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Highly selective fluorescent chemosensor for Na^+ based on pyrene-modified calix[4]arene derivative

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A novel calix[4]arene derivative with pyrene fluorophores at the upper rim and tetraester ionophores at the lower rim was synthesized in six steps, and its structure was proved by NMR and ESI-MS spectroscopies. Furthermore, the chemosensing behavior of the host compound for alkali and alkaline earth metal ions was investigated by fluorescence spectroscopy. The obtained results show that the calixarene host can selectively bind sodium ion with the complexation stability constant of 2190 $mol^{-1}\cdot L$. The complexation with sodium ion can pronouncedly induce the excimer emission to decrease and the monomer emission to increase, whereas the addition of the other alkali and alkaline earth metal ions does not cause appreciable changes in the fluorescence spectrum of the host compound. The present calix[4]arene derivative displays potential application as fluorescent chemosensor for sodium ion.

calix[4]arene, pyrene, sodium ion, fluorescent chemosensor

1 Introduction

Construction of efficient fluorescent chemosensors is one of considerable interests, which produces quantifiable fluorescence changes upon complexation with suitable guests, showing potential applications in analytical chemistry, biology, clinical diagnosis and environmental chemistry, and so on[1]. In this context, chemosensing of alkali and alkaline earth metal ions is very significant in clinical diagnostics. Among them, sodium ion is about 120—160 $mmol\cdot L^{-1}$ in whole blood of people, and the sodium channels are essential in the beat of the heart and the firing of a synapse[2,3]. As a result, scientists had paid much attention to the selective fluorescent chemsensors for sodium ion versus the other alkali and alkaline earth metals in recent years[4–8]. Fluorescent chemosensors for ions typically consist of an ion recognition unit (ionophore) and a fluorogenic unit (fluorophore) linked to the ionophore through a proper spacer.

As the third generation of supramolecular host molecules, calix[*n*]arenes have been demonstrated to be sophisticated scaffolds in designing fluorescent sensors for detecting metal cations and anions with the following two advantages. One is that the flexible conformation of calixarene framework requires small energy changes to accommodate guests, which makes them exceptionally become resourceful host molecules. The other is the facile modulation at the upper and lower rims of calix[*n*] arenes, which leads to attractive features in calix[*n*]arene derivatives[9]. Up to now, the fluorescent chemsensors for sodium ion based on the framework of calix[4]arene have been frequently reported[10–16]. Shinkai and coworkers have designed a calix[4]arene having two pyrene moieties on the lower rim as fluorescent chemsensor for sodium ion based on the ratio of the monomer vs. excimer emission[10]. In a similar system, a calix[4] arene bearing pyrene (as a fluorophore) and nitrobenzene (as a quencher) was synthesized, which was response to the sodium ion by the intramolecular photoinduced electron transfer process[11].

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In this paper, we synthesize a novel calixarene-based fluorescent chemosensor for sodium ion with pyrene as the fluorophore at the upper rim and tetraester groups as the ionophore at the lower rim. Pyrene has widely used fluorophore to recognize the ions because of its well-known photophysical excimer emission, which depends on the properties and environment-sensitive monomer or orientation of the two pyrene moieties[17]. Calix[4]arene tetraesters have been shown to be the benign ionophores to alkali and alkaline earth metals[18, 19]. In the absence of sodium ion, the host compound gave the typical excimer emission spectra of pyrene because of π-π stacking interaction of the two upper-rim pyrene moieties. Whereas in the presence of sodium ion, the excimer spectra decreased pronouncedly accompanied with the monomer spectra increased, indicating that the upper- rim pyrene dimer was separated by the complexation of the lower-rim tetraester moieties with sodium ion, and therefore, the present chemosensing mechanism is based on the complexation-induced conformational change of calixarene. The host compound resembles a molecular tweezer that can be somewhat triggered by sodium ion.

2 Experimental

2.1 Materials and apparatus

1-Pyrenemethylamine hydrochloride (95%) and dichloromethyl methyl ether were purchased from Sigma- Aldrich Company. Before using, 1-pyrenemethylamine hydrochloride was dissolved in water, and then concentrated $NH_3 \cdot H_2O$ was added, after filtration, 1- pyrenemethylamine was obtained. Other reagents and solvents were obtained from commercial supplies, and solvents were purified and dried using standard techniques. All reactions were carried out under nitrogen. ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer. ESI-MS was performed on VG ZAB-HS. Fluorescence spectra were measured with an Edinburgh Analytical Instruments FLS920 spectrometer (Edinburgh Instruments, Edinburgh, UK).

2.2 Synthesis of samples

The intermediate compounds **2**–**5** were synthesized from calix[4]arene material **1** according to literature procedures, and the structural identifications were proved by ^{1}H NMR and ESI-MS analysis, which were coincident with the reported data[20–23].

25,27-Bis(ethoxycarbonylmethoxy)-26,28-dihydroxy calix[4]arene (**2**). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 7.58 (s, 2 H), 7.05 (d, J = 7.5 Hz, 4 H), 6.91(d, J = 7.5 Hz, 4 H), 6.74 (t, J = 7.5 Hz, 2 H), 6.64 (t, J = 7.5 Hz, 2 H), 4.72 (s, 4 H), 4.50 (d, J = 13.2 Hz, 4 H), 4.36 (q, J = 7.2 Hz, 4 H), 3.41 (d, J = 13.2 Hz, 4 H), 1.35 (t, J = 7.2 Hz, 6 H); ESI-MS: *m/z* 619 $[M+Na]^+$.

5,17-Diformyl-25,27-bis(ethoxycarbonylmethoxy)-26, 28-dihydroxycalix[4]arene (**3**). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 9.78 (s, 2H), 8.68 (s, 2H), 7.62 (s, 4H), 6.98 (d, J = 7.5 Hz, 4H), 6.81 (t, J = 7.5 Hz, 2H), 4.72 (s, 4H), 4.49 (d, J = 13.2 Hz, 4H), 4.35 (q, J = 7.2 Hz, 4H), 3.53 (d, J = 13.8 Hz, 4H), 1.33 (t, J = 7.2 Hz, 6H); ESI-MS: *m/z* 675 $[M+Na]^+$.

5,17-Diformyl-25,26,27,28-tetrakis(ethoxycarbonylmethoxy)calix[4]arene (**4**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.56 (s, 2H), 7.13 (s, 4H), 6.69 (s, 6H), 4.94 (d, J = 13.8 Hz, 4H), 4.81 (s, 4H), 4.68 (s, 4H), 4.25–4.18(m, 8H), 3.36 (d, J = 14.1 Hz, 4H), 1.32–1.26 (m, 12H); ESI-MS: *m/z* 847 $[M+Na]^+$.

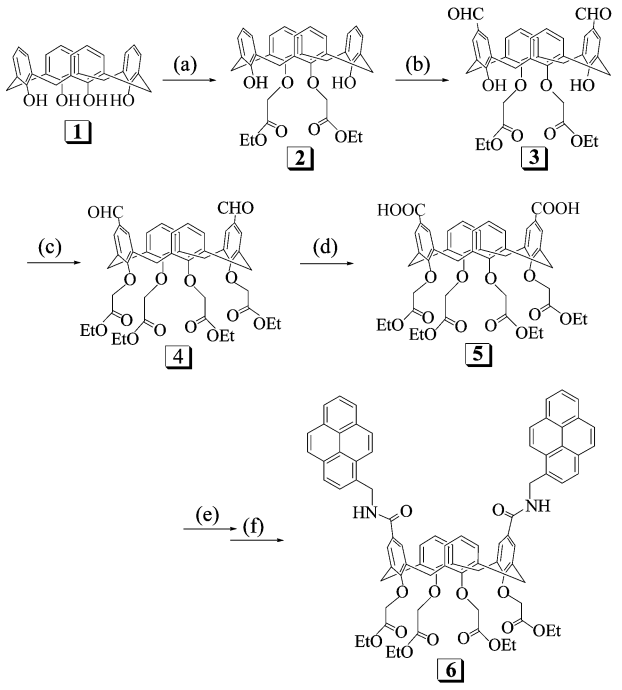
5,17-Dicarboxyl-25,26,27,28-tetrakis(ethoxycarbonylmethoxy)calix[4]arene (**5**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, J = 7.2 Hz, 4H), 7.06 (t, J = 7.2 Hz, 2H), 6.80 (s, 4H), 4.90 (d, J = 14.1 Hz, 4H), 4.52 (s, 4H), 4.27–4.15 (m, 8H), 3.27 (d, J = 14.1 Hz, 4H), 1.31–1.23 (m, 12 H), 1.26 (t, J = 7.2 Hz, 6H); ESI-MS: *m/z* 879 $[M+Na]^+$.

Compound **6**. Compound **5** (257mg, 0.3 mmol) was dissolved in dry CH_2Cl_2 (25 mL), $SOCl_2$ (2 mL) was added, and the mixture was refluxing for 10 h. The solvent was removed at reduced pressure, and the residue was directly used. Dry CH_2Cl_2 (15 mL) was added to dissolve the residue, and the CH_2Cl_2 (10 mL) solution containing 1-pyrenemethylamine (138 mg, 0.6 mmol) was gradually dropped to the solution for 10 min, and after that a CH_2Cl_2 (10 mL) solution of Et_3N (1 mL) was also dropped to the solution for 10 min. The mixtures were stirred overnight at the room temperature. The organic solution was washed with water (20 mL×2), and dried over by anhydrous sodium sulfate, and the solvent was removed at reduced pressure to give a residue. The residue was purified by silica-gel column chromatography using $CHCl_3$/CH_3COOEt (5/1) (*v*/*v*) as the eluent to give the product **6** (215 mg) as a yellowy powder at the yield of 56%. ^{1}H NMR (300 Hz, $CDCl_3$) : δ = 7.98–8.30 (18 H), 7.19 (s, 4 H), 6.52–6.45 (m, 8 H), 6.33 (t, J = 5.4 Hz, 2H), 5.27 (d, J = 5.4 Hz, 4H), 4.85 (d, J = 13.8 Hz,

4H), 4.75 (s, 4 H), 4.61 (s, 4 H), 4.21–4.11 (m, 8 H), 3.24 (d, J = 13.8 Hz, 4H), 1.27–1.21 (m, 12 H); ESI-MS: *m/z* 1305 $[M+Na]^+$. Anal. Calcd for $C_{80}H_{70}N_2O_{14}$: C, 74.87; H, 5.50; N, 2.18. Found: C, 74.77; H, 5.62; N, 2.22.

3 Results and discussion

The target compound **6** was synthesized in six steps starting from calix[4]arene **1**, as shown in Scheme 1. Compound **1** was substituted by 2 equivalents of $BrCH_2COOEt$ upon adding 1.1 equivalents of K_2CO_3 as the base in refluxing acetonitrile for 18 h, and the residue was purified by recrystallizing from $CHCl_3$/MeOH to yield compound **2.** The dialkyl derivative **2** was dissolved in dry $CHCl_3$, the solution was cooled to −15°C, and then Cl_2CHOCH_3 and $TiCl_4$ were rapidly added. The mixtures reacted for 19 h at room temperature under N_2 atmosphere, and then bisaldehyde compound **3** was obtained, purified by column chromatography using $CHCl_3$ as eluent. The tetraesters derivative **4** was prepared using the similar reaction route to compound **2** using Na_2CO_3 as base. Further, compound **4** was oxidated by NH_2SO_3H and $NaClO_2$ in the solution of $CHCl_3$/CH_3COCH_3 (1/1) beginning at 0℃, and then stirred at room temperature overnight, and product **5** was obtained with yield of 40%. Subsequently, compound **5** was transformed into the corresponding diacyl chloride derivative, and then reacted with 1-pyrenemethylamine, the target calix[4]arene derivative **6** was obtained in the yield of 56%. The ^1H NMR spectrum of compound **6** exhibits two doublets at 4.85 and 3.24 ppm in AB pattern with coupling constant of 13.8 Hz, corresponding to the protons of the methylene bridge, which suggests that compound **6** assumes the cone conformation[9].



(a) $BrCH_2COOEt$, K_2CO_3, CH_3CN, 18 h;
(b) $TiCl_4$, Cl_2CHOCH_3, $CHCl_3$, 19 h;
(c) $BrCH_2COOEt$, Na_2CO_3, CH_3CN, 19 h;
(d) NH_2SO_3H, $NaClO_2$, $CHCl_3$/CH_3COCH_3 (1/1), 12 h;
(e) $SOCl_2$, CH_2Cl_2, 10 h;
(f) 1-pyrenemethylamine, CH_2Cl_2, Et_3N, 12 h

Scheme 1

The selectively binding behavior of compound **6** for the alkali and alkaline earth metals (Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) was evaluated by fluorescence spectroscopy in DMSO/acetonitrile (1/9) at the concentration of 2.0×10^{-6} mol · L^{-1}. The corresponding fluorescence spectral changes are shown in Figure 1. Excited at 343 nm, free compound **6** exhibited the typical monomer and excimer emissions at 375 nm and 477 nm, respectively. The addition of 500 equivalents of alkali and alkaline earth metals to a solution of **6** did not cause appreciable changes in the fluorescence spectrum of both monomer and excimer emissions except the addition of sodium ion. Upon addition of sodium ion, the excimer emission of **6** at 477 nm was quenched too much, and concurrently, the monomer emission at 375 nm increased. That is, host compound **6** exhibits unique selective fluorescent chemosensing to Na^+ versus the other alkali and alkaline earth metal ions examined.

The fluorescence titration was further performed to give the binding ability of **6** to Na^+ by detecting the

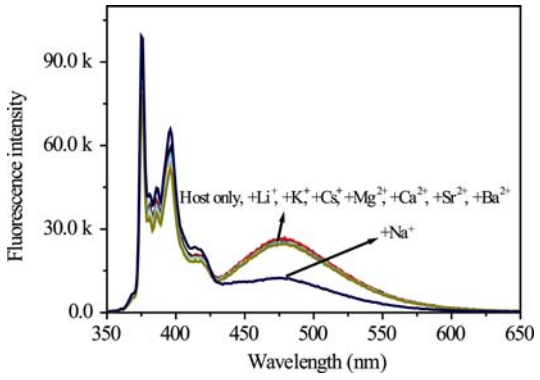


Figure 1 Fluorescence spectral changes of compound 6 (DMSO/acetonitrile (1/9), excited at 343 nm, 2.0×10^{-6} mol·L^{-1}) upon addition of 500 equivalents of alkali and alkaline earth metal ions.

emission changes trend by gradual addition of sodium ion. The inset in Figure 2 shows the dependence of the intensity of the excimer and monomer emission at 477 nm and 375 nm on Na^+, which indicates the formation of a complex between **6** and Na^+. The experimental dates could be well fitted using the nonlinear least-squares method[24] based on a "1∶1 host–guest stochiometry" model, and repeated as 1∶1 complex formation, thereby, the higher-order complexes could not be postulated. This was coincident with the reported results, and the tetraester groups at the low rim of calix[4]arene formed a 1∶1 stoichiometry complex with Na^+[10–14, 25]. We obtained the stability constant of compound **6** with sodium cation. The K_S value for the complexes was 2190 $mol^{-1} \cdot L$.

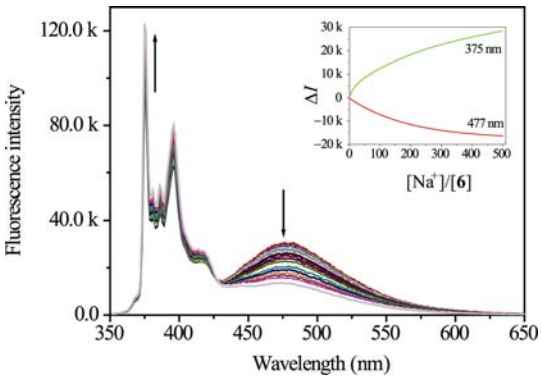
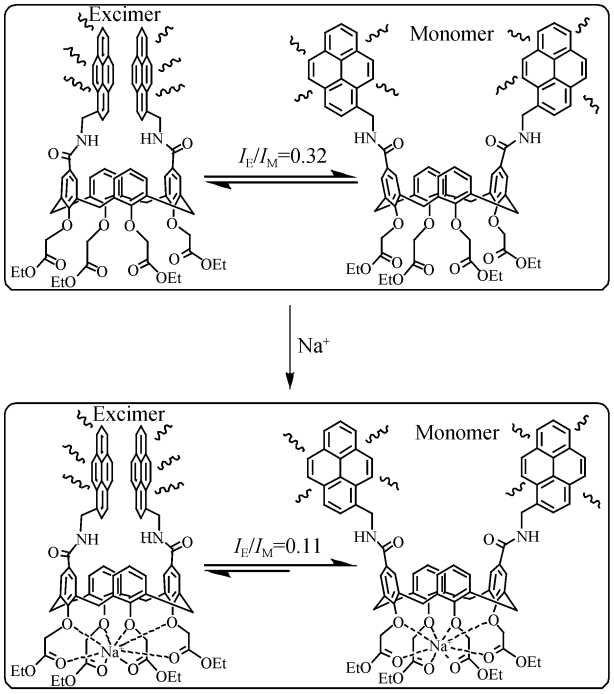


Figure 2 Fluorescence titration spectral changes of compound **6** (DMSO/acetonitrile (1/9), excited at 343 nm, 2.05×10^{-6} mol · L^{-1}) upon addition of 0 to 500 quivalents of Na^+.

The proposed model of compound **6** with Na^+ is shown in Scheme 2. In free **6**, the lower-rim tetraester groups can rotate freely in solution, thus the upper-rim pyrene rings are easy to approach each other, leading to the obvious excimer emission. But, when Na^+ is added, the tetraester carbonyls orientate inwards to encapsulate the sodium cation in the ionophoric cavity. In other words, the complexation of **6** with sodium ion induces its lower rim shrinking and upper rim extending. As a result, the collision probability of two pyrene fluorophores is reduced, and the excimer emission decreases and the monomer emission increases. It can be clearly reflected from the ratios of the excimer fluorescence intensity at 477 nm (I_E) to the monomer fluorescence intensity at 375 nm (I_M) in the absence and presence of sodium ion. The I_E/I_M value of free compound **6** is 0.32, and the I_E/I_M value decreases to 0.11 upon addition of 500 equivalents of sodium ion. During the course of the complexation with sodium ion, compound **6** acts as a molecular tweezer that the on-off process is manipulated by sodium ion. Compared with the fluorescent chemosensors based on calix[*n*]arenes reported previously,[10–16] compound **6** exhibits high selectivity to sodium ion, although with lower binding affinity.



Scheme 2 The reasonable model for fluorescence change of compound 6 before and after complexation with Na^+.

4 Conclusion

In summary, a novel highly selective fluorescent chemosensor for sodium ion was synthesized based on the scaffold of calix[4]arene. Among the alkali and alkaline earth metal ions examined, only the addition of sodium ion can induce the fluorescence change of host compound **6** that the excimer emission decreased, and the monomer emission increased. The fluorescent chemosensing process is attributed to the complexation-induced conformational change of calixarene framework.

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