

# Counter-ion and solvent effects on the acidity of calix[4]arene and *para-tert*-butylcalix[6]arene

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**Abstract** Spectrophotometric titrations of calix[4]arene and *p-tert*-butylcalix[6]arene with LiOH, NaOH, KOH, tetramethylammonium and tetrabutylammonium hydroxides as bases were carried in ethanol 95 % and acetonitrile. The dependence of  $pK_a$  of the first deprotonation of calix[4]arene with the nature of the cation was only modest in ethanol 95 %, spanning from 8.53  $pK_a$  unit for NaOH until 9.00 for LiOH, whereas in acetonitrile the proton transfer is quantitative. The first deprotonation of *p-t*-butylcalix[6]arene in both solvents is quantitative and the extension of the second deprotonation is very dependent of the nature of the cation in ethanol and acetonitrile. Tetramethylammonium hydroxide was the strongest base for both solvents, and both deprotonations proceed quantitatively and concomitantly in ethanol, followed by potassium hydroxide, and the weakest base was tetrabutylammonium hydroxide. This behavior indicates that the ability to form  $N^+-C-H-\pi$  and  $K^+-\pi$  interactions plays an important role to stabilize the mono and dianion calixarene. Lithium and sodium exhibit non-usual acid–base behavior in acetonitrile, attributed to aggregation of the species.

**Keywords** Calixarenes · Solvent effects ·  $pK_a$  · Supramolecular chemistry

## Introduction

A Brønsted acid–base reaction is concerned as a proton transfer from a protic acid to a base in water and other protic solvents, and usually the nature of the counter-ion is not considered because the counter-ion interacts with the solvent molecules and does not affect directly the reaction. However, associative processes with macrocyclic molecules like calixarenes (Fig. 1) display a major role to stabilize both conjugated base and acid species, which affects the overall Gibbs energy mediated by the size of the cavity and the ions, the ability to form hydrogen bonds and metal- $\pi$  interactions.

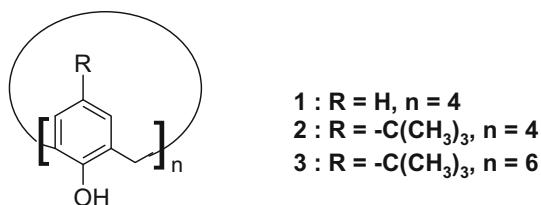
The acidity of water-soluble calixarenes like nitrocalixarenes, sulfonamide calix[4]arenes and *p*-sulfonatocalixarenes have been measured and the values are consistently lower than the corresponding phenols [1–3] and this behavior has been attributed to the stabilization of the conjugated base by intramolecular hydrogen bonding, although Böhmer [4] reported that mono-nitrocalixarenes shown a somewhat more acidic  $pK_a$  than the acyclic analogues. However, these early works did not mention the role of the counter-ion in the measure of  $pK_a$ .

It is well known that the nature of counter-ion influences the substitution and conformation of calixarene ethers [5], e.g. the derivatives of calixarenes with alkyloxy-carboxymethoxy, known to form complexes with alkaline and alkaline-earth metal cations and ammonium cations [6]. The association with alkaline metal cations with calix[4]arenes ethers has mainly electrostatic character, although the selectivity is related with the covalent term of

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**Fig. 1** General structure of calixarenes

the Klopmann–Salem equation [7], whereas the number of possible conformations of calix[6]arenes did not make possible correlations with electronic parameters.

Conversely, interactions of non-functionalized calixarenes are poorly reported, mainly by the low solubility of the compounds. In our report, we describe the role of the interaction of the association of the counter-ion on the acid behavior of calix[4]arene **1** and *p*-*tert*-butylcalix[6]arene **3** in ethanol and acetonitrile.

## Experimental

*Para*-*tert*-butylcalix[4]arene **2** was purchased from Aldrich Co., the reaction of de-*tert*-butylation [8] and the synthesis of *para*-*tert*-butylcalix[6]arene [9] were performed as described in the literature. The solutions of the cation hydroxides were freshly prepared using spectroscopic grade 95 % ethanol and spectroscopic grade acetonitrile without further purification and spectrophotometric titrations were carried, following 288 and 310 nm wavelengths.

The range of concentration of the solutions of **1** and **3** for titrations were from  $7 \cdot 10^{-5}$  to  $1.2 \cdot 10^{-4}$  mol L<sup>-1</sup> and the concentration of the added solution of base were  $1 \cdot 10^{-2}$  to  $1.5 \cdot 10^{-2}$  mol L<sup>-1</sup>; the aliquots were added using microsyringes and the absorbance was measured after the chemical equilibrium was reached. The experiments were carried at 298 K.

## Results

The reactions of proton transfer between calixarene and hydroxides were carried in ethanol and acetonitrile using LiOH, NaOH, KOH, tetramethylammonium hydroxide (TMAOH) and tetrabutylammonium hydroxide (TBAOH) as bases.

## Calix[4]arene in ethanol

The addition of hydroxide changes the spectra of calix[4]arene solution by the increase of the absorptions at 288 and the shoulder at 310 nm corresponding to the  $n\text{-}\pi^*$  transition and shows an isosbestic point at approx. 277 nm, as seen in Fig. 2. The variation of the absorbance at 310 nm corresponds to the raise of phenolate [10], was used to measure the concentration of the phenolate anion, with values of molar absorptivities around  $2,500\text{--}3,500$  L mol<sup>-1</sup> cm<sup>-1</sup>.

The profile for all reactions is the same with calix[4]arene (Fig. 3), with quantitative proton transfer, reaching a plateau from the 1:1 calix:base ratio as a hyperbolic shape. The second deprotonation was not observed for these hydroxides.

The model used to fit the curves was based on the chemical equilibrium showed in Fig. 4:

The low concentrations associated with the spectroscopic method allow for the use of simple concentrations rather than activities to define the constant  $K_{OH}$  in Eq. 1, for the reaction with hydroxide reaction:

$$K_{OH} = \frac{[calixO^-][H_2O]}{[calixOH][OH^-]} \quad (1)$$

We assumed that the concentration of water formed by the reaction is insignificant when compared with the water of ethanol 95 %. We can define a new constant  $K_1$  that includes the concentration of water, related with the  $K_{OH}$  as seen in Eq. 2:

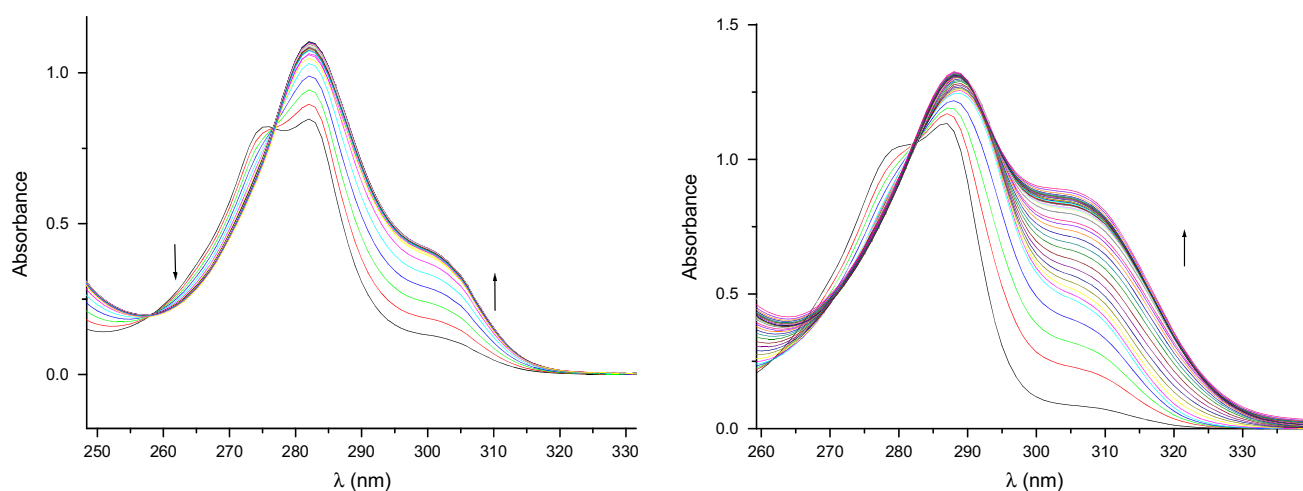
$$K_1 = \frac{K_{OH}}{[H_2O]} \quad K_1 = \frac{[calixO^-]}{[calixOH][OH^-]} \quad (2)$$

The rising in the absorbance at 310 nm comes from the formation of the phenolate of calix[4]arene, expressed by Eq. 3:

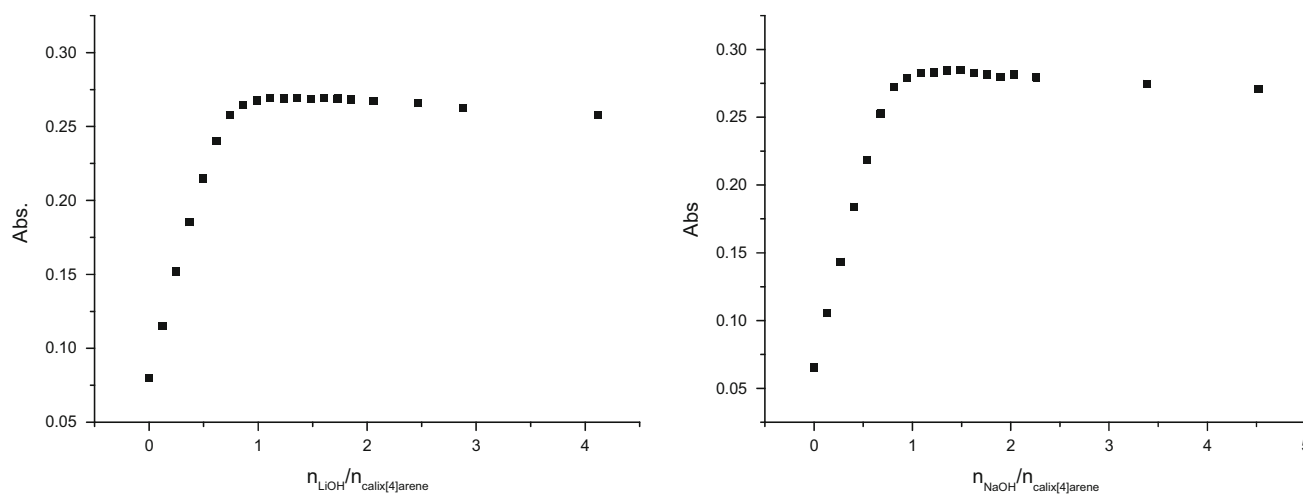
$$\frac{\Delta A_{310}}{\epsilon_{310}} = [calixO^-] \quad (3)$$

and  $\Delta A_{310}$  can be written as function of total added hydroxide  $[OH^-]_T$ , as shown in Eq. 4:

$$\Delta A_{310} = \frac{([calix]_0 + [HO^-]_T + 1/K_1) - \sqrt{([calix]_0 + [HO^-]_T + 1/K_1)^2 - 4[calix]_0[HO^-]_T}}{2} \epsilon_{310} \quad (4)$$

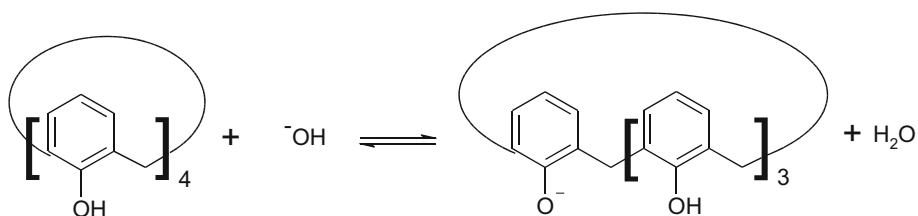


**Fig. 2** Ultraviolet spectra for the spectrophotometric titration of calix[4]arene with TBAOH in ethanol (*left*) and *p-t*-butylcalix[6]arene with KOH in ethanol (*right*)



**Fig. 3** Plots of absorbance at 310 nm of **1** with molar ratio  $n_{M+OH}/n_{calix[4]arene}$  for  $Li^+$  and  $Na^+$  in ethanol

**Fig. 4** Proton transfer reaction of **1** with hydroxide



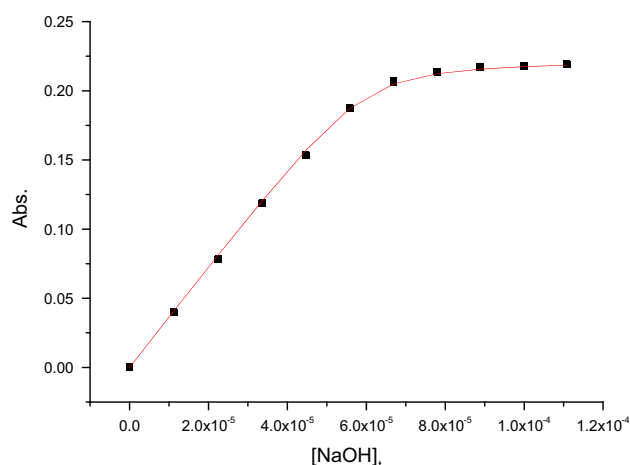
The values of  $\Delta A_{310}$  were plotted with  $[HO^-]_T$  and the curves obtained with the Eq. 4 fitted well the experimental data, as seen for the example with NaOH in Fig. 5. The values for  $K_1$  and  $\epsilon$  were allowed to vary in the iterations to achieve the best fit for the curves.

The  $pK_a$  of the acid was obtained by the Eq. 5, taking account that the hydroxide added is in equilibrium with ethanol and forms water and ethoxide, and the strength of the base is related with the properties of the solvent. This effect can be considered using the auto-ionization constant

for the mixture water/ethanol  $K_{w/EtOH}$ . The relation between  $pK_a$  and  $pK_{w/EtOH}$  is:

$$pK_a = pK_{w/EtOH} - \log K_1 \quad (5)$$

The value used for  $pK_{w/EtOH}$  in ethanol 95 % v/v was 17.4, using the values obtained by Fonrodona [11], whereas the values of  $pK_a$  obtained for ethanol 95 % were transposed to water using the linear relationship for substituted phenols obtained by Altun (Eq. 6) [12]:



**Fig. 5** Plot of absorbance at 310 nm of **1** with  $[\text{OH}^-]_T$ . The continuous line is the fit obtained with the Eq. (1)

$$pK_{a(w/EtOH)} = [0.565X + 1.046]pK_{a(water)} - 1.554X - 0.317 \quad (6)$$

$$\Delta A_{310} = \frac{([\text{calix}]_0 + [\text{HO}^-]_T) - \sqrt{([\text{calix}]_0 + [\text{HO}^-]_T)^2 - 4[\text{calix}]_0[\text{HO}^-]_T(1 + 1/K_e)}}{2(1 + 1/K_e)} \epsilon_{310} \quad (8)$$

where X represents the mole fraction of ethanol and is 0.854 for 95 % ethanol v/v. The values for the constants are summarized in Table 1.

There is a slight dependence between the acidity behavior of the calix[4]arene with the cation in ethanol, as seen by differences in the constants of proton transfer and molar absorptivities, and the sodium ion showed the low values for both. This is coherent with the data from the extraction of metal picrates from  $\text{H}_2\text{O}$  to  $\text{CHCl}_3$ , which showed selectivity toward sodium for esters derived of alkyloxy-carboxy-calix[4]arenes, because fits well the cavity formed by the  $\text{OCH}_2\text{C}=\text{O}$  groups [13]. The decrease of  $pK_a$  reflects this additional stabilization of the conjugated base of calix[4]arene promoted by interaction with

the sodium cation, although the value of  $\Delta\Delta G_{\text{Li}^+-\text{Na}^+}$  related to the difference of  $pK_a$  corresponds to  $-2.7 \text{ kJ mol}^{-1}$ .

### Calix[4]arene in acetonitrile

The model proposed for ethanol was tried for the data obtained from acetonitrile, but the quality of the fits were very poor, and in this case the concentration of water should be taken in consideration in the chemical equilibrium of calix and base. The equilibrium constant is defined by Eq. 7 below:

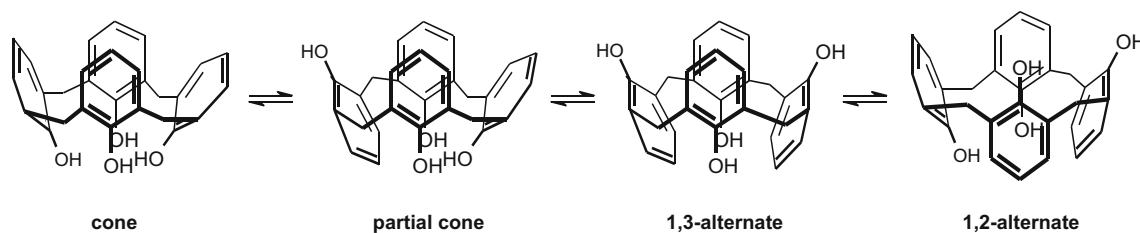
$$K_e = \frac{[\text{calixO}^-][\text{H}_2\text{O}]}{[\text{calixOH}][\text{OH}^-]} \quad (7)$$

and the increase in absorbance due to the phenolate ( $\Delta A_{310}$ ) is expressed by Eq. 8:

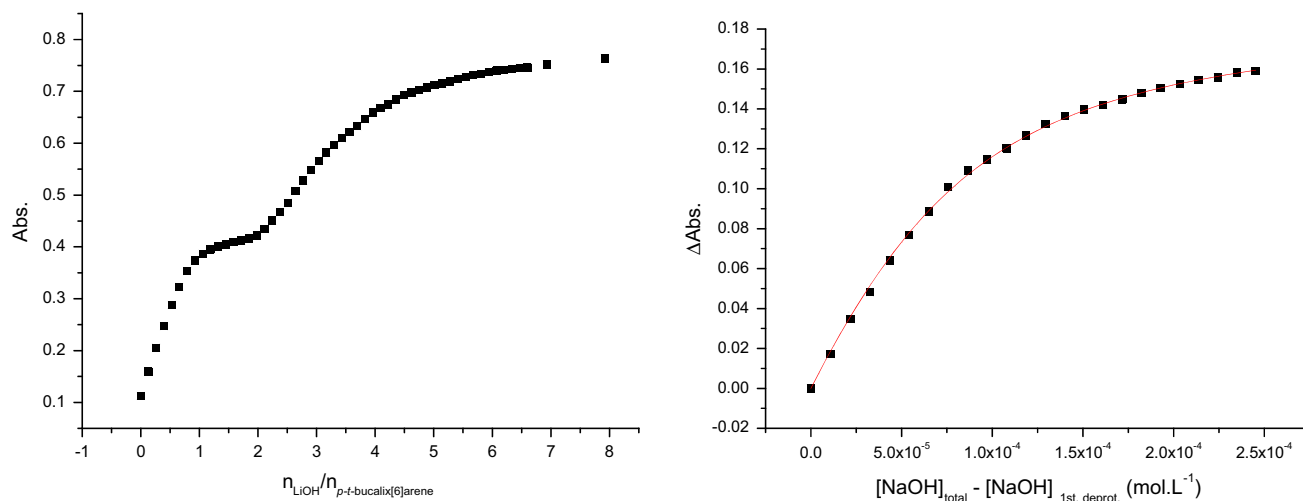
The model fits well the experimental curve and the proton transfer is quantitative for all cations, but the high value of constants  $K_e$ , above  $10^8$ , does not allow the to determine and compare the values of  $pK_a$  for different counter-ions for the proton transfer of calix[4]arene in acetonitrile, but its higher acid behavior in MeCN is noteworthy and run against the common sense in chemistry, for example, the  $pK_a$  of benzoic acid is 10.1 in ethanol and 20.7 in acetonitrile [14]. The anomalous behavior of the acid–base property of calixarenes is attributed to the stabilization of the conjugated base by the intramolecular hydrogen-bonding in acetonitrile without competition with intermolecular hydrogen-bonding in ethanol, related with the conformational equilibrium in both solvents.

**Table 1** Values of  $K_{app}$ ,  $\epsilon$ ,  $\log K_f$ ,  $pK_a$ (ethanol) and  $pK_a$ (water) for calix[4]arene using different hydroxides

Cation	$K_f$	$\epsilon$ , ( $\text{L mol}^{-1} \text{ cm}^{-1}$ )	$\log K_f$	$pK_a$ (ethanol 95 %)	$pK_a$ water
$\text{Li}^+$	$1.88 \cdot 10^5 \pm (4.58 \cdot 10^4)$	2,863 (58)	5.27	12.13	9.00
$\text{Na}^+$	$9.89 \cdot 10^5 \pm (2.22 \cdot 10^5)$	3,714 (33)	6.00	11.40	8.53
$\text{K}^+$	$2.42 \cdot 10^5 \pm (5.25 \cdot 10^4)$	3,448 (59)	5.38	12.02	8.94
$\text{TMA}^+$	$5.07 \cdot 10^5 \pm (6.47 \cdot 10^4)$	3,247 (13)	5.71	11.69	8.73
$\text{TBA}^+$	$4.93 \cdot 10^5 \pm (6.24 \cdot 10^4)$	3,012 (20)	5.69	11.71	8.74



**Fig. 6** Conformation equilibrium of calix[4]arene



**Fig. 7** Plots of absorbance at 310 nm of **3** with the molar ratio  $n_{\text{LiOH}}/n_{p\text{-}t\text{-butylcalix[6]arene}$  (left) and difference of  $[\text{NaOH}]_{\text{total}}$  and  $[\text{NaOH}]_{\text{1st. deprot.}}$  consumed in the first deprotonation in ethanol

Early values of  $pK_a$  of calix[4]arene were obtained by Nachtigall using an indirect approach from titrations with amines as 16.6 in acetonitrile [15], that agrees with the high acidity of these compounds, when compared with the analogous phenols [16]. Machado showed that the values of  $pK_a$  of phenols in acetonitrile and water displayed a linear relationship [17] ( $pK_a(\text{CH}_3\text{CN}) = 1.68 pK_a(\text{water}) + 9.80$ ), and when this approach is applied to calix[4]arene results in a  $pK_a$  of 4.05 when applied to the value obtained by Nachtigall.

Acetonitrile and ethanol have distinct interactive properties: ethanol is a better Lewis base acceptor than donor and interacts with anions better than cations, as seen by the AN (solvent acceptor number) and DN (solvent donor number) values (37.1 and 19.2), while acetonitrile has an almost even behavior for cations and anions (AN = 18.9; DN = 14.1), but we attribute this difference of acid behavior mainly to the ability of the solvent to compete with the intramolecular hydrogen bonding of calixarenes.

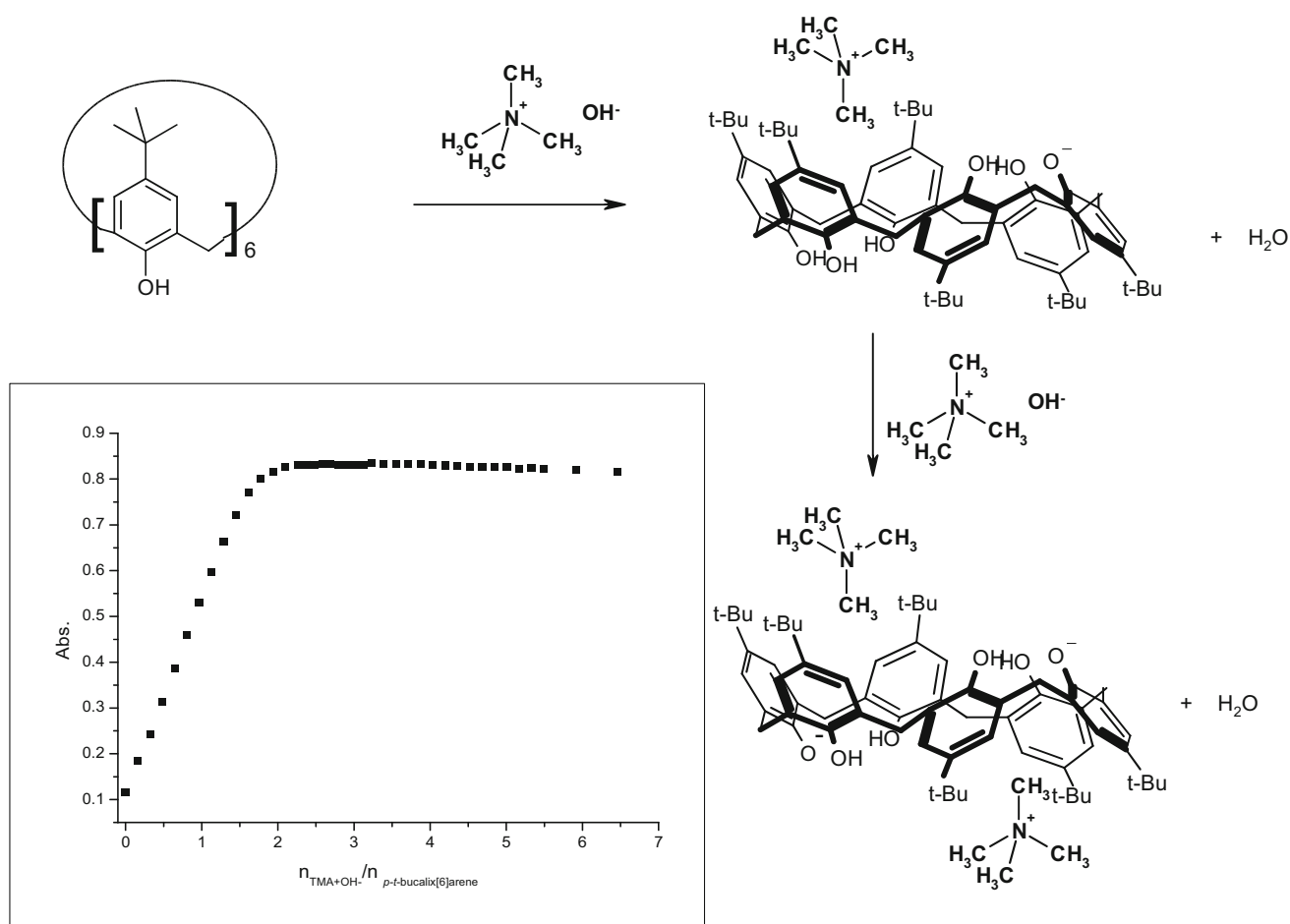
The conformational equilibrium of calix[4]arene in different solvents was reported by Gutsche [18], that pointed that solvents with acceptor hydrogen bond disrupts the intramolecular hydrogen bonds of calix[4]arene, increasing the participation of conformations other than cone, like 1,3-

alternate (Fig. 6). This brings the calixarene more likely than a phenol, and the stabilization by intramolecular hydrogen bonding is weaker than for cone conformation.

#### *Para-tert-butylcalix[6]arene in ethanol*

The spectrophotometric study of the equilibrium of proton transfer of *p-t-butylcalix[6]arene* to cation hydroxides (LiOH, NaOH, KOH, TMAOH and TBAOH) was also performed by the raise of the  $n\text{-}\pi$  absorption at 310 nm from the phenolate. Instead of calix[4]arenes, which showed a similar behavior for the hydroxides, **3** displayed a clear distinct behavior as the hydroxide used. The titration with cation hydroxides in 95 % ethanol displayed some identical characteristics: there are two proton transfer equilibria, but the magnitude of the second transfer depends of the cation.

The spectrophotometric titration of **3** with LiOH, NaOH and TBAOH (Fig. 7) are quantitative until 1:1 stoichiometry, when reaches a short plateau, and raised until an absorbance twice than the first increase. The second deprotonation promoted by LiOH only begins when base: calix ratio reaches a value higher than 5:1, as shown in the



**Fig. 8** Equilibrium of the inclusion of tetramethyl ammonium; plot of absorbance at 310 nm with the molar ratio  $n_{\text{TMAOH}}/n_{\text{p-t-bucalix[6]arene}}$  in ethanol in the box

**Table 2** Second deprotonation constants of **3** in ethanol

Cation	$K_I$	$\epsilon$ , ( $\text{L mol}^{-1} \text{cm}^{-1}$ )	$\log K_I$	$\text{p}K_a$ (ethanol 95 %)	$\text{p}K_a$ water
$\text{Li}^+$	$8.41 \cdot 10^4 \pm (4 \cdot 10^3)$	$2,168 \pm (8)$	4.92	12.48	9.24
$\text{Na}^+$	$3.47 \cdot 10^4 \pm (1 \cdot 10^3)$	$2,306 \pm (15)$	4.54	12.86	9.49
$\text{K}^+$	$5.74 \cdot 10^7 \pm (2.2 \cdot 10^6)$	$1,218 \pm (4)$	7.76	9.64	7.38
$\text{TMA}^+$	$>10^8$	$2,168 \pm (8)$	$>8$	$<9.4$	$<7.2$
$\text{TBA}^+$	$1.08 \cdot 10^2 \pm (8)$	$2,509 \pm (8)$	2.03	15.37	11.13

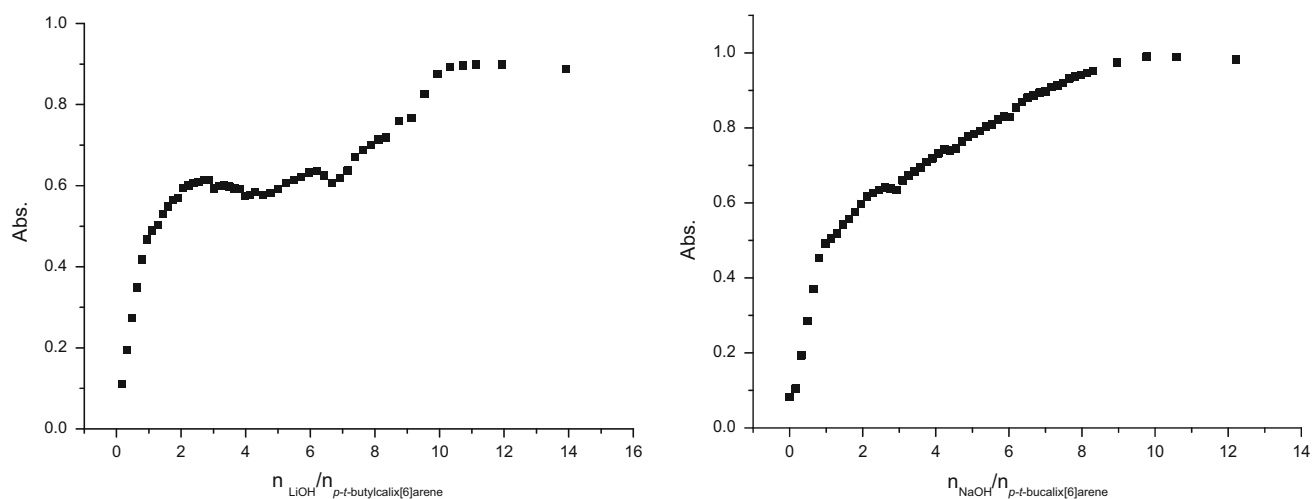
plot of absorbance with  $n_{\text{LiOH}}/n_3$ . The profile for the titration with NaOH and TBAOH are similar to LiOH, and the difference is that the second deprotonation begins at low base:calix ratios.

The titration with KOH does not show the plateau and the raising of the absorbance goes until the 3:1 metal:calix is reached, after which there are not substantial changes of the absorbance. There is a change in slope at 1:1, which is the normal behavior for a Brønsted acid with two distinct  $\text{p}K_a$  values.

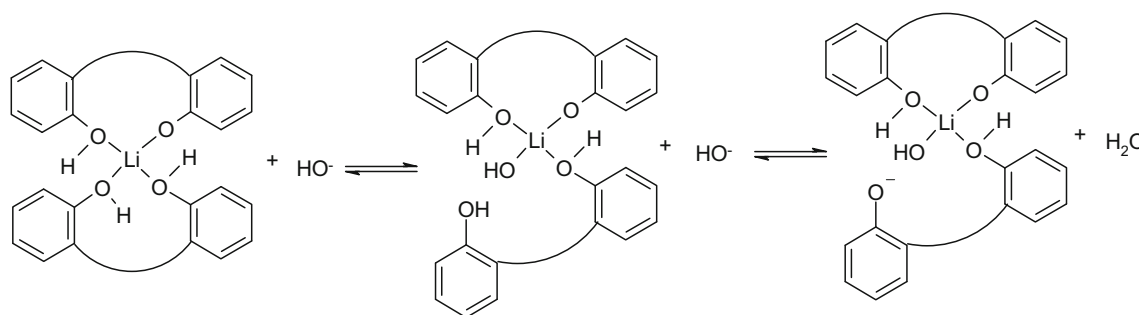
The curve of the titration using TMAOH as shown in Fig. 8 base has a completely distinct profile: the

absorptivity increases as a straight line until to reach the maxim at 2:1 TMAOH: calix ratio and there is not break between the first and second deprotonation and both are quantitative, with a slope of  $5,255 \text{ L mol}^{-1}$ .

The shape of the curve shows that both proton transfers occurs simultaneously, and we propose that the inclusion of the tetramethylammonium cation increases the degree of the second proton transfer in respect to the other cations, so it is not possible to establish even the discrete molar absorptivities related for each proton transfer. The high affinity between tetramethylammonium and calix[6]arene anion is well known by the formation of endo-complexes in



**Fig. 9** Plots of absorbance at 310 nm of **3** with molar ratio  $n_{\text{LiOH}}/n_{p\text{-}t\text{-}bucalix[6]arene}$  (left) and  $n_{\text{NaOH}}/n_{p\text{-}t\text{-}bucalix[6]arene}$  and NaOH (right) in acetonitrile



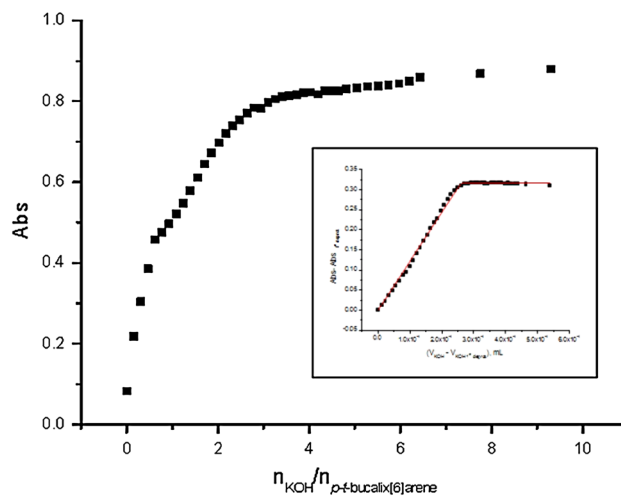
**Fig. 10** Hydroxyl-phenol exchange proposed for lithium salt with **3**

**Table 3** Values of the constants for the second proton transfer from **3** to the base in acetonitrile

Base	$K_1$ (2nd deprotonation)	$\epsilon$ , (L/mol <sup>-1</sup> cm <sup>-1</sup> ) (2nd deprotonation)
$\text{K}^+\text{OH}^-$	$6.42 \cdot 10^4 \pm (5.4 \cdot 10^3)$	$3,352 \pm (38)$
$\text{TMA}^+\text{OH}^-$	$2.00 \cdot 10^6 \pm (9.1 \cdot 10^5)$	$2,250 \pm (9)$
$\text{TBA}^+\text{OH}^-$	$1.15 \cdot 10^4 \pm (1.3 \cdot 10^3)$	$3,778 \pm (105)$

solid state [19], where the cation is deeply immersed in the cavity, as well for choline complex [20]. Competitive experiments of crystallization of dianion of **3** showed selectivity for tetramethylammonium salts in presence of alkaline cations. Interaction with  $\text{N}^+\text{-CH}_3$  has been reported including between neutral calixarenes in the complexation with paraquat [21].

In order to compare the values of  $K_1$  in Table 2, the TBAOH provides the value without specific interaction because the size of the cation tetrabutylammonium avoid inclusion in the cavity of calix, and does not interacts with non-bonding electron pairs. An attempt to quantify the



**Fig. 11** Absorbance profile at 310 nm for titration of **3** with KOH, with the detail of the 2nd proton transfer in box. The continuous line was obtained using the Eq. 2

difference of energy provided by specific interactions taking account of the differences of  $\text{p}K_a$  between the tetrabutylammonium and the other cations, using  $\Delta\Delta G$



(kJ mol<sup>-1</sup>)  $\approx 5.7$  ( $pK_a$  cation— $pK_a$  NBU<sub>4</sub><sup>+</sup>) at 298 K result in  $-10.8$  for Li<sup>+</sup>;  $-9.4$  for Na<sup>+</sup>;  $-21.4$  for K<sup>+</sup>, and  $<-22.4$  kJ mol<sup>-1</sup> for TMA<sup>+</sup>. These results allow to quantify these interactions. However, these differences were unexpected using a competitive solvent like ethanol and the low concentrations of the cations, that evidences the interaction of the calix anion with the cations.

### Para-tert-butylcalix[6]arene in acetonitrile

The profile of the titration with lithium and sodium, shown in Fig. 9, reveals a quantitative increase in the absorbance with the addition of LiOH until to reach the 1:1 [LiOH]:[calix], and thereafter the gain of absorbance slows down, but remains until to reach a plateau. The raise in the absorbance of this second step corresponds to approx. 50 % of the raise of the first deprotonation. The absorbance reaches a plateau-like, but the line is not straight, showing ups and downs in the absorbance, that evidences multiple equilibria instead of a single proton transfer.

To explain the profiles observed, we propose that the monoanion is formed quantitatively, and further addition of base forms the dianion of the calixarene, which interacts with the monoanion and other cations present in the solution. These equilibria lead to variations of molar absorptivities of the intermediate species, resulting in some instabilities of the graph of Abs. versus [LiOH], as seen in the Fig. 10.

The profile for the acid–base reactions using KOH, TMAOH and TBAOH changes and allows to identify two proton transfers and quantify the second constant using the Eq. 2, by the increase of absorbance after the first deprotonation is complete, as well the concentration of the added base. The values for the second constant are in Table 3. The plots (Fig. 11) for the overall and second deprotonation acid–base reactions for KOH are shown below:

Tetramethylammonium hydroxide again showed the highest strength as base, however in acetonitrile it was possible to distinguish both deprotonations by differences in the slopes of the increase of absorbance.

The first dissociation of 3 in acetonitrile could not be determined using hydroxide as base, and was measured by Cunningham as 15.56 [22] using amines as bases. This value, when transposed for water results in a  $pK_a = 3.45$ , so low to be measure using hydroxide. Successful prediction of phenol acidities by theoretical models requires only two water molecules were to stabilize the phenolate [23]. This pattern is mirrored for the diphenolate of 3, when two vicinal phenol units make hydrogen bonds to stabilize the phenolate unit. So, independently of the counter-ion, we could predict the same profile for the titrations using different hydroxides, and their differences are clear evidence

that the counter-ion has a role for these reactions in ethanol and acetonitrile.

The best attempt to understand this behavior came from X-ray data of the salts of 3, which suggest strong interactions between the deprotonated units of the calixarene. The aggregation can be promoted by metals to form stable species with lower acid characteristic. In the case of the tetramethylammonium cation, there is a strong inclusion of the cation in the cavity of the calix. The monoanion formed in the first deprotonation binds the tetramethylammonium by strong N<sup>+</sup>-Me— $\pi$  interactions, which neutralizes the first charge, and the second deprotonations operates in the same degree that the first.

### Conclusion

We showed that the magnitude proton transfer processes from calix[4]arene and *p*-tert-butylcalix[6]arene to hydroxide is related with the nature of the counter-ion and the solvent. In ethanol the variation is only modest, with  $pK_a$  around 7.0 units, where as in acetonitrile the transfer is quantitative, and early measures provided a  $pK_a = 4.05$  when transposed to water.

The influence in *p*-tert-butylcalix[6]arene is outstanding, with relation to the specific interactions of the conjugated base with the cation, and the TMAOH was the strongest base ( $K_e > 10^8$ ), and the TBAOH ( $K_e \approx 10^2$ ) was the weakest. The reactions with LiOH and NaOH in acetonitrile showed “instabilities” in the profiles, attributed to the aggregation processes, whereas for the other bases, it was possible to determine the constant of the second proton transfer, and again the TMAOH was the strongest base.

Although some numerical results could be under scrutiny by the limitations imposed by the mixture of solvents on the auto-protolysis constant of the water and the transposition of the values to water, the general behavior is clear: the expression of acidity of calixarenes is far from a single value, and the form that the counter-ion and solvents affect the acidity is different of common organic acids.

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