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Resolution of the Acid-base Fraction Curves of the Calixarene Derivatives with Chemometric Methods

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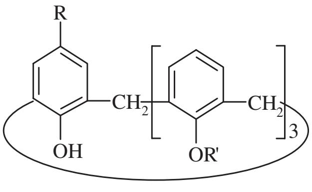
The acid-base properties of several new calix[4]arene derivatives were studied with chemometric methods by measurement of their UV absorbances under different pH. Resolving the acid-base fraction curves with chemometric methods, the pK_a of these derivatives were determined and the fraction curves and pure absorbing spectra of each absorbing component in the calixarene system were obtained. The proton dissociation behavior of these derivatives was also discussed in this paper.

Calixarenes are cyclic oligomers composed of phenol units linked by methylene. The hydroxy of phenol units frequently play one of the decisive roles in the supramolecular properties of calixarenes such as the stabilization of a cone conformation and the substrate selectivity.[1,2] In addition, the phenol proton dissociation was also often applied in the selective functionalization of clixarenes and syntheses of calixarene derivatives.[3–5] So to know the proton dissociation behavior of calixarene is indispensable to understand the chemistry of calixarene. However, the related researches have been very limited. Among literatures so far appeared, we only find that Böhmer's group and Shinkai's group have estimated the pK_a of several calixarene derivatives such as *p*-sulfonatocalix[4]arne and *p*-nitrocalix[4]arene with spectroscopic or potentiometric titration.[6–9] Furthermore, these studies just simply estimated the pK_a values of the calixarene derivatives. As far as we know, no further work appears dealing with the dissociation behavior of the phenol proton in the calixarene derivatives until now. The scarcity of the related researches may be ascribed not only to the difficulty in solubility of most calixarenes in water but also to the complication of the proton dissociation of calixarenes.

Here we have synthesized several new calixarene derivatives partly soluble in water and successfully introduced the chemometric methods to study their proton dissociations. Calixarenes frequently have several protons in one molecule resulting in the complication of the proton dissociation. If the pK_a values are at close range or the spectra of each absorbing species overlap seriously, the conventional computing methods can't give a satisfied result, even can't give any resolution. The chemometric methods display their advantages in this case, especially when the number of ionized proton is unknown under certain pH. Applying the chemometric methods allowed us to accurately resolve the acid-base fraction curves of the calixarenes. Besides determining their pK_a values, with these methods we could achieve the detailed information about the proton dissociation behavior, such as the pH range of each component and their pure absorption spectra.

The measured calixarene derivatives **2**–**4** were first synthesized (Figure 1). The starting derivative **1** was prepared according to the reported method.[10] Nitration of derivative **1** with nitric acid in the presence of glacial acetic acid gave the derivative **2** in good yield. The reduction of derivative **2** with $SnCl_2$ in ethanol yielded the amino product **4**. Treatment of derivative **2** with strong base NaOH afforded derivative **3**. All the derivatives gave satisfactory analytical results. The absorption spectra were obtained on a Lambada Bio40 UV–vis spectrophotometer (Perkin Elmer Corp.). The measurement was carried out in a solution of mixed solvent, water and tetrahydrofuran (V:V = 1:1) for **2** and **4**, water and ethanol (V:V = 3:7) for **3**. The pH values were adjusted using HCl, the buffer or NaOH.



1 R = H, R' = COPh;
2 R = NO_2, R' = COPh;
3 R = NO_2, R' = H;
4 R = NH_2, R' = COPh

Figure 1. Structure of the calixarene derivatives.

All the three derivatives displayed a pH-dependent spectral change. Owing to this chromophoric nature, we could obtain two-way data matrix and used the chemometric methods to study the proton dissociation of calixarenes. For each derivative, we first used principal component analysis (PCA)[11] to determine the number of the principal components of the measured systems. Operating PCA on the data matrix respectively, we can affirm there are both 3 absorptive components for derivative **3** and **4**, and 2 absorptive components for derivative **2** in the measured pH ranges. The existing pH range of each component was computed with evolving factor analysis (EFA).[12] For derivative **2**, the existing ranges of the two components are 3–7 and 4–7, respectively. For derivative **3**, the existing ranges of the three components are 0–4, 2–13.5, and 11–14, respectively. For derivative **4**, they are 0–2, 0–7, and 4–8, respectively.

The two-way data matrix of derivative **3** was further analyzed using iterative target transformation factor analysis (ITTFA).[13] ITTFA is a modelless method derived from the self-modeling curve resolution (SMCR). It takes advantages of the features of the two-way data itself and resolves the data matrix without any model. So it can overcome the drawbacks of the model-based methods and attain great accuracy. As for the derivatives **2** and **4**, because their first components existing in the acid range have only small absorption, we couldn't get satisfactory results with ITTFA. With target testing factor analysis (TTFA),[14] we still could gain perfect results for the two derivatives. Unlike ITTFA, TTFA is applicable to resolve the model-known data. Here a set of pK_a values is first supposed and then is optimized continually. When the difference between the calculated reproduction data and the original data reaches the minimum, the results are obtained. For each derivative, the fraction curves obtained with ITTFA or TTFA are illustrated in Figure 2 (shown as mark symbol). According to the fraction curves of each absorbing component, we can obtain the pK_a values. The pK_a value of derivative **2** was calculated to be 5.24. The first two pK_a values of derivative **3** were 3.63 and 12.53, and the two pK_a values of derivative **4** were 0.85 and 5.86. Inversely, according to the chemical equilibrium, using the pK_a values we can calculate the fraction curves. They were expressed as solid lines in Figure 2. In other words, we have used the chemometric methods ITTFA or TTFA in analyzing the measured data to obtain the fraction curves (experimental data, mark symbol in Figure 2) as well as the pK_a values, then used these pK_a values to calculate the fraction curves (theoretic data, solid line in Figure 2) inversely. The good accordance shown in all the figures implies the reliability of the results obtained with these chemometic methods. Treating the fraction carves obtained with the ITTFA or TTFA with least square regression, we could extract the pure absorption spectra of each absorbing component of these derivatives.

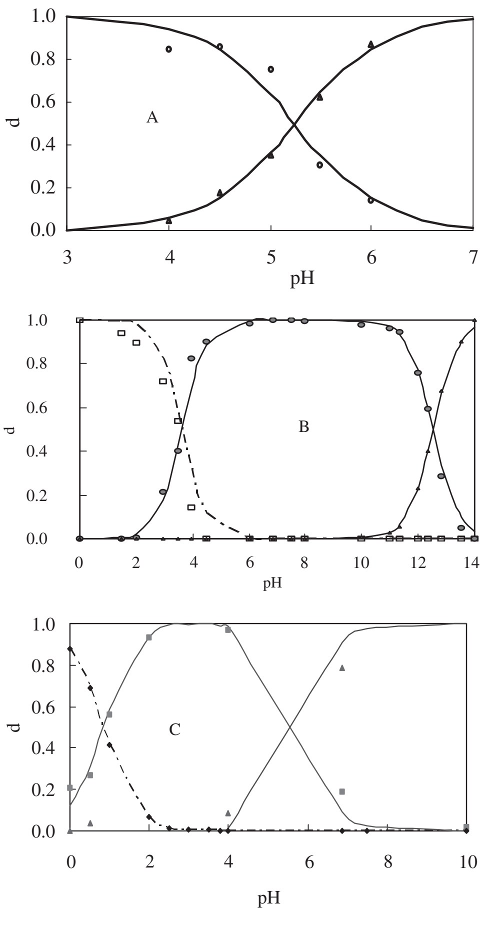


Figure 2. Distribution of the components (mark symbol: ITTFA or TTFA, solid line: calculated) A: derivatives **2**; B: derivative **3**; C: derivative **4**.

Thus, with above chemometric methods, we have analyzed the proton dissociation behavior of the calixarene derivative **2**–**4**. Chemometric methods provide us useful techniques to deal with the complicated calixarene systems. With these methods, we could systematically study the proton dissociation of a series of calixarene derivatives and find the rules of the proton dissociation of calixarenes and their derivatives.

The calculated results show us some interesting information of their proton dissociations. Derivative **4** has two pK_a values, although it has only one phenol proton. But its amino group on the upper rim can form ammonium ion in the acidic solution. So we attributed its pK_{a1} to the proton of this ammonium ion. Then the pK_a value of the phenol proton of derivative **4** should be pK_{a2} (5.86). The pK_a of derivative **2** (5.24) is little smaller than the pK_{a2} (attributed to the phenol proton) of derivative **4**. This can be rationalized with their different groups on the upper rim. The group of derivative **2** is nitro that has the ability of attracting electron, which can help the dissociation of the proton. On the contrary, derivative **4** has an electron-repulsive amino nitrogen on the upper rim. Derivative **3** has two protons ionized in the measured pH range (0–14). The first proton should be the proton of the phenol unit with the electron-attracting nitro group. Its pK_{a1} (3.63) is far smaller than the pK_a of derivative **2**, which is ascribed to the hydrogen bond formed by the oxide anion with the neighbor phenol hydroxy. Owing to the same reason, the other ionized proton should be the proton of the opposite phenol unit. The great gap between pK_{a1} and pK_{a2} (12.53) also is easily interpreted in terms of the hydrogen-bond interactions. When one proton ionized, the oxide anion is strongly stabilized by two hydrogen bonds. While two protons ionized, each oxide anion is stabilized by only one hydrogen bond. From above discussion, we could conclude that the group opposite phenol hydroxyl and the hydrogen bond formed by the oxide anion with the neighbor phenol hydroxy play important roles in the proton dissociation of calixarenes.

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