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# A highly selective fluoroionophore for the detection of lithium ions

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**Abstract**

*N*-(9-methylanthracene)-25,27-bis(1-propyloxy)-4-*tert*-butylcalix[4]arene-azacrown-3 (**I**) was synthesized and tested as a fluoroionophore for the selective detection of lithium cations. The efficiency of photoinduced electron transfer in this fluoroionophore is sensitive to the presence of lithium ions. When exposed to lithium ions in a 75:25 (v/v) dichloromethane/THF solvent mixture, the molecule acted as an "off–on" fluorescence switch exhibiting a >106-fold enhancement in fluorescence emission intensity. Selectivity studies demonstrated that **I** effectively discriminates against sodium and potassium: $\log K_{\mathrm{Li,Na}} = -3.8$ and $\log K_{\mathrm{Li,K}} = -2.3$.


*Keywords:* Fluoroionophore; Selectivity; Lithium ions

## 1. Introduction

The use of crown ethers that are covalently-bound to calix[4]arenes to selectively complex with specific ions has been studied extensively [1–15]. Casnati et al. reported on the selective binding of potassium ions to calix[4]arene-crown-5 structures, noting that the potassium/sodium selectivity was dependent on the calix[4]arene-crown conformation (i.e., cone, partial cone or 1,3-alternate) [1,2]. It was shown through these studies that the calix[4]arene-crown architecture provides an ideal framework for the development of highly selective hosts. For example, the calix[4]arene-crown-5 structures are able to achieve higher selectivities than that of valinomycin, a natural antibiotic that is used extensively as a highly selective potassium ionophore [1,2].

In the calix[4]arene-crown structures, the ion binding event occurs in a relatively rigid, pre-organized pocket with electrostatic stabilization provided by the oxygen groups in the crown as well as by cation–π interactions between the ion and the phenolic aromatic rings of the calixarene. The rigidity of the binding pocket combined with the possibility of varying the size of the pocket by changing the size of the crown through straightforward synthetic methods suggested to us the possibility of developing a systematic series of highly selective alkali metal ionophores and fluoroionophores that are based on a simple size-fit criterion. To this end we recently reported on the synthesis and complexation studies of a fluoroionophore for the detection of potassium ions that was based on a 1,3-alternate calix[4]arene group covalently linked to an azacrown ether that is *N*-substituted with a fluorescent 9-anthryl group [16]. This fluoroionophore acts as an "off–on" fluorescence switch that is triggered by ion complexation, i.e., in the absence of cation, the tertiary amine group quenches the anthryl excited singlet state by photoinduced electron transfer (PET), while in the presence of complexed cation, a partial removal of electron density from the nitrogen lone pair occurs and as a result disrupts the PET process, thereby switching on the anthryl fluorescence emission. Upon complete complexation with potassium (1:1 ion–fluoroionophore stoichiometry) an 8.5-fold enhancement in the fluorescence quantum yield was observed. Our studies demonstrated that the fluoroionophore is highly selective for potassium over other alkali metal cations, with excellent selectivity over sodium and lithium ($\log K_{\mathrm{K,Na}} \sim \log K_{\mathrm{K,Li}} = -3.5$), behavior that correlates well with the electrochemical results of the parent calix[4]arene upon which the structure was based. In order to confirm that varying the size of the binding site by changing the crown component of the molecule can provide a selective ionophore we have undertaken in this present study the development of an anthracene-containing calix[4]arene-azacrown-3 molecule for the optical detection of lithium ions.

High selectivity in ionophores and fluoroionophores is particularly important for the accurate detection of lithium ions in physiological media since ions that may interfere

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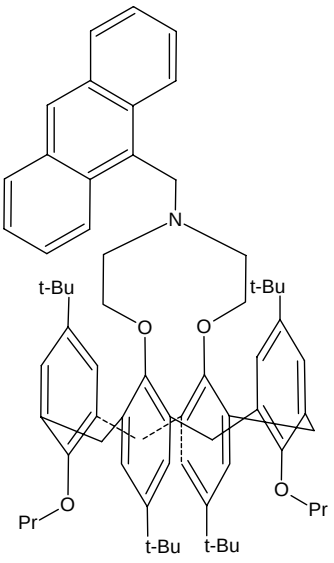
with lithium ion complexation, including sodium, are present at significantly higher concentrations. It is generally accepted that for an ionophore to accurately measure lithium ion concentration, it must have a selectivity ratio of lithium over sodium that is greater than $10^4$ [17]. Earlier studies of lithium ionophores involved a variety of crown ethers, including dibenzo-14-crown-4 [18]. When incorporated into an ion selective electrode (ISE) this system was found to be ~10 times more selective for lithium than sodium ions. In another study, a 10-fold improvement in lithium/sodium selectivity was attained by the use of bulky substituents on a series of lipophilic derivatives of 13- through 16-crown-4 ethers [19]. It was suggested that these substituents sterically hinder the complexation of larger cations while at the same time reducing the tendency of crown ethers to form 2:1 sandwich-type complexes with larger cations. A similar improvement, $\log K_{Li,Na} = -2.15$, was observed with the covalent linkage of benzyloxymethyl groups to 13- and 14-crown-4 rings [20]. More recently, a marked enhancement in lithium/sodium selectivity was achieved with the addition of a decalino subunit to a 14-crown-4, $\log K_{Li,Na} = -3.0$ [21]. A similar system exhibited an estimated selectivity $\log K_{Li,Na} < -4$ when incorporated into an optode [22]. However, when employed in an ISE, the same ionophore attained a significantly lower selectivity, $\log K_{Li,Na} = -2.5$ [21].

We report here the synthesis and testing of **I**. Compound **I** consists of a calix[4]arene group combined with an azacrown-3 moiety to create a considerably smaller binding pocket than in the calix[4]arene-azacrown-5 potassium-selective fluoroionophore we studied earlier. Our results show that **I** is highly selective for lithium over sodium and potassium. Described here are synthetic details, fluorescence results and the results of selectivity studies.




**(I)**

## 2. Experimental

### 2.1. General

Mass spectra were performed by Bayer HealthCare (Medfield, MA). Melting point data was obtained using a Mel–Temp capillary melting point apparatus and is not corrected. $^1$H and $^{13}$C NMR spectra were recorded with a Bruker Avance 400 in $CDCl_3$. All solvents and reagents were used as supplied from Aldrich unless stated otherwise. 4-*tert*-Butylcalix[4]arene was purchased from Fluka (Scheme 1).

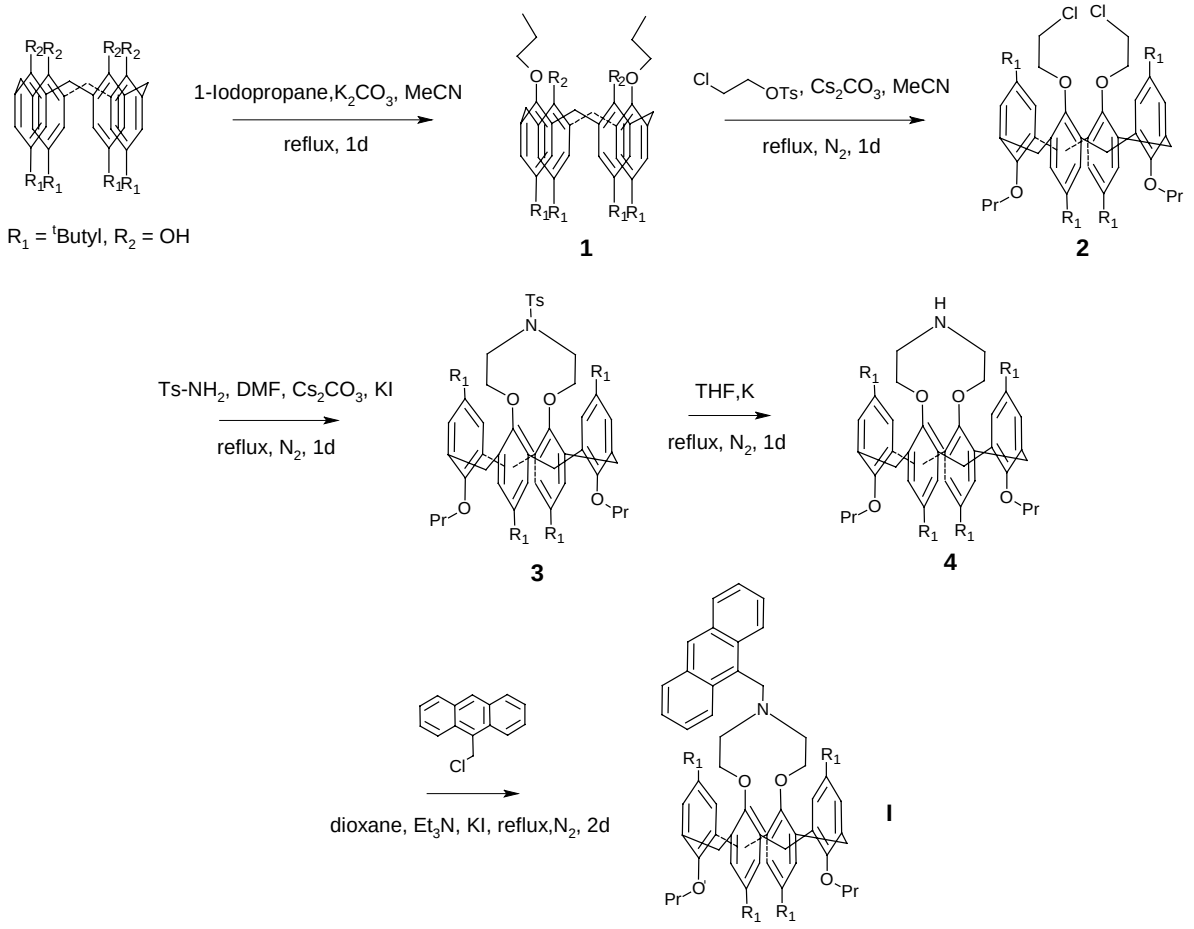
### 2.2. Synthesis of ***I***

#### 2.2.1. Dipropyl-4-tert-butylcalix[4]arene (*1*): CAS [137693-26-6]

In a 500 ml round bottom flask 6.489 g 4-*tert*-butylcalix-[4]arene (10 mmol), 4.10 g 1-iodopropane (24.1 mmol) and 4.14 g (30 mmol) $K_2CO_3$ were suspended in 300 ml dry acetonitrile and heated at reflux for 24 h. The solvent was removed in vacuo and 50 ml 2 N HCl and 50 ml $CH_2Cl_2$ were added and the phases were separated. The aqueous phase was extracted two times with 30 ml $CH_2Cl_2$, the organic phases were combined, dried with $Na_2SO_4$ and the solvent removed in vacuo. The crude product was recrystallized from methanol/$CH_2Cl_2$ (5:1) and gave 5.57 g (76%) of dipropyl-4-*tert*-butylcalix[4]arene (**1**) as white crystals. $^1$H NMR (400 MHz, $CDCl_3$); $\delta$ 1.03 (s, 18H,), $\delta$ 1.26 (s, 24H), 2.03 (m, 4H), 3.31 (d, 4H, $J = 12.9$ Hz), 3.95 (t, 4H, $J = 6.4$ Hz), 4.30 (d, 4H, $J = 12.8$ Hz), 6.88 (s, 4H, Ar), 6.93 (s, 4H, Ar), 8.00 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$); $\delta$ 11.3 ($CH_3$), 23.9 ($CH_2$), 31.5, 32.1 ($CH_3$), 32.3, 34.2, 34.4 ($CH_2$), 78.5 (C), 125.5, 125.9, 128.1, 133.3, 141.6, 147.1, 150.4, 151.3 (Ar).

#### 2.2.2. Dipropyl-(di-2-chloroethoxy)-4-tert-butylcalix[4]arene (*2*)

To a solution of 7.33 g (10 mmol) dipropyl-4-*tert*-butylcalix[4]arene (**1**) in 300 ml dry acetonitrile, 9.39 g (40 mmol) 2-chloroethyl-*p*-toluenesulfonate and 9.77 g (30 mmol) $Cs_2CO_3$ were added and the mixture was refluxed under nitrogen for 24 h. The solvent was removed in vacuo and 50 ml 2N HCl and 50 ml $CH_2Cl_2$ were added and the phases were separated. The aqueous phase was extracted two times with 30 ml $CH_2Cl_2$, the organic phases were combined, dried with $Na_2SO_4$ and the solvent removed in vacuo. The crude product was recrystallized from methanol/$CH_2Cl_2$ (3:1) and gave 4.89 g (57%) of dipropyl-(di-2-chloroethoxy)-4-*tert*-butylcalix[4]arene (**2**) as white crystals. $R_f = 0.2$ (10:1 hexane/$CH_2Cl_2$). mp dec. 260 °C. $^1$H NMR (400 MHz, $CDCl_3$); $\delta$ 0.55 (t, 6H, $J = 7.5$ Hz), 0.93 (m, 4H), 1.26 (s, 18H), 1.31 (s, 18H), 2.60 (m, 4H), 3.30 (t, 4H, $J = 7.5$ Hz), 3.52 (m, 4H), 3.83 (m, 8H), 6.95 (s, 4H), 6.97 (s, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$); $\delta$ 10.1 ($CH_3$), 22.4 ($CH_2$),




Scheme 1.

31.5, 31.7 ($CH_3$), 34.9, 34.0, 39.1, 40.1, 68.8, 71.3 ($CH_2$), 125.2, 125.6, 132.7, 133.0, 144.5, 144.6, 153.3, 155.0 (Ar). ESI MS *m/z* (%) calcd. for $C_{54}H_{75}Cl_2O_4$ [$M + H^+$] 857.48 found 857.40(100), calcd. for [$M + Na^+$] 879.48 found 879.43 (95), calcd. for [$M + K^+$] 895.45 found 895.29 (43).

### 2.2.3. *N-Tosyl 25,27-bis(1-propyloxy)-4-tert-butylcalix[4]arene-azacrown-3 (**3**)*

A solution of 2.58 g (3 mmol) dipropyl-(di-2-chloroethoxy)-4-*tert*-butylcalix[4]arene (**2**), 0.513 g (3 mmol) *p*-toluenesulfonamide, 4.89 g (15 mmol) $Cs_2CO_3$ and 0.17 g (1 mmol) KI in 150 ml dry DMF was heated at reflux under nitrogen for 24 h. The solvent was removed in vacuo and 50 ml 2N HCl and 50 ml $CH_2Cl_2$ were added and the phases were separated. The aqueous phase was extracted two times with 30 ml $CH_2Cl_2$, the organic phases were combined, dried with $Na_2SO_4$ and the solvent removed in vacuo. The crude compound was recrystallized from methanol/$CH_2Cl_2$ (4:1) and gave 1.45 g (51%) of N-Tosyl-25,27-bis(1-propyloxy)-4-*tert*-butylcalix[4]arene-azacrown-3 (3) as white crystals. $R_f$ = 0.7 ($CH_2Cl_2$). mp = 250–252 °C. $^1$H NMR (400 MHz, $CDCl_3$); $\delta$ 0.56 (t, 6H, $J$ = 7.5 Hz), 0.68 (m, 4H), 1.11 (s, 18H), 1.26 (s, 18H), 2.20 (m, 4H), 2.39 (s, 3H), 3.14 (m, 4H), 3.36 (m, 4H), 3.94 (m, 8H), 7.04 (s, 8H), 7.19 (d, 2H, $J$ = 8.0 Hz), 7.48 (d, 2H, $J$ = 8.2), $^{13}$C NMR (100 MHz, $CDCl_3$); $\delta$ 10.1 ($CH_3$), 21.9 ($CH_2$), 31.7, 31.9 ($CH_3$), 34.2, 40.1 ($CH_2$), 50.7 ($CH_3$), 72.5, 74.2 ($CH_2$), 126.5, 126.8, 127.2, 130.0, 132.5, 134.2, 137.0, 143.0, 144.0, 145.7, 155.0, 155.6 (Ar). ESI MS *m/z* (%) calcd. for $C_{61}H_{81}NO_6SNa$ [$M + Na^+$] 978.57 found 978.73 (94).

### 2.2.4. *25,27-Bis(1-propyloxy)-4-tert-butylcalix[4]arene-azacrown-3 (**4**)*

To a solution of 1.2 g (1.25 mmol) *N*-tosyl-25,27-bis-(1-propyloxy)-4-*tert*-butylcalix[4]arene-azacrown-3 (**3**) in 80 ml dry THF was carefully added 1 g potassium metal under nitrogen. The mixture was heated at reflux for 24 h, at which temperature the potassium was molten, and then allowed to cool to rt. The main excess of potassium was removed and the rest was carefully hydrolyzed with water. The solvent was removed in vacuo and 50 ml 1 N KOH and 50 ml $CH_2Cl_2$ were added and the phases were separated. The aqueous phase was extracted two times with 30 ml $CH_2Cl_2$, the organic phases

were combined, dried with $Na_2SO_4$ and the solvent removed in vacuo. The crude compound was recrystallized from methanol/$CH_2Cl_2$ (4:1) and gave 0.82 g (82%) of 25,27-bis(1-propyloxy)-4-*tert*-butylcalix[4]arene-azacrown-3 (**4**) as white crystals. $R_f$ = .15 (50:1, $CH_2Cl_2$/$Et_3N$). mp = 97–98 °C. $^1$H NMR (400 MHz, $CDCl_3$); $\delta$ 0.55 (t, 6H, $J$ = 7.5 Hz), 0.81 (m, 4H), 1.23 (s, 18H), 1.27 (s, 18H), 1.89 (m, 4H), 3.10 (m, 4H), 3.26 (m, 4H), 3.95 (m, 8H), 5.30 (s, 1H), 6.95 (s, 4H), 6.99 (s, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$); $\delta$ 10.0 ($CH_3$), 22.0 ($CH_2$), 31.5, 31.6 ($CH_3$), 33.9, 34.0, 39.8, 47.8, 68.1, 72.7 ($CH_2$), 125.9, 126.0, 132.4, 133.1, 143.9, 144.9, 154.0, 155.7 (Ar). ESI MS *m/z* (%) calcd. for $C_{54}H_{76}NO_4$ [$M + H^+$] 802.56 found 802.52 (100).

#### 2.2.5. *N-(9-methylanthracene)-25,27-bis(1-propyloxy)-4-tert-butylcalix[4]arene-azacrown-3 (**I**)*

A mixture of 200 mg (0.25 mmol) 25,27-bis(1-propyloxy)-4-*tert*-butylcalix[4]arene-azacrown-3 (**4**), 85 mg (0.37 mmol) 9-(chloromethyl)anthracene, 75 mg (0.75 mmol) triethylamine and 17 mg (0.1 mmol) KI in 80 ml of dry dioxane was refluxed for 48 h under nitrogen and protected from light. The solvent was removed in vacuo and 50 ml 2N KOH and 50 ml $CH_2Cl_2$ were added and the phases were separated. The aqueous phase was extracted two times with 30 ml $CH_2Cl_2$, the organic phases were combined, dried with $Na_2SO_4$ and the solvent removed in vacuo. Eighty milligrams of the crude product was purified on preparative TLC using $CH_2Cl_2$ /$Et_3N$ (50:1) ($R_f$ = 0.25). This fraction was almost pure and yielded after recrystallization from methanol/$CH_2Cl_2$ (4:1) 26 mg (31%) of the pure *N*-(9-methylanthracene)-25,27-bis(1-propyloxy)-4-*tert*-butylcalix[4]arene-azacrown-3 as slightly yellow crystals. mp dec. 240 °C. $^1$H NMR (400 MHz, $CDCl_3$); $\delta$ 0.55 (t, 6H, $J$ = 7.4), 0.70 (m, 4H), 1.10 (s, 18H), 1.27 (s, 18H), 1.70 (m, 4H), 3.15 (m, 4H), 3.52 (m, 4H), 4.01 (m, 8H), 4.06 (s, 2H), 7.00 (s, 4H), 7.05 (s, 4H), 7.40 (m, 4H), 7.92 (m, 2H), 8.20 (m, 2H), 8.31 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$); $\delta$ 10.2 ($CH_3$), 21.9 ($CH_2$), 31.8, 31.9 ($CH_3$), 34.2, 34.3, 40.2, 49.7, 51.4, 70.2, 74.5 ($CH_2$), 125.1, 125.6, 125.7, 126.6, 126.8, 127.3, 129.1, 131.5, 131.7, 131.8, 132.2, 134.3 143.6, 145.3, 155.5, 155.9 (Ar). ESI MS *m/z* (%) calcd. for $C_{69}H_{86}NO_4$ [$M + H^+$] 992.63 found 992.69 (82).

### 2.3. Fluorescence measurements

Fluorescence emission and excitation spectra were obtained with a Perkin Elmer LS-50B Fluorimeter in 75:25 (v/v) dichloromethane/THF. Six micro molar benzyltrimethylammonium hydroxide was added as a proton scavenger. Fluorescence was measured as a function of metal ion concentrations where the metal ions were added as the hexafluorophosphate salts. Fluorescence areas were determined by integrating the spectrum over a fixed wavelength range.

### 2.4. Calculations

Molecular modeling was preformed on an SGI 320 running Windows NT. Calculations were carried out using the Molecular Operating Environment (MOE) version 2000.02 computing package (Chemical Computing Group Inc., Montreal, Que., Canada). Structures were minimized first using the AMBER94 potential control under a solvent dielectric of 5. PEF95SAC was used to calculate partial charges. Minimized structures were then subjected to a 30 ps molecular dynamics simulation employing the NVT statistical ensemble. The structures were heated to 400 K, equilibrated at 310 K and cooled to 290 K in the dynamics thermal cycle at a rate of 10 K/ps. The lowest energy structures obtained from these dynamics calculations were then minimized again. Electrostatic calculations were then performed on the molecules using the default parameters.

## 3. Results and discussion

### 3.1. Solvent effects

Previous studies of anthryl-benzocrown ether calixarenes indicated a considerable and complex solvent effect on the intensity of fluorescence [5] and a similar effect was observed in our study of an anthryl-azacrown ether calixarene [16]. In both systems, in the absence of ions, the addition of methanol to dichloromethane solutions of the fluoroionophore caused an increase in the fluorescence intensity at small methanol concentrations and then a decrease as the methanol concentration was increased further. It has been suggested previously [5,16] that at low methanol concentrations, a hydrogen bonding interaction occurs between methanol and the azacrown nitrogen atom, disrupting the electron transfer quenching process and leading to the increase in fluorescence emission intensity observed. Conversely, the polar environment provided by higher methanol concentrations can increase the efficiency of electron transfer and cause a decrease in emission intensity. Furthermore, it can be reasonably expected that the polarity effect will dominate at high methanol concentration while a specific solute–solvent interaction will be more important at low methanol concentration.

The effect of methanol on the emission of **I** is different. Fig. 1 shows the fluorescence emission of **I** as a function of the mole fraction of methanol in dichloromethane solution (the values in the plot are normalized to the fluorescence intensity with the highest mole fraction of methanol). With only small additions of methanol there is a dramatic decrease in the fluorescence quantum yield, i.e. there is no intensity increase at low methanol concentration. The fluorescence is completely quenched by the addition of methanol at a mole fraction of 0.15. This effect can be attributed to a more pronounced stabilization of charge separation in **I** than in other anthryl-benzocrown- and anthryl-azacrown-calixarenes.

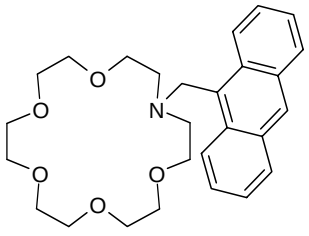
This is supported by the results of previously reported solution thermodynamics studies of calix[4]arene-crown-3 systems [23,24]. In these studies, it was observed that molecules with the crown-3 structure can complex small neutral molecules, such as nitromethane and malonitrile (and likely methanol) with relatively high stability constants ($\log K_s = 1$–$2$ in $CDCl_3$). $^1H$ NMR data from this previous work show that an interaction occurs between the guest molecule and the π-systems of the calix[4]arene aromatic rings [23]. At the same time it was suggested that larger systems (e.g., crown-5) have weaker binding with neutral molecules due to the higher flexibility of the crown, suggesting that **I** is more highly solvated in methanol. Since higher solvation by methanol can be expected to enhance the electron transfer efficiency, the observed quenching effect of methanol on the emission intensity is understandable.

This solvent effect causes a practical problem in experiments on ion complexation since it masks the effect of ion binding on the emission intensity. As a result, all subsequent experiments on ion complexation were carried out in 75:25 (v/v) dichloromethane/THF using the hexafluorophosphate salts of the alkali metals, which are reasonably soluble in this solvent system.

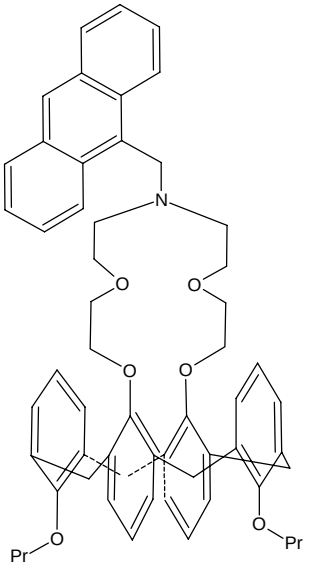
### 3.2. Fluorescence emission of *I*

Fig. 2 shows the fluorescence spectra obtained for **I** in the absence and presence of added concentrations of lithium hexafluorophosphate in 75:25 (v/v) dichloromethane/THF. The fluorescence behavior of **I** clearly demonstrates that the PET "off–on" switching mechanism occurs in response to ion complexation. In the absence of ions the anthryl fluorescence is at a minimum and increases with addition of lithium hexafluorophosphate yielding a maximum 106-fold enhancement.

Other PET based systems exhibit dramatic increases in fluorescence intensity but few have shown enhancements of this magnitude. The size of the fluorescence enhancement is directly related to the magnitude of the charge density of the bound ion that is experienced by the lone pair of the azacrown nitrogen atom, i.e., the electrons involved in the PET process. This is best illustrated by a comparison of the results for **I** with those for 9-anthryl-azacrown-6 (**II**) and 9-anthryl-calix[4]arene-azacrown-5 (**III**) both of which are fluoroionophores that signal the binding of potassium ions by the PET process (as we reported previously [16]).




**(II)**




**(III)**

For **II** and **III**, the fluorescence enhancements observed were 50- and 8-fold, respectively. Modeling studies of **II** indicate that the most stable ion-fluoroionophore complex possesses a $K^+ \cdots N$ distance = 3.0 Å while for **III** this distance is 3.5 Å. This difference could be expected to result in a significantly smaller effective charge density from the complexed ion (due to the increased distance) at the azacrown nitrogen lone pair in complexes of **III** than in complexes of **II**, producing fluorescence enhancements consistent with those observed. The increased distance of the cation from the amine in **III** can be attributed to interactions between the cation and the calixarene π-systems in **III**, an effect that has been observed for other host–guest molecules [25–27]. Modeling of **I**, however yields a minimized structure with a $Li^+ \cdots N$ distance = 3.8 Å, considerably greater than either **II** or **III** and if taken on its own, counter to the observed fluorescence behavior. However, the lithium ion possesses a much larger intrinsic charge density, 1.47 versus 0.74 q $Å^{-1}$ for lithium and potassium ions, respectively, and this difference is sufficient to explain the observed enhancement.

### 3.3. Selectivity

While the strength of the metal ion-fluoroionophore complex in **I** is governed by electrostatic interactions, particularly with the azacrown oxygen atoms, and through cation–π interactions, selectivity is controlled primarily by a size fit effect and steric effects from the *t*-butyl substituents appended to the two rotated aryl rings of the calix[4]arene [1]. Compound **I** was designed with the goal of excluding on a size-fit basis all ions larger than lithium (ionic radius = 0.68 Å). The structure of **I** was based in part on 14-crown-4 derivatives which are an appropriate size match for lithium. This crown was incorporated into **I** as an azacrown-3. In addition to providing an appropriately sized pocket, we

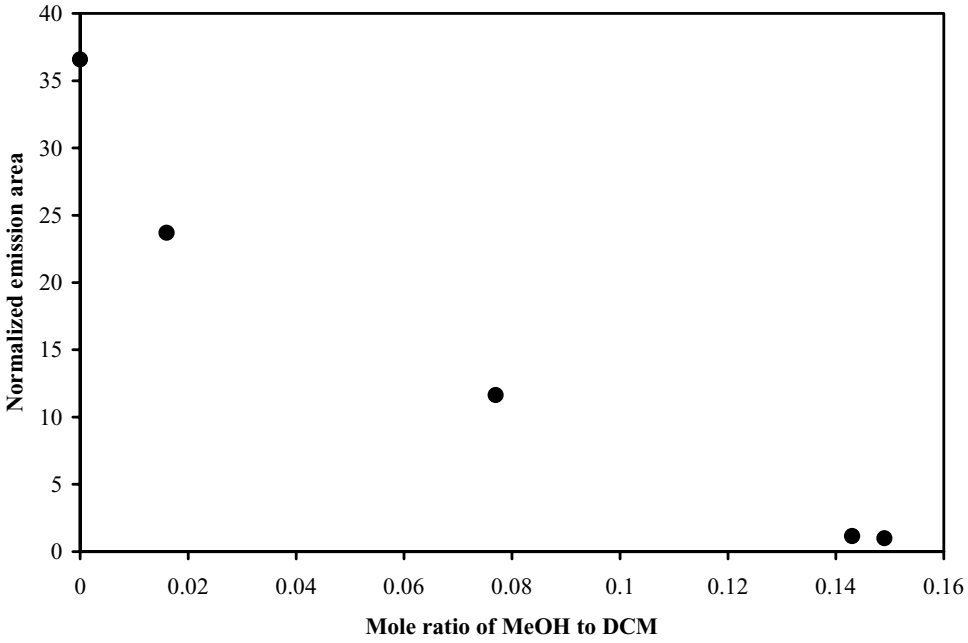



Fig. 1. Normalized emission area of **I** ($\lambda_{ex} = 355$ nm, $1 \times 10^{-6}$ M) as a function of the mole ratio of MeOH in dichloromethane.

expected that the bulky nature of the calix[4]arene structure would reduce the possibility of 2:1 sandwich-type complexes forming with larger cations. As part of our design process, molecular dynamics calculations were performed to determine the suitability of **I** for selectively binding lithium ion. Fig. 3 shows the results of molecular dynamics calculations for **I** in the complexed state with lithium ion (left) and sodium ion (right) (ionic radius = 0.95 Å). The minimized structure shows the lithium cation centered within the cavity with $Li^+ \cdots O$ distances of 1.90, 2.02, 1.94, 1.95 Å. This is in contrast to sodium, which is positioned asymmetrically in the binding site ($Na^+ \cdots O$ distances of 2.85, 2.44, 2.12, 2.13 Å) and is a considerably greater distance from the aza-crown nitrogen atom ($Na^+ \cdots N$ distance = 4.84 Å versus $Li^+ \cdots N$ distance = 3.80 Å). The calculations also indicate that the sodium complex is ca. Twenty five kilocalorie per

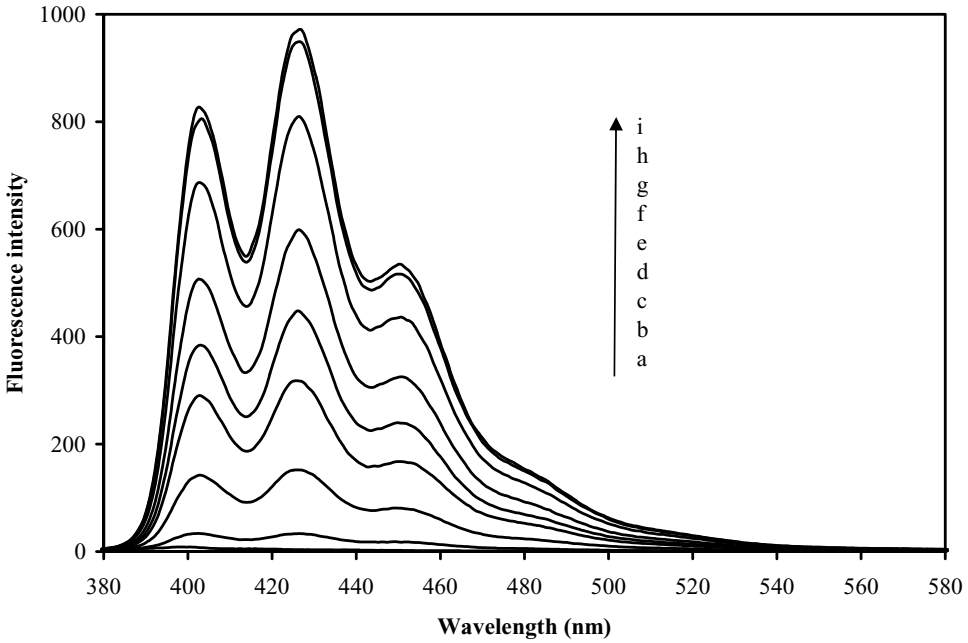



Fig. 2. Fluorescence emission spectra ($\lambda_{ex} = 355$ nm) of **I** ($2 \times 10^{-6}$ M) in 75:25 (v/v) dichloromethane/THF with added BTMAH ($6.0 \times 10^{-6}$ M) as a function of $[Li^+]$. (a) 0 μM, (b) 2 μM, (c) 3 μM, (d) 4 μM, (e) 4.5 μM, (f) 5.5 μM, (g) 6.5 μM, (h) 8 μM, (i) 15 μM.

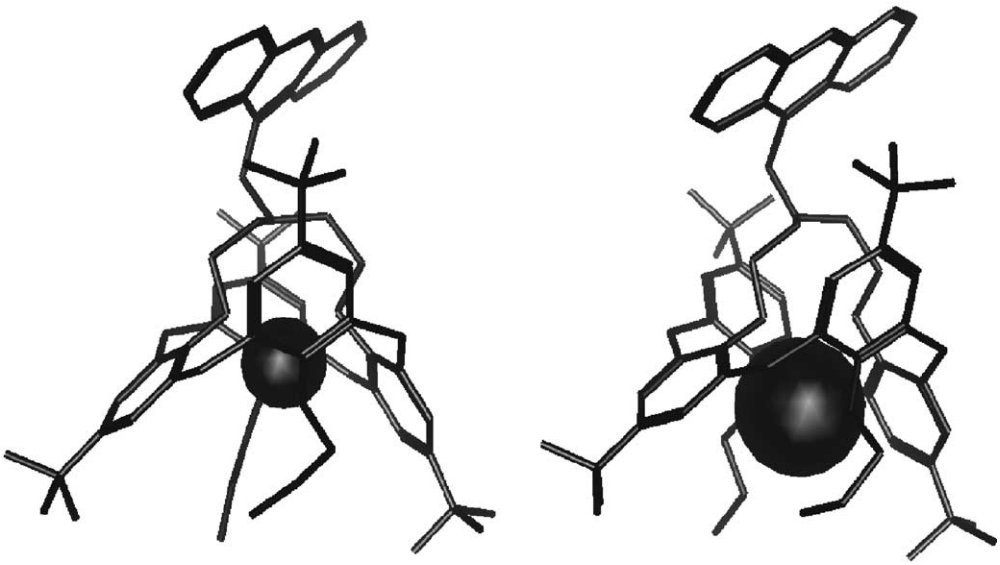


Fig. 3. Minimized structures of **I** with $Li^+$ (left) and $Na^+$ (right).

mol less thermodynamically stable than the lithium complex. As expected, calculations for potassium ion (ionic radius = 1.33 Å) complexes with **I** (not shown) yielded structures in which the cation was pushed out of the binding pocket entirely ($K^+ \cdots N$ distance of 5.98 Å). Although these calculations are qualitative, they suggested that **I** should have a high degree of discrimination over sodium and potassium cations.

Fig. 4 shows the dependence of the emission intensity of **I** on cation concentration for lithium, sodium and potassium. (The values in the plot are normalized to the fluorescence intensity in the absence of ion.) These results suggest high selectivity of **I** to lithium in comparison with the other alkali metal cations studied.

From Fig. 4 it is clear that for potassium and sodium ions, the integrated fluorescence intensity as a function of added ion initially increases until it reaches a plateau, beyond which it is constant up to the maximum concentration tested. In the case of lithium ions, the fluorescence intensity increases, plateaus at ca. 10 μM and then begins to decrease beyond 50 μM. This fluorescence quenching behavior is similar to other PET based systems and has yet to

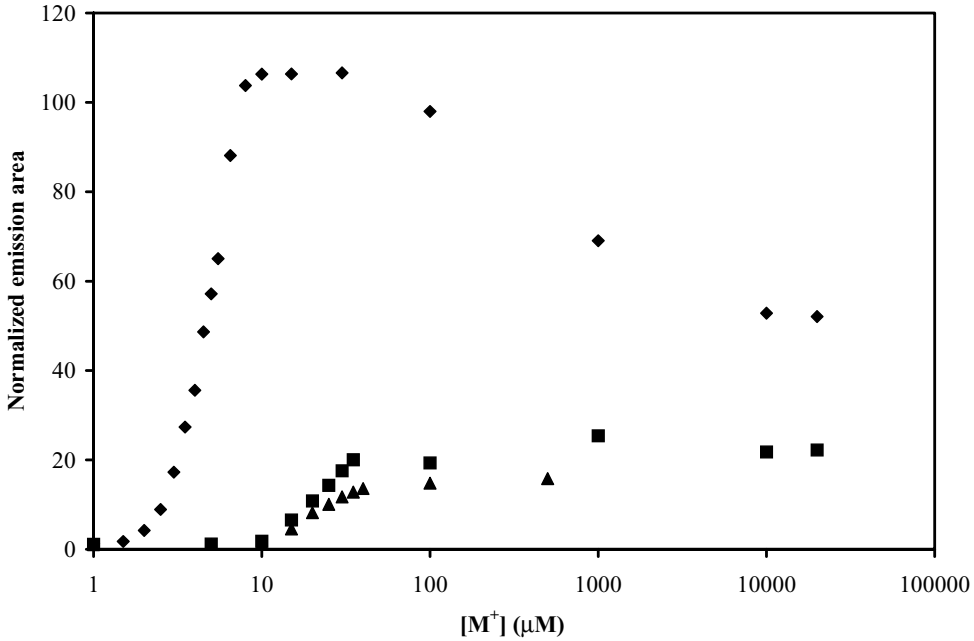



Fig. 4. Normalized emission area of **I** ($2 \times 10^{-6}$ M) in 75:25 (v/v) dichloromethane: THF with added BTMAH ($6.0 \times 10^{-6}$ M) vs. the concentration of various alkali metal ions: Li (◆), Na (■), K(▲).

be satisfactorily explained, although it has been suggested that the decreasing response is due to a medium effect stemming from the increase of ionic strength [3–8]. It is also clear that the enhancement in fluorescence emission in the presence of lithium ions is significantly larger for sodium or potassium. The selectivity was calculated from Eq. (1)

$$\log K_{i,j} = \log\left(\frac{[i]}{[j]}\right) \quad (1)$$

where $i$ is primary ion, $j$ is interfering ion [16].

Here, [$j$] is the highest tested concentration of the interfering ion in the plateau region of the plot, 20 and 5 mM, for sodium and potassium ions, respectively. The primary ion concentration, [$i$] (lithium), is the concentration that produces the same fluorescence response as the maximum fluorescence produced by the interfering ion and as such represents a minimum unambiguous detection limit for the primary ion, (3.2 and 2.8 μM for sodium and potassium, respectively). In the case of sodium, the calculation yields a selectivity value for lithium versus sodium, $\log K_{\mathrm{Li,Na}} = -3.8$. However, this concentration represents the solubility limit of the sodium salt used and therefore, this selectivity should be regarded as a lower limit only. Similar results were obtained for lithium versus potassium, $\log K_{\mathrm{Li,K}} = -2.3$. We note that again this is a lower limit. The value quoted is less than that for lithium/sodium selectivity because the potassium salt used was less soluble and we were limited to a maximum concentration of 0.5 mM. However, as with sodium the actual selectivity is likely much higher. In fact, given that the ionic radius of potassium is larger than that of sodium, and that from the molecular dynamics calculations the potassium complex is less stable than that of sodium, the lithium/potassium selectivity is expected to be at least two orders of magnitude greater than the lower limit quoted.

## 4. Conclusions

The *N*-(9-methylanthracene)-25,27-bis(1-propyloxy)-4-*tert*-butylcalix[4]arene-azacrown-3, **I**, acts as a fluoroionophore in the presence of the alkali metal ions (lithium, sodium, potassium). In the absence of ion, fluorescence of the anthryl group is substantially quenched by photoinduced electron transfer (PET) from the nitrogen atom in the azacrown moiety. In the presence of complexed ion, the electric field of the ion disrupts the PET process, thereby switching on the anthryl fluorescence emission. For lithium, the enhancement in fluorescence is dramatic (>106-fold).

Molecular dynamics calculations predicted high selectivity of **I** for lithium ion over sodium and potassium ions on the basis of a size-fit effect. This is confirmed by smaller fluorescence enhancements for the latter two ions. Selectivity was calculated based on the observed fluorescence behavior, yielding $\log K_{\mathrm{Li,Na}} = -3.8$. and $\log K_{\mathrm{Li,K}} = -2.3$. These values are regarded as lower limits due to limited solubilities of the sodium and potassium salts used in the experiments. Nevertheless, the observed selectivities indicate that **I** is one of the most selective lithium ligands reported.

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