

Selective Nitration of Thiacalix[4]arene and an Investigation of Its Acid–Base Properties with a Chemometric Method

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The selective dinitro-substituted derivative of thiacalix[4]arene was synthesized by a three-step route and characterized. Its acid–base properties in a water solution were studied by UV–vis spectroscopy. Its four pK_a values were determined by Target Testing Factor Analysis (TTFA).

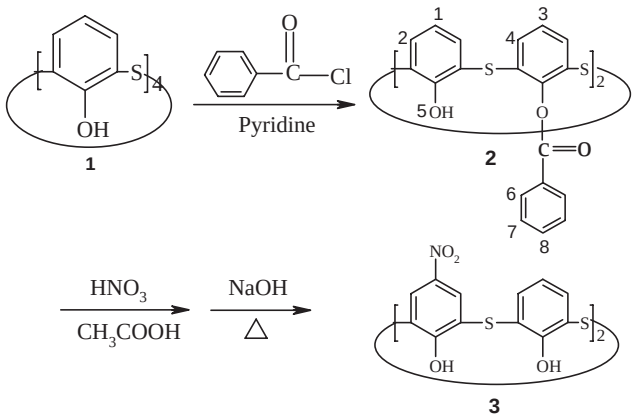
The calixarenes, a class of molecules with excellent binding affinity to various substrate molecules, have caught the eyes of chemists from all over the world.[1] A large number of substituted calixarenes have been synthesized with the aim to modify their binding properties.[2,3] Substitution of the original methylene bridges between the aromatic rings in calixarene by sulfur has recently been reported.[4] The properties of these thiacalixarenes are different from these of the original calixarenes due to the substitution of methylene bridge groups with sulfur atoms,[5] which make thiacalixarenes become a new type of building blocks and molecular scaffolds for molecular receptors.

A variety of thiacalixarene derivatives with all kinds of functional groups[6–10] on the lower rims have been synthesized after Kumagai reported on the facile synthesis of tetra(*p*-*t*-butyl)tetrathiacalix[4]arene **1**.[4] The derivatives of thiacalix[4]arene with nitro groups on the upper rims are desirable precursors for the amino-substituted derivative of thiacalix[4]arene, which is a versatile intermediate to many larger molecular blocks. The tetranitration of thiacalix[4]arene has been reported by Parola et al. using nitrosium nitrate.[11]

Here, the region-selective nitration derivative **3** of thiacalix[4]arene with two nitro groups on the upper rims was synthesized by a three-step route with 65–68% HNO_3 as the nitrating reagent. Its acid–base properties in aqueous solution were studied by UV–vis spectroscopy, and the four pK_a values of **3** in water solution, as determined by Target Testing Factor Analysis (TTFA),[12,13] are also reported. The results presented here will be helpful for their further chemical modification[14] and exploration of the molecular recognition properties[15] of **3**.

Results and Discussion

Synthesis and Characterization. Guillet has reported on a method for the mono-substituted derivative of calix[4]arene.[16] By this method, three of four hydroxy groups on the lower rims of calix[4]arene were benzoylated, and then the upper rim of the unbenzoylated hydroxy group was modified with the desired functional groups. However, for thiacalix[4]arene, this method only led to the dibenzoylated derivative of thiacalix[4]arene, not the tribenzoylated ones. That is to say, the selective dinitration of thiacalix[4]arene on the upper rims can be achieved using this method.



Scheme 1. Procedures for the dinitration of thiacalix[4]arene.

In the first step of benzoylation (this reaction was carried at low temperature), the dibenzoylated derivative of thiacalixarene was insoluble in pyridine and separated out after benzoyl chloride was added (Scheme 1). The IR spectrum of **2** showed a large absorption peak of carbonyl at 1739 cm^{-1}, which was not observed in the IR spectrum of **1**. On the ^1H NMR spectra of **2** the signals of H_6 and H_{14} were observed overlapping at $\delta = 7.48$ to 7.51, and the structure of **2** was confirmed by H–H COSY, HSQC, and HMBC.

In the nitration of the above product, glacial acetic acid was chosen as the regulating reagent of acidity, rather than conc. H_2SO_4, which is preferred for the nitration of calixarenes.

The debenzoylation was performed in a hot NaOH solution. The dinitro thiacalix[4]arene **3** were easily associated with two THF molecules in the recrystallization, which could be attributed to the inclusion properties of **3** with THF. These were certified in the characterization of **3**. ^1H NMR of **3** showed two

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Published on the web January 13, 2005; DOI 10.1246/bcsj.78.138

large peaks at $\delta = 3.74$ and 1.85, which were signals of THF protons; the associating ratio (1:2) of **3** and THF could be confirmed by the integral intensities of the ^{1}H NMR signals of **3** and THF. An elemental analysis of **3** also evidenced this associating ratio of **3** and THF. However, in the ESI-MS of **3**, the -585 m/z peak (100%) showed that **3** was separated from THF and negatively ionized after losing one H^+.

The Acid–Base Properties of 3, as Studied by UV–Vis Spectroscopy. The dinitro-substituted derivative **3** of thiacalix[4]arene is a kind of compound with strong acidic properties. In a water solution, the four hydrogen atoms of phenolic hydroxy groups of **3** could be dissociated successively along with an increase in the solution pH. Thus, **3** is a tetraprotonic acid, and can be defined as H_4L. H_3L^-, H_2L^{2-}, HL^{3-}, and L^{4-} will correspond to the loss of one, two, three, and four H^+ ions, respectively, from **3**.

Figures 1(a)–(c) show the UV–vis absorption spectra of **3** in a water solution under different pH conditions and the spectra for the five pure species (H_4L, H_3L^-, H_2L^{2-}, HL^{3-}, and L^{4-}) of **3** provided by TTFA. As Fig. 1(a) shows, the absorption band around 385 nm rose along with an increase in the solution pH from 3.77 to 4.38. The shapes of the absorption spectra of **3** were similar to the spectrum of the pure species (H_4L) at pH < 3.77, and were close to the spectrum of the pure species (H_3L^-) at pH > 4.38. That is to say, an isolated single-step acid dissociation occurred in this pH region. This change can be described by

$$H_4L \overset{K_{a_1}}{\rightleftharpoons} H_3L^- + H^+. \quad (1)$$

In Fig. 1(b), an obvious red shift of the absorption peak around pH $= 7.29$ and two isosbestic points at 303 and 342 nm show that there is a second acid dissociation occurring in this pH region. This acid dissociation can also be depicted by

$$H_3L^- \overset{K_{a_2}}{\rightleftharpoons} H_2L^{2-} + H^+. \quad (2)$$

From pH $= 10.3$ to 13.6 (Fig. 1(c)), a continuous increase in the absorption was observed between 410 and 455 nm. This can be interpreted as only one acid-dissociation occurring in this pH region. However, by TTFA, two pK_a values could be conducted in this pH region. These two acid dissociations of **3** can be described by the following equations:

$$H_2L^{2-} \overset{K_{a_3}}{\rightleftharpoons} HL^{3-} + H^+, \quad (3)$$

$$HL^{3-} \overset{K_{a_4}}{\rightleftharpoons} L^{4-} + H^+. \quad (4)$$

The Determination of Four p$K_{a,n}$ (n = 1–4) Values of 3 by TTFA. Table 1 gives the four pK_a values of **3** in aqueous solution (the four pK_a values of **4**,[17] **5**,[18] and **6**[19] are also listed in Table 1 for a comparison). The p$K_{a,1} = 3.95$ of **3** is far lower than the subsequent pK_a values. This indicates that the first acid dissociation of the phenolic OH groups of **3** is far easier than further acid dissociations. As speculated by several researchers,[19,20] these may be attributed to stabilization of the monophenolate species through strong intramolecular hydrogen bonding between the phenolate O^- and its flanking OH groups (see Fig. 2). This stabilization effect also makes it possible that the first pK_a of **3** is far lower than the pK_a of *p*-nitrophenol (7.15).

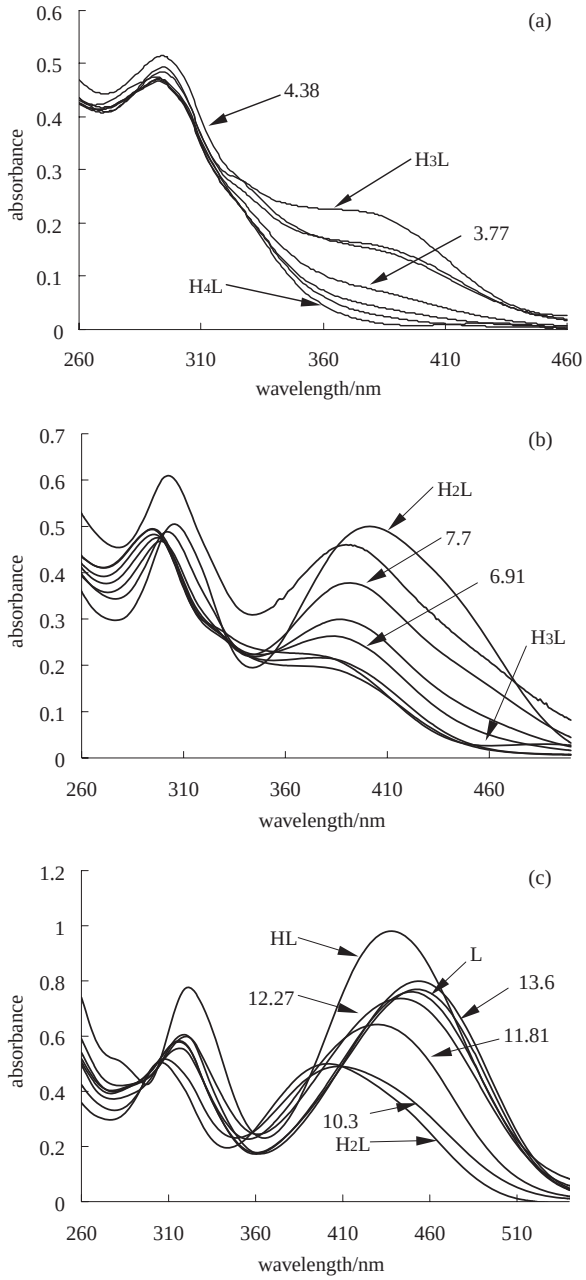


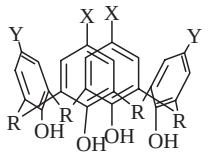
Fig. 1. (a) UV–vis absorbance spectra of **3** at solution pH: 2.21, 2.9, 3.77, 4.38, 4.92 and the pure species (H_4L, H_3L^-). (b) UV–vis absorbance spectra of **3** at solution pH: 5.26, 5.81, 6.91, 7.29, 7.7, 8.87 and the pure species (H_3L^-, H_2L^{2-}). (c) UV–vis absorbance spectra of **3** at solution pH: 10.3, 11.81, 12.27, 13.4, 13.6 and the pure species (H_2L^{2-}, HL^{3-}, L^{4-}).

It is interesting to note that the pK_a values of **4** are almost less than the corresponding pK_a values of **3**. This may be related to the stronger electron-withdrawing effect of the *p*-nitro groups of **4** than that of **3**. The phenolate species of **3** and **4** can all be partially stabilized by the delocalization of anionic charges through the electron-withdrawing effects of the *p*-nitro groups, leading to an enhancement of the acid dissociation. But the number of *p*-nitro groups of **4** is two more than that of **3**, giving rise to a stronger electron-withdrawing effect of

Table 1. pK_a Values of **3**, **4**, **5**, and **6**

Compound	p$K_{a,1}$	p$K_{a,2}$	p$K_{a,3}$	p$K_{a,4}$	RSD
3	3.95	7.61	12.00	12.35	0.0024
4	2.75	6.48	7.60	13.35	0.0029
5	2.18 ± 0.04	8.45 ± 0.10	11.99 ± 0.15	11.62 ± 0.12	—
6	2.9 ± 0.3	10.9 ± 0.1	12.3 ± 0.2	>14	—

The compounds **3**, **4**, **5**, and **6** are depicted in Scheme 2.



3. X= NO_2, Y=H, R = S
4. X=NO_2, Y=NO_2, R = S
5. X=SO_3^-, Y=SO_3^-, R = S
6. X=NO_2, Y=NO_2, R = CH_2

Scheme 2. Structures of **3**, **4**, **5**, and **6**.

the *p*-nitro groups of **4** than that of **3**. Thus, the acid dissociations of the occurring species of **4** are easier than that of **3**.

The pK_a values of **4** all are less than those of **6**. This may be attribute largely to the presence of the vacant 3d-orbital of the sulfide linkage, which allows a resonance-like interaction with the π-orbital of the adjacent aromatic rings to delocalize anionic charges, resulting in an enhancement of the acid dissociation.[18] However, another noteworthy feature is that the pK_a values of **3** were almost larger than that of **6**, which may be ascribed to the dominant electron-withdrawing effect of the *p*-nitro groups over the resonance-like interaction of the vacant 3d-orbital of the sulfide linkage with the π-orbital of adjacent aromatic rings.

On the other hand, the first pK_a values of **3** and **4** are all larger than that of **5**, which may be due to the stronger electron-withdrawing effect of the *p*-sulfonate groups than that of the *p*-nitro groups under these conditions, or for other unknown reasons.

Experimental

General. All of reagents were obtained from a commercial source and used without further purification. ^{1}H NMR and ^{13}C NMR were measured using Bruker 500 MHz NMR and JEOL 600 MHz spectrometers, respectively. Infrared spectra were obtained using a Nicolet FT-IR spectrometer (Model: Nexus 912A0446). ESI-MS was measured using an Agilent spectrometer (Model: 1100/LC-MSD). UV–vis spectra were measured using an Agilent spectrometer (Model: 8453). Elemental analyses were performed at Shanghai Institute of Pharmaceutical Industry of (Shanghai, P. R. China).

Synthesis. 25,27-Dibenzoyloxy-26,28-dihydroxythiacalix[4]arene (2): Thiacalix[4]arene **1**[21] (2 g) was dissolved in pyridine (120 mL) and cooled in an ice bath. Benzoyl chloride (1.5 mL) was added, and the mixture was stirred at 0 °C for 2 h and then allowed to warm slowly to room temperature over another hour. The precipitate was collected and washed with pyridine, water, and methanol to obtain a white powder. The white powder was recrystallized from $CHCl_3/CH_3OH$ to obtain a colorless crystal powder 1.12 g (39.4%). IR ν_{max} (KBr) 1739, 3417 (broad) cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.11 (t, 2H, $J = 8.04$ Hz, H_1), 6.95 (t, 4H, H_7), 7.11 (d, 4H, $J = 7.0$ Hz, H_6), 7.24 (d, 4H, $J = 8.1$ Hz, H_2), 7.48–7.51 (m, 4H, H_3 and H_8), 7.93 (d, 4H, $J = 8.0$ Hz, H_4), 7.97 (s, 2H, H_5). ^{13}C NMR (150 MHz, DMSO-d_6) δ 120.53, 120.78, 127.62, 127.87, 128.73, 129.74, 130.32, 134.00, 135.00, 135.21, 151.65, 156.88, 163.31. Anal. Calcd for $C_{38}H_{24}O_6S_4$: C, 64.77; H, 3.41; S, 18.18%. Found: C, 64.74; H, 3.45; S, 18.13%.

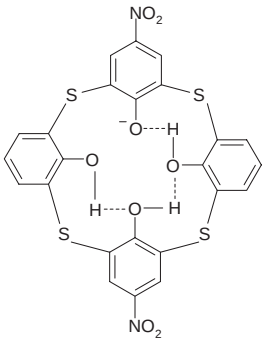


Fig. 2. Schematic representation of possible intramolecular hydrogen bonding mode.

5,17-Dinitro-25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiacalix[4]arene (3): 25,27-Dibenzoyloxy-26,28-dihydroxy-2,8,14,20-tetrathiacalix[4]arene (**2**) (0.5 g) was dissolved in $CHCl_3$ (200 mL). Glacial acetic acid (4.5 mL) and 65–68% HNO_3 (3.5 mL) were added to the solution. The solution was stirred at room temperature for 40 min. The produced precipitate was collected and washed with water 2–3 times, and was then dried at 60–70 °C to yield a pink powder. The pink powder was then added into a NaOH solution (24 g NaOH/300 mL water) and stirred at 80 °C for 5 h. Then, the red transparent water solution was cooled to room temperature and added to conc. hydrochloric acid, until adjusting pH > 1 to cause a yellow precipitate. The yellow precipitate was collected and recrystallized from THF/acetone to obtain a yellow crystal powder 0.29 g (71%). IR ν_{max} (KBr) 1336, 1521, 3332 (broad) cm^{-1}. ESI-MS *m/z*: −585 $[M-H]^-$ (100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (t, 2H, $J = 7.7$ Hz, ArH), 7.71 (d, 4H, $J = 7.7$ Hz, ArH), 8.51 (s, 4H, HAr–NO_2), 9.44 (br, 4H, HO–Ar). Anal. Calcd for $C_{24}H_{14}N_2O_8S_4 \cdot 2THF$: C, 52.6; H, 4.11; N, 3.84; S, 17.53%. Found: C, 52.52; H, 4.08; N, 3.85; S, 17.61%.

The Acid–Base Properties of 3 as Determined by UV–Vis Spectroscopy. The UV–vis absorption spectra were recorded for aqueous solutions containing the dinitro derivative **3** of thiacalix[4]arene (5×10^{-5} mol·L^{-1}) at appropriate pH intervals under the conditions of 298 K and $I = 0.2$ M with NaCl.

The Determination of Four p$K_{a,n}$ (n = 1–4) Values of 3 by TTFA. Assume that the spectra collected during a distribution profile can be arranged against the measurement time and form a data matrix, $\boldsymbol{Y}$. The size of the matrix is $nt \times nw$, where nt denotes the number of measurement times and nw the number of corresponding wavelengths. The data matrix, $\boldsymbol{Y}$, is allowed to be decomposed to the pure absorption spectral matrix, $\boldsymbol{S}$, and the distribution profiles matrix, $\boldsymbol{D}^T$. The relationship can be described by

$$\boldsymbol{Y} = \sum_{i=1}^{nc} \boldsymbol{S}_i \boldsymbol{d}_i{}^{\mathrm{T}} + \boldsymbol{E}_1 = \boldsymbol{S}\boldsymbol{D}^{\mathrm{T}} + \boldsymbol{E}_1, \quad (5)$$

where nc is the number of the absorbing species; $\boldsymbol{d}_i{}^{\mathrm{T}}$ (column vector) and $\boldsymbol{s}_i$ (row vector) represent the distribution profile and the absorption spectrum of the ith component, respectively. Superscript T denotes the transpose of a matrix or a vector. $\boldsymbol{E}_1$ is the residual matrix. A principal component analysis (PCA) is a widely used chemometric technique. By using it, the data matrix $\boldsymbol{Y}$ can be decomposed to two orthogonal matrices, a score matrix, $\boldsymbol{T}$, and a loading matrix, $\boldsymbol{P}^{\mathrm{T}}$. That is,

$$\boldsymbol{Y} = \boldsymbol{T}\boldsymbol{P}^{\mathrm{T}} + \boldsymbol{E}_2. \quad (6)$$

If the pure absorption spectra of the components in the samples are unknown, the concentration distribution of the components can be calculated through a series of acid-ionization constants according to the principle of material equilibrium. Denote the samples as H_nL, and the corresponding acid ionization constants as $K_1, K_2, \cdots, K_{n-1}$. The distribution coefficient model is as follows:

$$d_i = \frac{[H]^{n-i} \cdot K_1 \cdots K_i}{[H]^n + [H]^{n-1} \cdot K_1 + \cdots + K_1 K_2 \cdots K_{n-1}}. \quad (7)$$

The question is how to calculate this distribution coefficient. Concerning the background conditions, we assume some experiential values to the series of K_i, and calculate the corresponding concentration distribution to obtain the test target, $\boldsymbol{D}_{test}{}^{\mathrm{T}}$ ($nc \times ns$). Then, according to the following partial least-squares regression equation, we obtain the target transformed matrix:

$$\boldsymbol{R} = \boldsymbol{D}_{test}{}^{\mathrm{T}} \boldsymbol{P}. \quad (8)$$

Having the target transformed matrix, we obtain the corresponding pure absorption spectrum matrix, $\boldsymbol{S}_{test}$ ($nc \times ns$), through the equation $\boldsymbol{S} = \boldsymbol{T}\boldsymbol{R}^{-1}$. The residual matrix, $\boldsymbol{Y}_{res}$, of the original data is

$$\boldsymbol{Y}_{res} = \boldsymbol{Y} - \boldsymbol{S}_{test} \boldsymbol{D}_{test}{}^{\mathrm{T}}. \quad (9)$$

Using the sum square of the matrix $\boldsymbol{Y}_{res}$ as the target function, denoted by **SSQ**, we can obtain the minimum value of **SSQ** after optimizing of K_i.

When the value of **SSQ** is minimum, the corresponding $\boldsymbol{S}_{test}$ and $\boldsymbol{D}_{test}{}^{\mathrm{T}}$ can be seen as the actual spectrum matrix and the concentration distribution matrix; therefore, the concentration distribution model can be calculated. We used a global search or the NGA algorithm[22] to optimize the parameters.

The RSD was used to evaluate the result.

$$\boldsymbol{RSD} = \sqrt{\frac{\boldsymbol{SSQ}}{nt \times (nw - nc)}}. \quad (10)$$

The key to this method is optimizing the test target through a factor analysis, the so-called Target Testing Factor Analysis (TTFA).[12,13]

Conclusion

The selective dinitro-substituted derivative **3** of thiacalix[4]-arene was synthesized and characterized. The acid–base properties of **3** in aqueous solution were studied by UV–vis spectroscopy. Four pK_a values of **3** in a water solution were determined by TTFA. Further modifications of **3** are under way, such as reducing the nitro groups on the upper rims to amino groups.

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