, 7413), such that $G = G_{AB} + G_P$, where $G_{AB} = H_{AB}^{ZPE} + G_{AB}^{0T} + E_{AB}^{elec}$, with the three AB terms being the zero-point nuclear vibrational energy, the thermal correction term, and the internal electronic energy (ΔE in Table 7), respectively, and G_P is the free energy of the proton at −6.3 kcal/mol (−26.3 kJ/mol) (Hirschfelder, J. O.; Curtiss, C. F.; Bird, R. B. *Molecular Theory of Gases and Liquids*; Wiley: New York, 1964). Chipman quotes the combined $H_{AB}^{ZPE} + G_{AB}^{0T}$ as G_{AB}^{nuc}, and it's equal to −7 to −9 kcal/mol for a range of acids (H_2O, MeOH, PhOH (−8.1 kcal/mol, −34 kJ/mol), HCO_2H, $MeCO_2H$, and $PhCO_2H$) calculated by HF/6-31+G* and B3LYP/6-31+G* models; the value for phenol was used here.

Measurement of a second pK_a value for calix[6]arene also proved difficult. Titration with 1 equiv of a strong base such as **3** gave the UV−vis spectrum of the mono-deprotonated calixarene H_5A^-. Further titration with **3** yielded a product with a λ_{max} at 310 nm. This product is assigned as the dianion, H_4A^{2-}, with a H_5A^-/H_4A^{2-} pK_a well above 21.19 (where titration with **7** showed only mono-deprotonation) and just below 25.49 (the pK_a of **3**). Isosbestic points at 271 and 285 nm were slightly shifted from those for mono-deprotonation (262 and 283 nm).

Titration with **3** and the weaker base DBU **4** (pK_a = 24.34) yielded a second pK_a value for calix[6]arene, i.e., for H_5A^-/H_4A^{2-} (Table 6).

Titration with Verkade's superbase **2** appeared to give a curved increase in absorbance in the H_5A^-/H_4A^{2-} region above 300 nm before leveling off after 1.5−2.0 equiv, and then a further sharper increase after this. However, the final spectrum, even after 4.5 equiv, was the same as that corresponding to the dianion obtained using **3** and **4**. It is not clear to us why this base (alone) shows this behavior, although given its pK_a (33.53) there may be some complication caused by deprotonation of the solvent.

Computational Studies. The calixarenes and their anions were modeled using the B3LYP DFT method, which is preferred to HF because of the significant difference in electron distribution between the acid and anionic forms. Given the sizes of the molecules, the tetra-*t*-Bu-depleted H-calixarenes were used, as well as the economical 6-31G* basis set. All calculated structures are shown in the Supporting Information.

The B3LYP/6-31G* geometry-optimized structure for H-calix[4]arene in the preferred cone conformation[35,36] gives geometric parameters that compare favorably to those found using an earlier model[35] and to experimental data.[37] For the monoanion, semiempirical calculations by Grootenhuis et al.[38] indicated little difference in energies in water for the various conformers, cone, partial cone, 1,2-alternate, or 1,3-alternate. However, it seems sensible to assume a cone conformation, which maximizes internal hydrogen bonding in a solvent such as MeCN, whose ability to solvate anions is poor. The B3LYP/6-31G* energy difference between H_3A^- and H_4A is given as ΔE in Table 7. The B3LYP/6-31G*-optimized cone-derived dianion gave a much larger ΔE for H_3A^-/H_2A^{2-}, with that for a 1,2-alternate dianion larger still.

For H-calix[6]arene, experimental evidence indicates that three conformers are most common: the "pinched" cone, the "winged" cone, and the 1,2,3-alternate.[1f,3] Modeling at both MM[39] and B3LYP/6-31G* levels for H-calix[6]arene gave the pinched cone as the lowest-energy structure, and results were similar for the monoanion. Only one H-calix[6]arene dianion was chosen, which derived from the winged−winged cone conformer, in which the greatest cross-cone O−O separation is possible. A calix[6]arene trianion was also based on the winged−winged conformation, and was found to be at high energy.

Extensive conformational searching was not feasible for H-calix[8]arene and its monoanion, so calculations were made solely on the basis of the pleated loop conformation.[40] There is some experimental evidence that a dianion might prefer the 1,2,3,4-alternate cone conformation,[41] and this is supported by MM calculations; so this dianion was optimized at B3LYP/6-31G*. As for the calix[6]arene, a trianion (based on a twisted loop) is much higher in energy.

Discussion

The measured pK_a values for the three calixarenes are gathered in Table 7. The increased aqueous acidity, by

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ca. 6 pK_a units, of calixarenes relative to phenol (pK_a^{water} = 10.0)[42] has been noted before,[14] but in MeCN (phenol pK_a^{MeCN} = 26.6)[25,43] this difference is magnified to 8−11 units. Clearly, in the anion-unfriendly MeCN, the importance of internal hydrogen bonding is significant. Acidity is also increased in acetonitrile relative to benzonitrile solvent by 0.2−3 units.[15] The computational studies suggest a difference relative to phenol of 22−28 units in the gas phase. A semiqualitative assessment of acidity in other solvents, perhaps suitable as a guide for synthetic transformations, can be made by considering these differences and the range across **1a**−**1c**, e.g., for mono-deprotonation in water, 0.5 unit (3.62−4.11);[14] MeCN, 3.5 units (15.59−19.06) (this work); benzonitrile, 2.3 units;[15] gas phase, 6 units (this work).

The order of acidity **1b** p$K_a(1)$ < **1c** p$K_a(1)$ < **1a** p$K_a(1)$, etc., can be rationalized by consideration of charge separation and hydrogen bonding. Insight is provided by the quantum mechanical calculations whose DFT-calculated gas-phase acidities (Table 7) show a trend in broad agreement (making due allowance for the complexity of the system) with the experimental pK_a^{MeCN} data.

For calix[4]arene, the tetra-*t*-Bu-depleted H-calix[4]arene serves as a model, and the B3LYP/6-31G* structure shows a cyclic pattern of hydrogen bonding. The B3LYP/6-31G* structure for the monoanion shows an increase in the hydrogen bonding to the anionic $-O^-$ (ring A) from the two adjacent −OH groups (rings B and D) as reflected in the shortening of the O−O distance (see Supporting Information for structures and tables of distances), but a decrease in the secondary hydrogen bonding from the furthest −OH (ring C). This is because as rings B and D tilt their −OH groups toward the $-O^-$, ring C is forced to tilt outward, moving the −OH further from the $-O^-$. This is different than the bifurcated hydrogen bonding for ring C proposed by Grootenhuis et al., on the basis of semiempirical MO calculations.[38] It shows that full hydrogen bonding involvement for all −OH groups in H_3A^- is not possible, and explains the relatively high pK_a of calix[4]arene.

The B3LYP/6-31G*-optimized pinched cone structure of H-calix[6]arene also shows all six −OH groups involved in a cycle of hydrogen bonding. Surprisingly, the changes on mono-deprotonation are very similar in nature and magnitude to those calculated for the H-calix[4]arene. There is a shortening of the distances from the $-O^-$ (ring A) to the adjacent −OH groups (rings B and F), and a tilting of the −OH of the ring opposite the anion (ring D) away from the $-O^-$, although it is still just about within the distance (2.78 Å) for hydrogen bonding to its neighbor (ring E). So, all five −OH groups are involved in a “relay” of hydrogen-bonding stabilization of the anion, and it appears that the increased acidity of calix[6]arene relative to calix[4]arene is simply due to the increased number of hydrogen bonding interactions in the relayed stabilization of the anion.

However, a simple correlation of acidity with the number of hydrogen-bonding relays in the anion cannot be carried too far. Experimentally, the calix[8]arene, despite the potential for more hydrogen bonds than in calix[6]arene, shows a significantly higher p$K_a(1)$. Although the B3LYP/6-31G* calculations do not quite replicate this, the calculated ΔE for calix[8]arene is not significantly lower than that for calix[6]arene, despite the calculated structure showing an increased number of hydrogen bonds. Clearly, the strength of the hydrogen bond is important.

TABLE 8. UV−Vis Spectrophotometric Data for Calixarenes in MeCN at 25 °C

calixarene	$\lambda_{max}^{calixarene}$ (ϵ)	$\lambda_{max}^{monoanion}$ (ϵ)	$\lambda_{max}^{dianion}$ (ϵ)
1a	279, 287 (10000, 8300)	315 (3800)	
1b	280, 286 (12300, 12900)	305 (sh) (5700)	310 (10000)
1c	283, 289 (22600, 28000)	310 (sh) (9200)	310 (sh) (17300)

The experimental ΔpK_a is 1.6, corresponding to a $\Delta(\Delta E)$ of <9 kJ mol^{-1}, a value well within the range attributable to hydrogen bonding. Several factors determine the strength of a hydrogen bond, but particularly the O−O distance. Comparison of the individual O−O distances shows that they are in all cases shorter for calix[6]arene than for calix[8]arene. Furthermore, for calix[6]arene, some distances fall into the range in which the greatest variability in strength is likely. Hibbert and Emsley have proposed a correlation of hydrogen bond strength with O−O distance.[44] The correlation can be divided into three categories: weak bonding of the order of 25 kJ mol^{-1} that changes little over the O−O distance of 2.80−2.55 Å, strong bonding of ca. 100 kJ mol^{-1} that changes little over the range of 2.40−2.20 Å, and intermediate bonding that changes dramatically from 25 to 100 kJ mol^{-1} between 2.55 and 2.40 Å. The critical $O{-}H\cdots O^-\cdots H{-}O$ distances for calix[6]arene (2.49, 2.52 Å) are just within the intermediate category, so that the small but important shortening relative to calix[8]arene (2.54, 2.55 Å) could easily compensate for the more numerous (but weaker) hydrogen bonds in the latter.

The variation in p$K_a(1)$ is reflected semiquantitatively in the UV−vis spectrophotometric data (Table 8) with the trend in $\Delta\lambda_{max}$: **1b** (25, 19 nm) < **1c** (27, 21 nm) < **1a** (36, 28 nm). This may reflect increased delocalization of the negative charge into the aromatic ring (to give the keto resonance contribution) in the less extensively hydrogen-bonded calix[4]arene compared with the calix[8]arene and the calix[6]arene.

As expected all the second pK_a values (p$K_a(2)$: dideprotonation) are higher than all the first, and they span a much wider range. No p$K_a(2)$ is observed for calix[4]arene **1a** below ca. 33, so clearly the generation of two negative charges within the restricted confines of the so-called lower rim (hydroxy rim) is not possible. This is supported by the B3LYP/6-31G* model, which calculates the H-calix[4]arene second deprotonation to be much higher in energy than that in H-calix[6]arene and H-calix[8]arene. Experimentally, the p$K_a(2)$ for calix[6]arene **1b** is observable in MeCN (at 23.85), but is significantly higher than the first, by more than 8 units. Computationally, the winged−winged cone dianion has each $-O^-$

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group (rings A and D) hydrogen-bond-stabilized by only its two adjacent neighbors, effectively giving two separate three-oxygen systems, and the $-O^{-}\cdots{}^{-}O-$ (rings A and D) distance is 8.45 Å.

In contrast to calix[6]arene, the pK_a(2) for calix[8]arene **1c** at 20.29 is higher than the first by only 3 units. Consideration of the H-calix[8]arene 1,2,3,4-alternate conformation (see Supporting Information) shows that this dianion consists of two separate four-oxygen systems, although the fourth −OH in each "half-system" (rings C and G) is quite far from its neighbor (2.82 Å), and may not contribute much to the hydrogen bonding. So it is probably the greater separation of the $-O^-$ groups (11.01 Å) in the calix[8]arene dianion compared to its calix[6]arene analogue that accounts for the much smaller difference between the pK_a(1) and pK_a(2) values in the former.

No higher deprotonations (e.g., pK_a(3)) are observed in MeCN, even with the relatively strong Verkade's base **2**. Since the pK_a of **2** is close to the accepted autoprotolysis constant of MeCN (p$K_{\text{autoprotolysis}} > 33$), it appears that a di-deprotonated state (mono-deprotonated for calix[4]arene) is the maximum possible in this solvent.

In conclusion, the recently established consistent scale of amine basicity in MeCN has been put to use to determine all accessible pK_a values for calix[4]arene, calix[6]arene, and calix[8]arene in MeCN. For mono-deprotonation, the dominant factor in calixarene acidity is the anion's ability to form internal hydrogen bonds that are not only numerous but also strong. For di-deprotonation, the ability to spatially separate the anions becomes important.

Experimental Section

Chemicals. The calixarenes were obtained commerically as puriss grade, and were checked for purity by microanalysis, ^{1}H NMR, and mp before use.

The following bases were obtained commercially and used as received: 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane **2**, 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine **3**, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **4**, pyrrolidine **9**, 1-(*o*-tolyl)-biguanide **10**, triethylamine **12**, 4-aminopyridine **14**, benzylamine **15**, and 2-amino-1-methylbenzimidazole **16**.

The following bases were prepared by literature procedures using commercially available reagents and starting materials: (2,6-dichlorophenylimino)tripyrrolidinophosphorane **13**,[21] (4-bromophenylimino)tripyrrolidinophosphorane **7**,[21] (2-chlorophenylimino)tris(dimethylamino)-phosphorane **11**,[18,45] 2-phenyl-1,1,3,3-tetramethylguanide **8**,[22] (phenylimino)tripyrrolidinophosphorane **6**,[21] and (4-methoxyphenylimino)tripyrrolidinophosphorane **5**.[21] The laboratory-prepared bases gave satisfactory combustion analyses and (for solids) sharp melting points close to the literature values. Salts (either HCl, HPF_6, or $HBPh_4$) of the synthesized phosphorane bases were prepared to check the stability of the protonated forms, and gave sharp melting points and satisfactory combustion analyses. The exceptions were **6**, a low melting solid, its **6**·$HBPh_4$ salt, and **8**·$HBPh_4$, for which satisfactory combustion analysis could not be obtained. However, the salts did give sharp melting points, and base **6** was not used for any precise pK_a calculation.

Commercial MeCN with a supplier-stated water content of <0.0065% was used. When MeCN was dried by reflux over CaH_2 and distilled, no difference in the result was apparent.

Trifluoromethanesulfonic acid was used as received.

Typical Procedure for UV−Vis Spectroscopic Titrations. 4-*tert*-Butylcalix[4]arene (0.0073 g) was dissolved in MeCN (250 cm^3) at 20 °C, giving a 45 μM solution. *o*-Tolylbiguanide (0.0148 g) was dissolved in MeCN (50 cm^3), giving a 1.55 mM solution. 4-*tert*-Butylcalix[4]arene solution (3.0 cm^3) was added by pipet to a cuvette (10 mm), and a UV spectrum was taken at 25 °C on a UV−vis spectrometer. Successive aliquots (10 mm^3) of the *o*-tolylbiguanide solution were added to the stoppered cuvette using a microsyringe, and a UV spectrum was taken after each addition. Additions were repeated 19 times, until a total of 200 mm^3 had been added (2.3 equiv), and a titration curve was plotted of Abs/c_{HA} vs c_B/c_{HA}. All standard solutions were prepared at 20 °C, and the titrations were carried out at 25 °C.

Calculation of pK_a Values from UV−Vis Spectroscopic Measurements. For an acid−base equilibrium involving HA, A^-, B, and BH^+, the equilibrium concentration of any species in dilute solution can be calculated from the observed absorbance (Abs), the various extinction coefficients (ϵ_{HA}, etc.), and the known stoichiometry (eqs 2−6).

$$\text{Abs} = \epsilon_{HA}[HA] + \epsilon_{A^-}[A^-] + \epsilon_B[B] + \epsilon_{BH^+}[BH^+] \quad (2)$$

$$[A^-] = [BH^+] \quad (3)$$

$$[HA] = c_{HA} - [A^-] = c_{HA} - [BH^+] \quad (4)$$

$$[B] = c_B - [BH^+] \quad (5)$$

$$[BH^+] = \frac{\text{Abs} - \epsilon_{HA}c_{HA} - \epsilon_B c_B}{\epsilon_{A^-} + \epsilon_{BH^+} - \epsilon_{HA} - \epsilon_B} \quad (6)$$

The extinction coefficients for HA (non-deprotonated calixarenes), B, and BH^+ are known, and the important value for the anion A^- can be determined under conditions of complete deprotonation (of the relevant group only). In many experiments, the determination of concentration, e.g. $[BH^+]_{eq}$, was facilitated by the use of suitable wavelengths; for example, in some cases, B, BH^+, and HA were not found to absorb above 300 nm, whereas A^- absorbed strongly. In other cases, determination was at a HA/A^- isosbestic point where changes in absorbance were caused only by B/BH^+. For the equilibrium between acid HA and base B, the equilibrium constant K is given by eq 7.

$$K = \frac{[BH^+]^2}{(c_{HA} - [BH^+])(c_B - [BH^+])} \quad (7)$$

From this, the pK_a of HA can be found (eq 8) from the known value for BH^+.

$$\text{p}K_a(\text{HA}) = \text{p}K_a(\text{BH}^+) - \log_{10} K \quad (8)$$

In some case (see Results), the condition $[A^-] = [BH^+]$ did not hold, and the more general form of the equation (eq 9) requiring independent measurement of $[A^-]$ and $[BH^+]$ was used.

$$K = \frac{[BH^+][A^-]}{(c_{HA} - [A^-])(c_B - [BH^+])} \quad (9)$$

The equilibrium constant K was calculated at different levels of c_B (typically 10 spaced over 1 equiv), and the values were averaged. To check that K was being determined under conditions where reasonable amounts of all components (HA, A^-, B, BH^+) were present, the experimental Abs/c_{HA} vs c_B/c_{HA} plot was compared with one constructed on the basis of "no deprotonation" (i.e., $[HA] = c_{HA}$, $[B] = c_B$, $[A^-] = 0$, $[BH^+] = 0$), and with another corresponding to "complete deprotonation" (i.e., $[HA] = c_A - c_B$, $[A^-] = [BH^+] = c_B$, $[B] = 0$); when feasible, only points showing significant deviation from these two extremes were used. Finally, a calculated Abs, derived from values of the component concentrations calculated from the newly determined K, was plotted (as $\mathrm{Abs_{calc}}/c_{HA}$) against c_B/c_{HA} and visually inspected for closeness of fit to the experimental plot.

Uncertainties in weight and volume measurements are negligible compared with the standard deviations in K and pK_a (given in the tables) across the range of c_B used. The final pK_a value in each table is the simple average of those from each base, whereas the quoted uncertainty in the final pK_a value is either the standard deviation of this average or the simple average of the individual deviations, whichever is larger.

Computational Calculations. All calculations were carried out using the Spartan '04 program.[46] Typically, the target structure was constructed using the build menu, and minimized by molecular mechanics (MM) using the MMFF force field. In some cases (e.g., for the conformationally labile calix[6]arenes), molecular mechanics (MMFF) was used to obtain the equilibrium conformer. For DFT calculations, the structure obtained following MM geometry optimization (including the equilibrium conformer) was modified to replace the *tert*-butyl groups with hydrogen atoms (e.g., H-calix[6]arene), and then geometry-optimized using the B3LYP/6-31G* model. The quoted energies are those obtained using the same model.

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Supporting Information Available: Details of chemicals, purification and syntheses of bases. Graphical structures and tables of bond lengths, angles, total energies, and Cartesian coordinates from computational studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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