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Synthesis and Fluorescence Sensing Properties of Calix[4]arenes Containing Fluorophores

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New fluoroionophores 4 and 5 derived from calix[4]arene triester monoacid chloride with 2-amino-4-(1,3-benzothiazol-2-yl)phenol and 4-aminoquinaldine, respectively, have been synthesized. A preliminary test showed that the fluorescence intensity of 5 was very low, so only 4 was subjected to cation recognition investigation. In methanol, the fluorescence intensity of 4 was quenched by Na^+. The fluorescence intensity decreased linearly with increasing Na^+ concentration with a stability constant of $\log K = 2.91 \pm 0.08$. No significant response was observed for other alkali metal ions under the same experimental conditions.

Keywords: Calixarene; Fluorescence sensor

INTRODUCTION

The alkali metal ions Na^+ and K^+ are found in human organisms and are of importance in ion channels and ion pumps [1]. Disorders in the metabolism of these ions can severely affect the state of health. Detection of these metal ions is therefore crucial in clinical diagnosis and there are numerous detection techniques in use today. Spectrofluorometry is one such technique that measures emission and excitation intensities of a fluorescent molecule [2,3]. An approach to the problem was the introduction of metal chelating groups into fluorescent dyes with the aim of forming derivatives that would undergo changes in fluorescence intensity and/or wavelength upon formation of metal complexes [4]. As changes in their photophysical properties can be observed upon ion binding, they offer powerful tools for ion recognition [5–11].

Calixarene derivatives have received much attention as cation, anion and neutral molecule receptors and as building blocks in the design of fluoroionophores [12]. Calix[4]arene triesters that exhibit high selectivity towards Na^+ have been synthesized [12]. Shimizu *et al*. [13] found that calix[4]arene triesters containing chromophores showed selectivity towards Li^+. Jin [14] has synthesized calix[4]arenes containing pyrene derivatives at the lower rim; these compounds were highly selective towards Na^+. Benco *et al*. [15] showed that an optode based on aminorhodamine covalently linked to a calix[4]arene triester fluoroionophore was also selective towards Na^+.

We have focused on synthesizing alkali metal ion receptors using calix[4]arene as a building block. Thiazole has often been used as a signaling unit for the construction of chromogenic and fluorogenic ionophores because of its high quantum yield and ease of synthesis [10]. In this paper, we describe the synthesis of a new calix[4]arene fluoroionophore derivatized from the thiazole function. The binding abilities of the synthesized compounds towards alkali metal ions were investigated.

RESULTS AND DISCUSSION

Synthesis

The synthesis of 2-amino-4-(1,3-benzothiazol-2-yl)-phenol, **1c**, is shown in Scheme 1. Nitration of *p*-hydroxybenzaldehyde using acetic acid and nitric acid in acetonitrile resulted in a brown solid **1a** (93% yield). Condensation of **1a** with *o*-aminothiophenol

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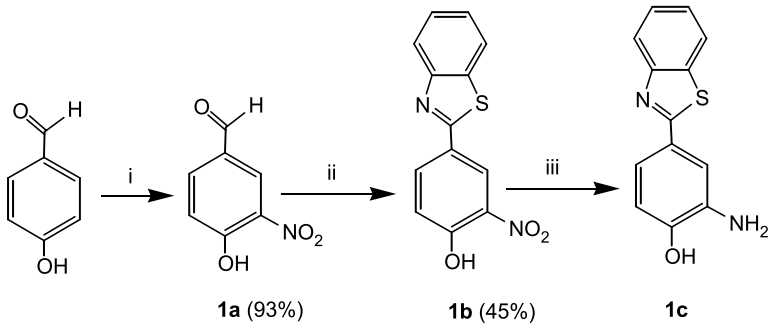
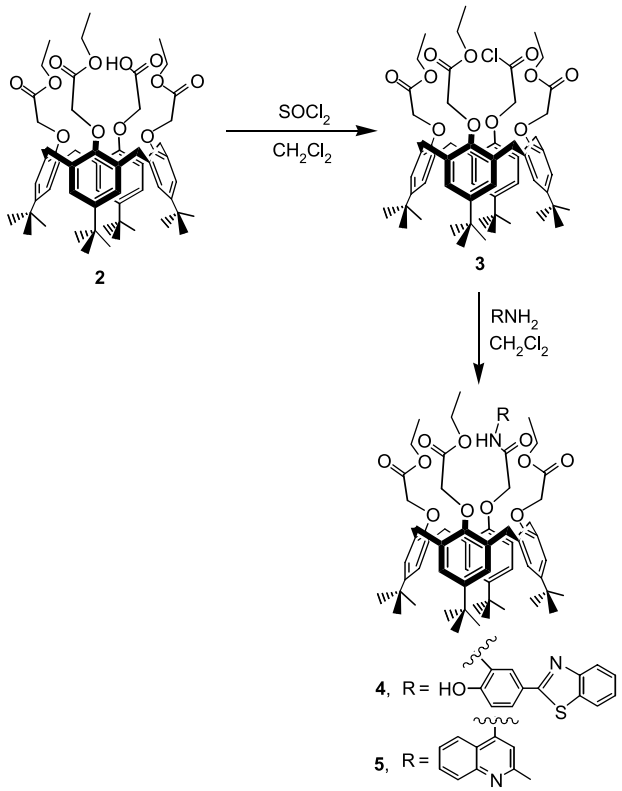


SCHEME 1 Reagents and conditions: (i) $HOAc/HNO_3$, CH_3CN; (ii) *o*-aminothiophenol, THF; (iii) Raney Ni, $NH_2NH_2{\cdot}H_2O$, $EtOAc/CH_3OH$.

in tetrahydrofuran gave **1b** as a yellow–green solid (45% yield). Reduction of **1b** by Raney nickel and hydrazine yielded **1c** as a white solid. To avoid decomposition, **1c** was used immediately for further reaction.

Syntheses of **4** and **5** are illustrated in Scheme 2. Compound **2**, *p-tert*-butylcalix[4]arene triester monoacid chloride, was prepared as described previously [16–18]. Chlorination of **2** with thionyl chloride resulted in **3**. Compound **3** was further reacted with **1c** immediately to produce **4** in 47% yield. Reaction between **3** and commercially available 4-aminoquinaldine produced **5** in 25% yield. Compound **5** was synthesized to compare different selectivities towards alkali metal ions. Compounds **4** and **5** are very soluble in CH_2Cl_2 and CH_3OH, and slightly soluble in CH_3CN.



SCHEME 2 Synthesis of compounds **4** and **5**.

Complexation Studies of 4 and 5 Towards Alkali Metal Ions

Compounds **4** and **5** contained 5-(1,3-benzothiazol-2-yl)-2-hydroxylaminobenzene and 4-aminoquinaldine, respectively, as fluorophores. Cation recognition through ion-dipole interactions can be monitored by the cation complexation-induced change in emission intensity by fluorimetric titration.

Quantum yields of free **4** and **5** are 0.67 and 0.01, respectively, referred to anthracene [19]. Fluoroionophore **5** displays a fluorescence emission band at 450 nm ($\lambda_{ex} = 370$ nm). A preliminary test showed that the fluorescence emission intensity of **5** was very low. Therefore, addition of alkali metal ions to a solution of **5** resulted in only a negligible change in its fluorescence spectra. Hence only **4** was subjected to further investigation.

Fluoroionophore **4** showed a fluorescence emission around 442 nm ($\lambda_{ex} = 370$ nm), which is typical of the benzothiazolyl group as shown in Fig. 1 [10]. Upon addition of Na^+(9.7×10^{-5} to 6.8×10^{-4} M) to the solution of **4** in methanol (5.1×10^{-6} M), the fluorescence intensity of **4** decreased (Fig. 2). The ^1H NMR spectrum of **4** showed that signals for NH, OH and aromatic protons on the benzyl benzothiazol group shifted upfield upon complexation with Na^+ (Table I). Upon addition of up to 200 equivalents of alkali metal ions, only Na^+ showed a fluorescence quenching effect (Fig. 3). Measurement of fluorescence intensity $[I_F^0/(I_F - I_F^0)]$ as a function of the inverse of Na^+ concentration fit a linear relationship, indicating a 1:1 stoichiometry for the $\mathbf{4} \cdot Na^+$ complex [20,21].

The stability constant ($\log K$) of the $\mathbf{4} \cdot Na^+$ complex was calculated to be 2.91 ± 0.08 using the method described by Valeur and coworkers [4]. The sensitivity of **4** towards Na^+ was found to be 83 au/mM. Other alkali metal ions such as K^+ and Li^+ show almost negligible fluorescence changes at 442 nm.

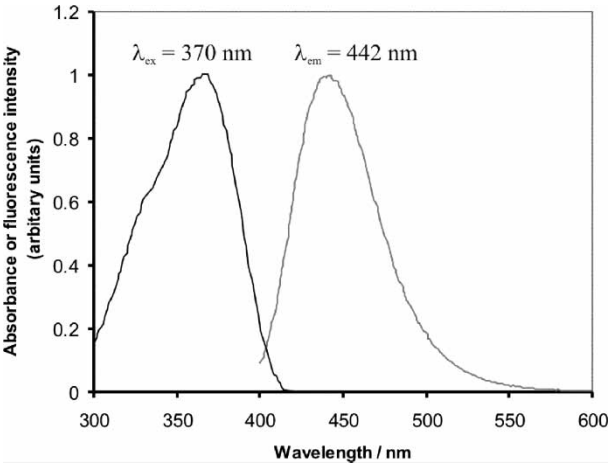


FIGURE 1 Absorption and emission spectra of **4** in MeOH.

The possible mechanism for the fluorescence quenching phenomenon can be rationalized as a reverse PET1 mechanism [22]. The free fluoroionophore **4** undergoes intramolecular hydrogen bonding between RNH—(C═O)— and the adjacent O-atom of the carbonyl ester function. Upon binding Na^+, the intramolecular hydrogen bond is broken, as shown in Fig. 4, and the fluorescence is quenched, probably by this mechanism. A similar fluorescence quenching effect was reported by Murakami and Shinkai [23].

CONCLUSION

We have synthesized fluoroionophores **4** and **5** consisting of a calix[4]arene triester and amide. The carbonyl oxygens on **4** formed a cavity that was selective to sodium ions while the amide nitrogen played a major role in signaling. The rupture of intramolecular hydrogen bonding by sodium ion complexation may cause the quenching of the fluorescence intensity of **4**. Other alkali metal ions did not fit into the cavity of **4** resulting in negligible signal changes.

TABLE I Chemical shifts of ^1H NMR signals of compound **4** (in $CDCl_3$) in the free form and in the presence of Na^+

	Chemical shift (ppm)	
	Free **4**	**4** + Na^+
ArOH	10.11	9.86
NH	9.44	9.29
m-ArOH	8.48	8.25
H_A, $ArCH_2Ar$	5.10, 4.95	4.77, 4.71
H_B, $ArCH_2Ar$	3.30	3.49, 3.41
Ar-calix	6.92, 6.81	7.14
$OCH_2(C{=}O)$	4.83, 4.73	4.90

EXPERIMENTAL

General Procedure

NMR spectra were recorded on a Varian 400 MHz spectrometer. All samples were dissolved in deuterated chloroform. Chemical shifts were recorded in parts per million (ppm) using a residue proton solvent as internal reference. Elemental analysis was carried out on CHNS/O analyzer (Perkin Elmer PE 2400 series II). EI mass spectra were recorded on a Micromass Platform II. Absorption spectra were measured on a Varian Cary 50 UV–vis

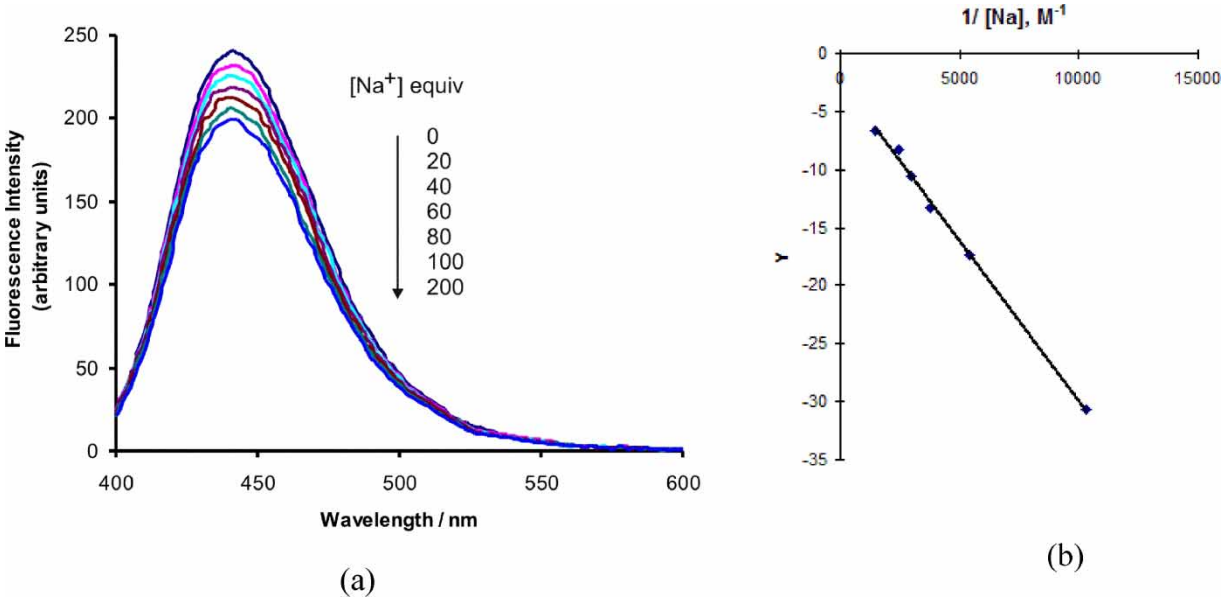


FIGURE 2 (a) Fluorescence spectra of fluoroionophore **4** (5.1×10^{-6} M in methanol) as a function of $[Na^+]$. (b) Plot of $Y = \{[I_F^0/(I_F - I_F^0)]\}$ vs. $1/[Na^+]$.

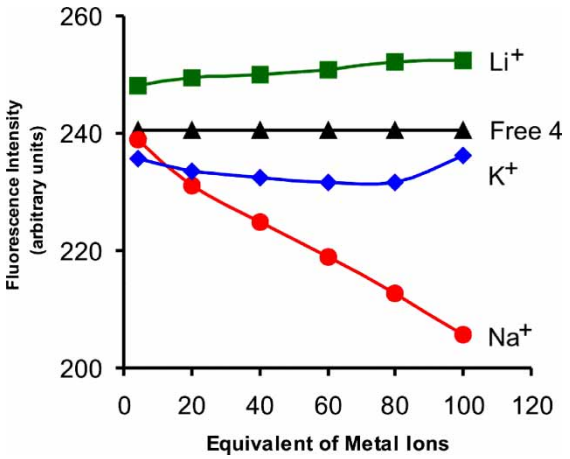


FIGURE 3 Change in fluorescence intensity of fluoroionophore **4** (5.1×10^{-6} M in methanol) upon addition of alkali metal ions up to 100 equiv.

spectrophotometer and fluorescence spectra were obtained on a Varian Cary Eclipse spectrofluorometer.

Unless otherwise specified, the solvent and all materials were reagent grades purchased from Fluka, BDH, Aldrich, Carlo Libra, Merck or Lab Scan and were used without further purification. Commercial-grade solvents such as acetone, dichloromethane, hexane, methanol, toluene and ethyl acetate were purified by distillation before use. Acetonitrile, dimethylformamide and dichloromethane were dried over calcium hydride and freshly distilled under nitrogen before use.

Column chromatography was carried out using silica gel (Kieselgel 60, 0.063–0.200 nm, Merck). All manipulations were carried out under a nitrogen atmosphere. Methanol and ethanol for fluorescence measurements (AR grade, Merck) were dried over molecular sieves.

Synthesis and Characterization

Preparation of Compound 1c

A mixture of *p*-hydroxybenzaldehyde (2.446 g, 20.0 mmol), acetic acid (20 mL), nitric acid (1.50 mL) and acetonitrile (40 mL) was refluxed for 3 h. After cooling to room temperature, the solvent was evaporated off under reduced pressure. Ethyl acetate (30 mL) and water (30 mL) were added to the residue and the aqueous solution was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was dried under reduced pressure to obtain a brown solid **1a** (93% yield). Compound **1a** (0.187 g, 1.11 mmol) was reacted with *o*-aminothiophenol (0.16 mL, 1.30 mmol) by refluxing for 16 h in tetrahydrofuran (20 mL). The solvent was evaporated off under reduced pressure. The crude product was purified by column chromatography (SiO_2, hexane/dichloromethane 1:3) to give **1b** as a yellow–green solid (45% yield). Raney nickel (0.338 g, 5.78 mmol) was added to the solution of **1b** (0.174 g, 0.64 mmol) in 19 mL of ethyl acetate and 14 mL of methanol. Hydrazine (1.30 mL) was then added with occasional stirring at room temperature. The mixture was then refluxed for 2 h. After cooling to room temperature, the suspension was filtered off and washed with methanol. The filtrate was evaporated to dryness under reduced pressure. The residue was taken up with dichloromethane (25 mL) and extracted with water (5 × 25 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give **1c** as white solid. Compound **1c** was air and moisture sensitive and was used immediately for further reaction.

1a: ^{1}H NMR (400 MHz, $CDCl_3$): δ (in ppm) 10.05 (s, 1H, ArCHO), 8.68 (s, 1H, ArOH), 8.18 (d, $J = 7$, 1H, Ar), 7.37 (d, $J = 8$, 1H, Ar), 7.35 (s, 1H, Ar).

1b: ^{1}H NMR (400 MHz, $CDCl_3$): δ (in ppm) 10.85 (s, 1H, $OHArNO_2$), 8.50 (s, 1H, $ArNO_2$), 8.38 (d, $J = 7$, 1H, $ArNO_2$), 8.10 (d, $J = 8$, 1H, $ArNO_2$), 7.55 (d, $J = 7$, 1H, Ar), 7.54 (t, $J = 7$, 1H, Ar), 7.36 (t, $J = 8$, 1H, Ar), 7.33 (d, $J = 9$, 1H, Ar).

Preparation of Compounds 4 and 5

Under a nitrogen atmosphere, 4-*tert*-butylcalix[4]-arene triester monoacid chloride, **2**, (0.335 g, 0.35 mmol) was dissolved in thionyl chloride (2.5 mL) and refluxed for 30 min. Excess thionyl

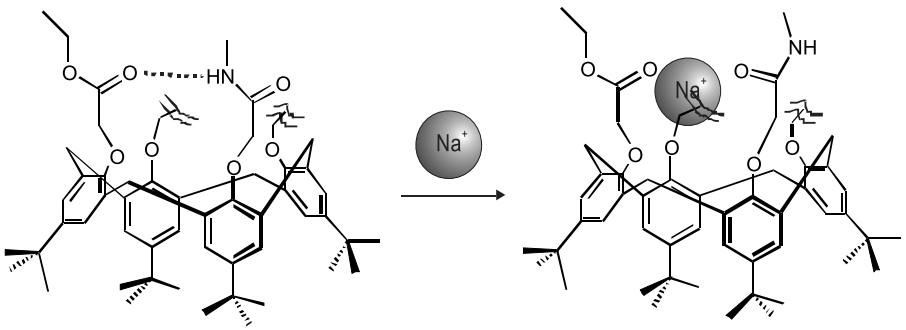


FIGURE 4 Possible structures of free **4** and **4**·Na^+ (two ester substituents are omitted for clarity).

chloride was evaporated off. The residue was dissolved in dried dichloromethane (3 mL) and the solution evaporated to remove excess thionyl chloride. The white crystalline residue of **3** was dissolved in dry methylene chloride (10 mL). The solution was then transferred via a cannula to a stirred solution of fluorophore **1c** (0.162 g, 0.67 mmol) and triethylamine (0.40 mL) in dry dichloromethane previously cooled to 0°C. Stirring was continued for 2 h at 0°C and then 16 h at room temperature under nitrogen. Dichloromethane (30 mL) was added and the solution was washed with 2 M hydrochloric acid (3×25 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated off under reduced pressure. The crude product was purified by column chromatography (SiO_2, 10–25% methanol in dichloromethane) to give fluoroionophore **4** as a light brown solid (0.195 g, 47%).

Compound **5** (0.089 g, 25%) was synthesized by a similar procedure to compound **4**, but fluorophore **1c** was replaced by 4-aminoquinaldine.

Characterization For 4

δ_H ($CDCl_3$) 10.11 (s, 1H, ArOH), 9.44 (s, 1H, NH), 8.48 (s, 1H, *m*ArOH), 8.08 (d, $J = 8$ Hz, 1H, ArOH), 7.93 (d, $J = 8$ Hz, 1H, ArOH), 7.53 (t, $J = 8$ Hz, 1H, ArH), 7.42 (t, $J = 8$ Hz, 1H, ArH), 7.18 (d, $J = 9$ Hz, 1H, ArH), 6.94 (d, $J = 6$ Hz, 1H, ArH), 6.92, 6.81 (s, 8H, Ar-calix), 5.10(d, $J = 16$ Hz, H_A, $ArCH_2Ar$), 4.95 (d, $J = 13$ Hz, H_A, $ArCH_2Ar$), 4.83 (s, 2H, OCH_2), 4.75 (d, $J = 14$ Hz, $2H_A$, $ArCH_2Ar$), 4.73 (s, 6H, OCH_2), 4.67 (d, $J = 16$ Hz, H_B, $ArCH_2Ar$), 4.27 (q, $J = 7$ Hz, 2H, CH_2CH_3), 4.03–3.91 (m, 4H, CH_2CH_3), 3.30 (d, $J = 14$ Hz, $3H_B$, $ArCH_2Ar$), 1.30 (t, 3H, CH_3), 1.18 (s, 9H, *t*-Bu), 1.08 (s, 27H, *t*-Bu), 1.07 (t, $J = 8$ Hz, 6H, CH_3). MS: *m/z* 1212 [$(M + Na^+)$]. Anal. Calcd for $C_{71}H_{84}N_2O_{12}S$(%): C, 71.69; H, 7.12; N, 2.36. Found C, 71.66; H, 7.17; N, 2.35.

Characterization For 5

δ_H($CDCl_3$) 9.90 (s, 1H, NH), 8.19 (d, $J = 8$ Hz, 1H, Ar), 8.12 (d, $J = 8$ Hz, 1H, Ar), 7.74 (t, $J = 7$ Hz, 1H, Ar), 7.70 (t, $J = 9$ Hz, 1H, Ar), 7.18 (s, 1H, *H*ArN), 6.87, 6.81 (s, 8H, Ar-calix), 4.97 (s, 2H, OCH_2), 4.81 (s, 6H, OCH_2), 4.76 (m, 4H, CH_2ArCH_2), 3.81 (m, 2H, CH_2CH_3), 3.66 (m, 4H, CH_2CH_3), 3.46 (m, 4H, CH_2ArCH_2), 2.80 (s, 3H, CH_3ArN), 1.28 (s, 9H, *t*-Bu), 1.20 (s, 27H, *t*-Bu), 1.00 (t, $J = 7$ Hz, 6H, CH_3), 0.90 (t, $J = 7$ Hz, 3H, CH_3). MS: *m/z* 1128 [$(M + Na^+)$]. Anal. Calcd for $C_{68}H_{84}N_2O_{11}{\cdot}CH_2Cl_2$(%): C, 69.66; H, 7.29; N, 2.36. Found C, 70.89; H, 7.61; N, 2.53.

Fluorescence Titrations

Typically, a stock solution of 5.1×10^{-6} M of a ligand was prepared in 0.01 M tetrabutylammonium perchlorate in methanol. A stock solution of 2.04×10^{-3} M of an alkali metal ion (Li^+, Na^+ and K^+ as perchlorate salt) in dried methanol was prepared in a 25 mL volumetric flask.

Fluorescence spectra of all ligands and cation complexes were recorded at ambient temperature. The solution of a guest was added directly to 2.00 mL of 5.1×10^{-6} M ligand in a cuvette with a microburette and stirred for 40 s. Fluorescence spectra were measured after each addition.

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