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A novel photochemical approach to the synthesis of naphthalene-containing lariat-type crown ethers and an evaluation of their metal cation binding and fluorescence sensing properties

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Abstract

A novel method has been developed for the synthesis of naphthalene chromophore containing, lariat-type crown ethers. The route employs SET-promoted photocyclization reactions of polyether-tethered 2,3-naphthalimides to generate the variously ring-sized crown ether cores and an allylsilane *N*-acyliminum ion addition process to install amino ether side chains. The metal cation binding properties of the lariat-crown ethers, prepared in this manner, were evaluated. In addition, the ability of the lariat-crown ethers to serve as SET-based, fluorescence sensors of metal cations was probed. The results show that although the novel lariat-crown ethers strongly complex alkali metal cations (Na, K, Rb, Cs), this complexation is not associated with enhanced fluorescence from the naphthalene chromophores as would be expected if cation binding impeded SET quenching by the tertiary amine donor in the side chains. In contrast, the novel lariat-crown ethers serve as sensitive sensors for the divalent metal cations of Mg and Cu and the monovalent cation of Ag.

Keywords: Naphthalene-containing; Lariat-type crown ethers; Photocyclization

1. Introduction

Previous studies in our laboratories have led to the discovery, mechanistic delineation and synthetic application of a variety of photochemical processes that are promoted by excited state single electron transfer (SET) [1]. In linked electron donor–acceptor substrates **1** (Scheme 1), these processes take place through the intermediacy of zwitterionic biradicals **2**, which by design possess α-electrofugal groups (SiR_3 or SnR_3). As a result, rapid heterolytic fragmentation reactions ($\sim R_3Si^+$ or $\sim R_3Sn^+$) ensue leading to formation of biradicals **3** that undergo C–C bond formation to generate cyclic products **4**. The earlier investigations have demonstrated that photochemical reactions following this general pathway can be used to produce a wide variety of functionally and structurally complex targets [2]. In addition, the processes have served as platforms for studies aimed at gaining information about the chemistry of cation radicals and the factors governing their reactivity [3].

More recent efforts in this area have provided information about the factors that control the chemical and quantum efficiencies of SET-promoted photoreactions of linked acceptor–polydonor systems [4]. In this work, we uncovered photocyclization reactions of trimethylsilyl-terminated polydonor-linked phthalimides that serve as highly efficient methods to construct macrocyclic poly-ethers, -thioethers

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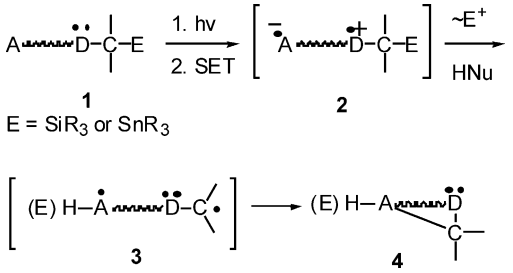
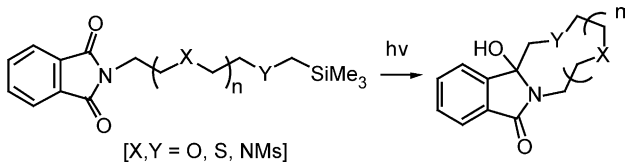


Scheme 1.



Scheme 2.

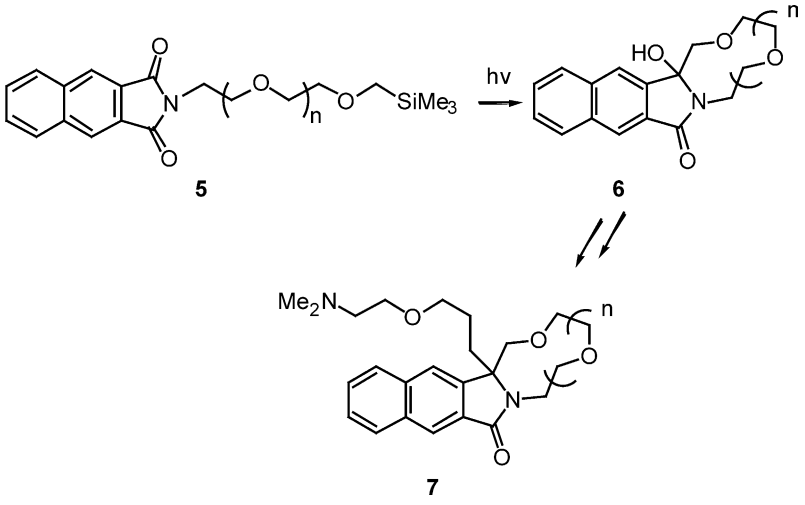
and -sulfonamides (Scheme 2) [5]. The processes serve as the foundation of new strategies for the preparation of functionally interesting macrocyclic substances in the crown ether families. From the time of the early studies by Pedersen, Cram and Lehn [6], a large number of crown ethers, calixarenes and cryptands have been prepared and their metal and ammonium ion complexation properties have been probed. In this light, the SET-promoted photochemical method for crown ether synthesis uncovered in our recent efforts comes at a rather advanced stage of this area of science. However, the simplicity and high efficiencies of these processes make studies of their applications to the synthesis of functional crown ether worthwhile.

One goal of our continuing investigations of SET-promoted photocyclization reactions of acceptor–polydonor substrates is to develop concise methods of preparing new types of metal ion, fluorescence sensors. As shown earlier by de Silva and others [7], SET based fluorescence sensors are useful materials that signal guest binding by blocking SET-quenching of excited states of fluorophores that are appended to the host. Following this principle, we have prepared prototypical naphthalene-containing fluorescence sensors of general structure **7** by employing photocyclization reactions of 2,3-naphthalimido-polyethers **5** (Scheme 3). The macrocyclic photoproducts **6** are then transformed to tertiary amine side chain containing, lariat-type [8] crown ether sensors **7**. The amine grouping in **7** is designed to serve as an electron donor to SET-quench the fluorescence of the naphthalene chromophore when a metal cation guest is absent. We anticipated that metal cation binding to **7** would be assisted by the pendant side chain oxygen (and perhaps nitrogen) and, as a result, it would be accompanied by a dislocation of the side chain tertiary amine moiety with a concomitant reduction in intramolecular quenching of the naphthalene fluorescence. Fluorescence and metal cation binding studies have been performed with these substances in order to determine if they serve as useful SET-based metal cation sensors. The results of this effort are reported below.

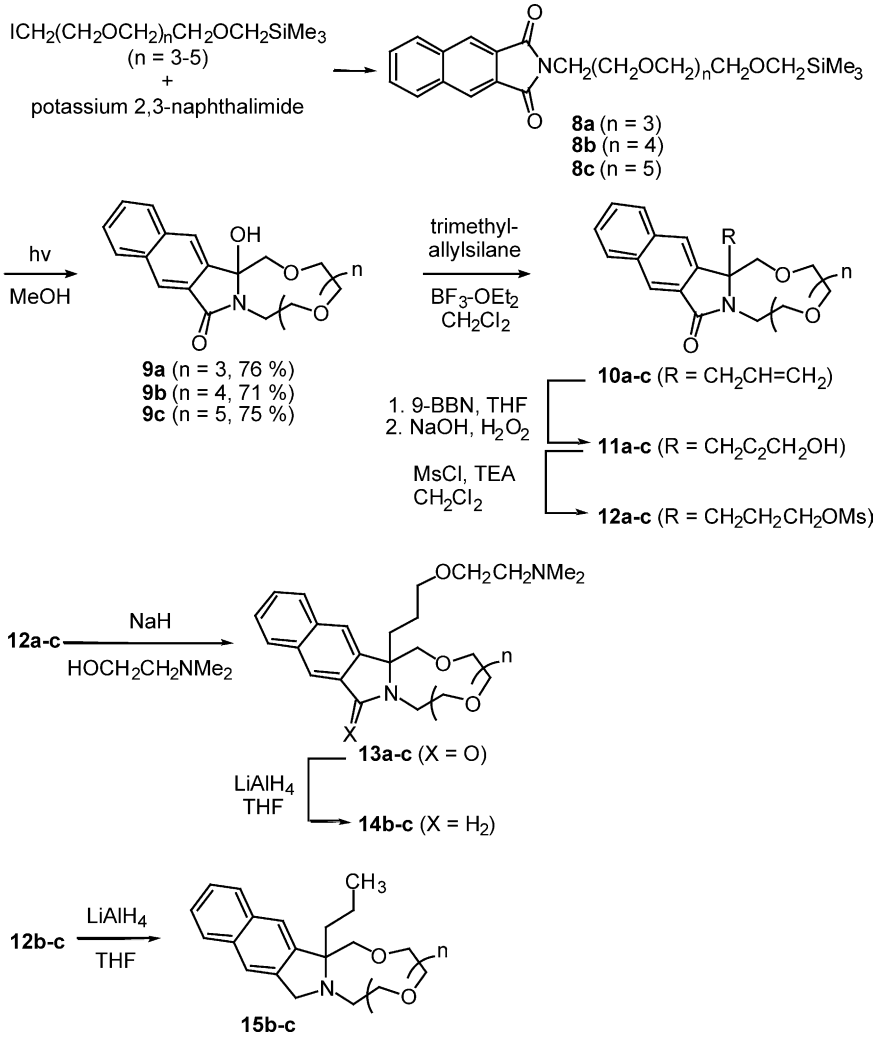
2. Results

2.1. Synthesis of the lariat-type crown ethers

The preparative routes used to construct a representative series of lariat-type crown ethers that have metal cation sensing potential begin with synthesis of the trimethylsilyl-terminated 2,3-naphthalimide polyethers **8a–c** (Scheme 4). Reactions of potassium 2,3-naphthalimide with the known polyethylene glycol derived iodides [9] produce the naphthalimides **8a–c**, which undergo photomacrocyclization processes when irradiated in methanol solutions to efficiently form the macrocyclic-amidols **9a–c** (71–76%). Incorporation of functionalized sided chains into these substances takes advantage of allylation reactions of *N*-acyliminium ions formed by treatment of **9a–c** with a Lewis acid. Accord-



Scheme 3.



Scheme 4.

ingly, reactions of amidols **9a**–**c** with trimethylallylsilane in the presence of boron trifluoride generate the corresponding allyl derivatives **10a**–**c**. Hydroboration–oxidation of **10a**–**c** to form the respective alcohols **11a**–**c**, followed by sequential mesylate **12a**–**c** formation and reaction with sodium *N*,*N*-dimethylaminoethoxide, gives the naphthalamide containing, tertiary amine appended, lariat-type crown ethers **13a**–**c**.

In order to form the corresponding naphthalamine analogs **14b** and **c**, the amide groups in **13b** and **c** are reduced by treatment with lithium aluminum hydride. Similar reactions of the mesylate containing macrocyclic amides **12b** and **c** yields the respective propyl-naphthalamine crowns **15b** and **c**.

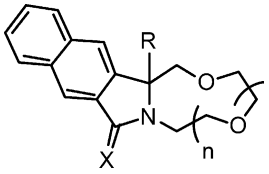
2.2. Metal cation binding by the crown ethers

Alkali metal cation binding properties of the naphthalamide and naphthalamine crown ethers were evaluated by using the well-known extraction method [10]. Accordingly, UV-spectroscopic measurements of the concentrations of metal picrates (metal concentrations of 5.0×10^{-5} M) in water and methylene chloride mixtures containing the crown ethers (1.5×10^{-4} M) give the percentages (extraction constants) of the metal picrates that are complexed to the crown ethers. In addition, crown ether concentration dependencies of the extraction constants showed that 1:1 complexes are formed between the metal cations and all of the crown ethers. The data obtained in this manner with the lariat-type naphthalamide and naphthalamine crowns **13b** and **14b** and **c**, and the allyl amide and propyl amine crowns **10b** and **15b** and **c**, along with those for 18-crown-6 and aza-18-crown-6 are displayed in Table 1.

2.3. Fluorescence measurements

Fluorescence properties of the crown ethers were determined in order to evaluate the effects of the side chain and macrocyclic ring embedded tertiary amine groups on emission from the naphthalene fluorophore. Relative fluorescence efficiencies of the crowns in anhydrous acetonitrile at 25 °C were determined by measuring the emission intensities of equally absorbing (excitation at 290 nm) solutions (ca. 10^{-5} M). As seen by viewing the data in

Table 1
Relative fluoresence efficiencies[a] and alkali metal cation extraction constants[b] for naphthalimide derived crown ethers



Crown ether				Φ_f (rel)	Extraction constant (%)			
	X	R	*n*		Na^+	K^+	Rb^+	Cs^+
10b	O	Allyl	4	1.0	3	3	3	1
10c	O	Allyl	5	1.0	–	–	–	–
13b	O	Amine-ether	4	0.38	19	53	54	54
13c	O	Amine-ether	5	0.26	–	–	–	–
14b	H_2	Amine-ether	4	0.04	12	54	64	62
14c	H_2	Amine-ether	5	0.03	10	28	39	47
15b	H_2	Propyl	4	–	32	62	28	30
15c	H_2	Propyl	5	0.16	17	22	49	56
18-Crown-6					3	8	6	4
Aza-18-crown-6					3	47	43	42

[a] Derived from fluorescence intensities at 351 nm for equally absorbing solutions (ca. 1×10^{-5} M) of the crown ethers in MeCN solutions at 25 °C.
[b] Determined by using the known (ref. [10]) extraction method for 1.5×10^{-4} M methylene chloride solution of the crown ether and 5.0×10^{-5} M water solutions of the metal picrates.

Table 1, the allyl-naphthalamide crowns **10b** and **c** emit most strongly and are assigned relative fluorescence quantum yields of unity. In contrast, crowns **13b** and **c**, which possess dimethylaminoethoxypropyl side chains, are less intensely fluorescent. Also, the fluorescence efficiencies of the propyl-naphthalamine crown **15c** are significantly lower than that of the analogously substituted naphthalamide crown **10c**. Finally, the lowest relative fluorescence quantum yields are

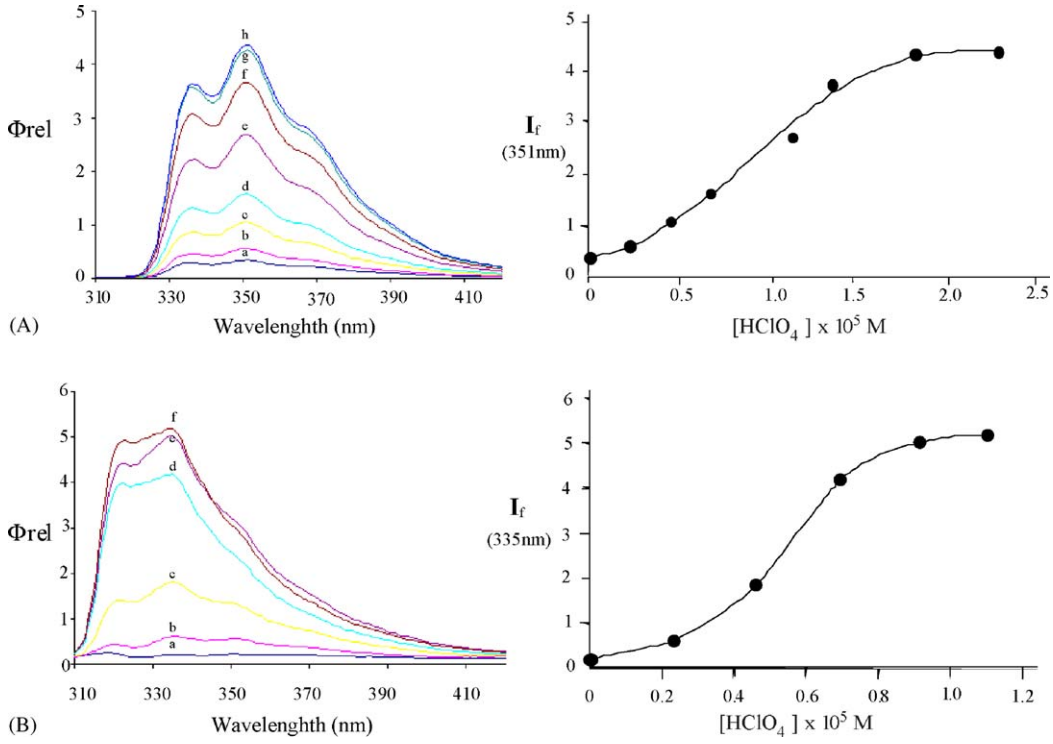


Fig. 1. Fluorescence spectra of (A) **13b** in MeCN (1.4×10^{-5} M, 25 °C) containing $HClO_4$: (a) 0, (b) 2.3×10^{-6}, (c) 4.6×10^{-6}, (d) 6.9×10^{-6}, (e) 1.2×10^{-5}, 1.4×10^{-5}, 1.8×10^{-5}, 2.3×10^{-5} (M) and a replot of the data; (B) **14b** in MeCN (8×10^{-6} M, 25 °C) containing $HClO_4$: (a) 0, (b) 2.3×10^{-6}, (c) 4.6×10^{-6}, (d) 6.9×10^{-6}, (e) 9.1×10^{-6}, (f) 1.1×10^{-5} (M) and a replot of the data.

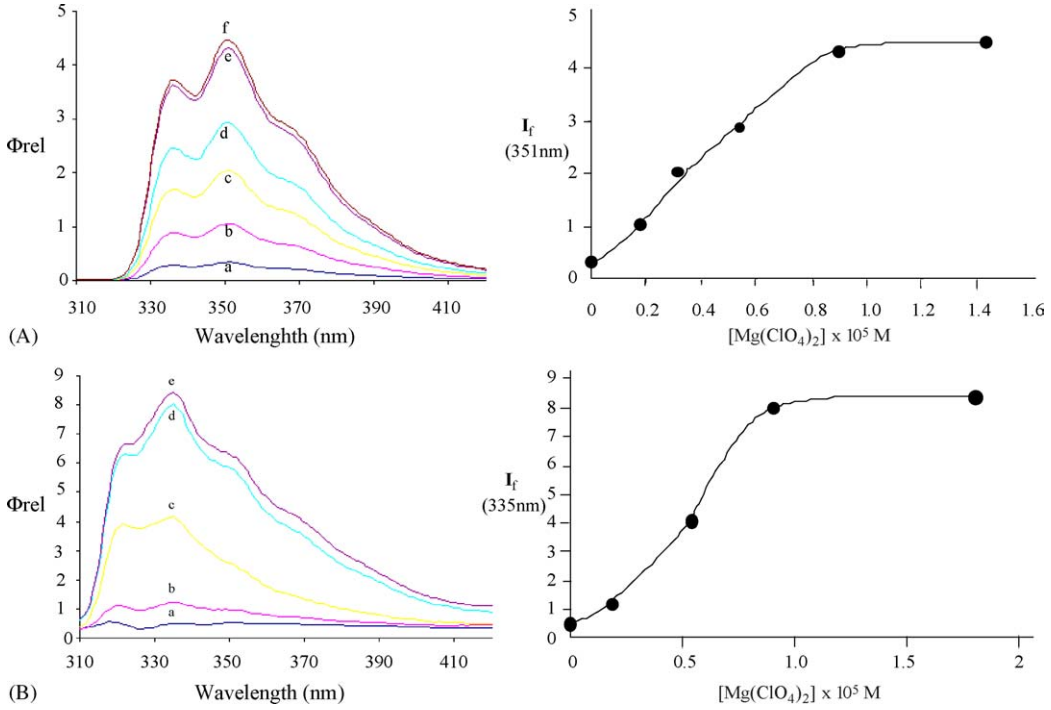


Fig. 2. Fluorescence spectra of (A) **13b** in MeCN (1.4×10^{-5} M, 25 °C) containing $Mg(ClO_4)_2$: (a) 0, (b) 1.8×10^{-6}, (c) 3.2×10^{-6}, (d) 5.4×10^{-6}, (e) 9.0×10^{-6}, (f) 1.4×10^{-5} M) and a replot of the data; (B) **14b** in MeCN (8×10^{-6} M, 25 °C) containing $Mg(ClO_4)_2$: (a) 0, b: 1.8×10^{-6}, (c) 5.4×10^{-6}, (d) 9.0×10^{-6}, (e) 1.8×10^{-5} M) and a replot of the data.

displayed by the tertiary amine side chain containing naphthalamine crowns **14b** and **c**.

To gain information about the source of the differing fluorescence efficiencies, the effects of acid on the emission intensities of these substances were evaluated. As seen by viewing the results displayed in Fig. 1, the fluorescence intensities of **13b** and **14b** (1.4×10^{-5} and 8.6×10^{-6} M, respectively, in MeCN) increase in a regular manner as the concentrations of added perchloric acid are increased. Interestingly, in each case the fluorescence intensity reaches a maximum when ca. 1 mole-equivalent of the acid is present.

The effect of metal cations on fluorescence efficiencies of the naphthalene-containing crown ethers was explored. For this purpose, fluorescence intensities of MeCN solutions of crown ethers **10b**, **13b** and **14b**, containing a range of concentrations of alkali metal (Na, K, Rb, Cs) perchlorates were measured. In each case, no changes in the emission intensities were noted even when exceptionally high concentrations (ca. 10^{-3} M) of these salts were present. In contrast, magnesium perchlorate pronouncedly enhances the fluorescence efficiency of the side chain amine tethered naphthalamide and naphthalamine crown ethers **13b** and **14b** (Fig. 2). In both instances, fluorescence intensities reach a maximum when ca. 1 mole-equivalent of magnesium perchlorate is present. A similar effect is observed when silver perchlorate and copper(II) triflate are added to MeCN solutions of **13b** (Fig. 3) and when the silver salt is present in MeCN solutions of **14b** (Fig. 4).

3. Discussion

The results presented above show that SET-promoted photocyclization reactions of trimethylsilyl-terminated, polyether-tethered naphthalimides serve as efficient methods to construct macrocyclic polyethers. In addition, the amido-alcohol functionality present in the photoproducts of these reactions is an ideal handle for introduction of functionalized side chains into the cyclic ether scaffold. As such, this chemistry can be used to prepare interesting lariat-type crown ethers that contain fluorescing, polycondensed arene chromophores.

The data accumulated in these studies (Table 1) show that the alkali metal cation binding affinities of the simple allyl-appended naphthalamide crown **10b** match those of 18-crown-6. Incorporation of an aminoethoxy side chain into these substances (as in **13b**) has a pronounced effect on alkali metal cation binding. The extraction constants measured for the lariat-type crown ether **13b** are much larger than those of its allyl-analog **10b**. These results strongly suggest that groups in the aminoethoxy side chain participate as ligands in the metal cation complexation processes.

The alkali metal cation complexation abilities of the propyl-tethered naphthalamine crowns **15b** and **c** closely match those of the related aza-18-crown-6. Moreover, the metal cation extraction constants of these substances are not affected by introduction of an aminoethoxy side chain (as in **14b** and **c**). Thus, unlike the naphthalamide containing lariat-

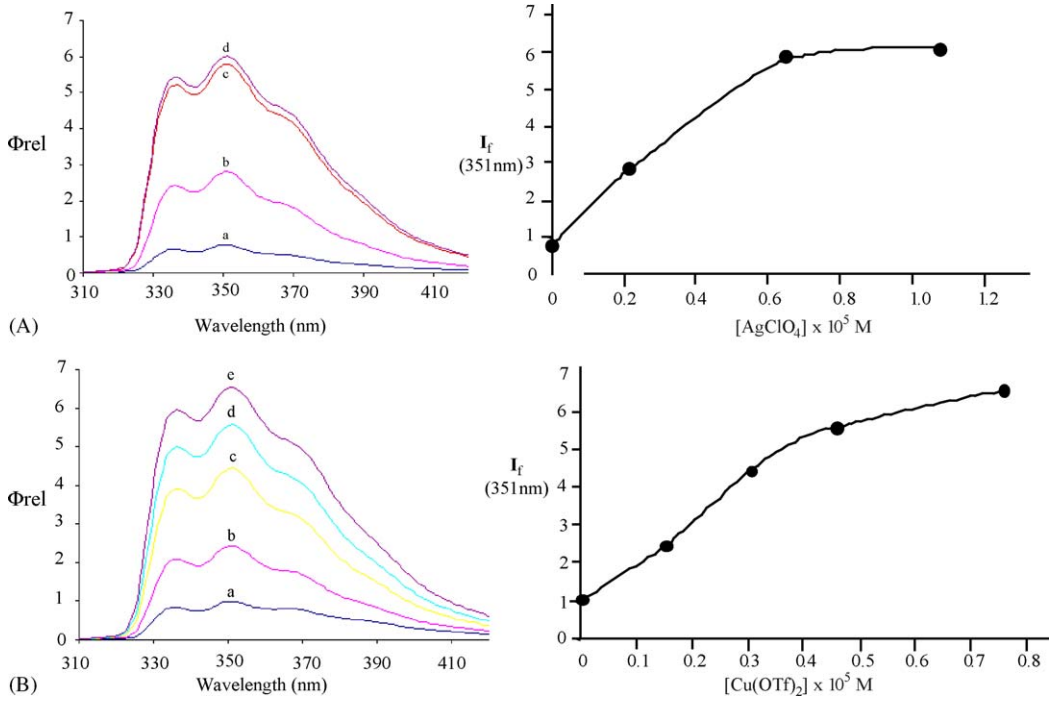


Fig. 3. Fluorescence spectra of (A) **13b** in MeCN (1.3×10^{-5} M, 25 °C) containing $AgClO_4$: (a) 0, (b) 2.2×10^{-6}, (c) 6.5×10^{-6}, (d) 1.1×10^{-5} M) and a replot of the data; (B) **13b** in MeCN (1.3×10^{-5} M, 25 °C) containing $Cu(OTf)_2$: (a) 0, (b) 1.5×10^{-6}, (c) 3.0×10^{-6}, (d) 4.6×10^{-6}, (e) 7.6×10^{-6} M) and a replot of the data.

type crown **13b**, the nitrogen and oxygen donor groups in the side chain in **14b** and **c** appear to play a minor, if any, role in binding to alkali metal cations.

As expected, fluorescence efficiencies of the naphthalene-containing crown ethers are influenced by tertiary amine groups present in the side chain or macrocyclic ring. The ca. 3-fold lower fluorescence efficiencies of the aminoethoxy tethered naphthalamides **13b** and **c**, as compared to the allyl-analogs **10b** and **c**, can be attributed to quenching of the emitting naphthalene singlet excited states by reversible SET from the side chain tertiary amine donor groups. Although the quenching is significant, it is not as large as is expected based on the results of earlier studies with similarly structured aminoalkyl-naphthalene and -anthracenes [11]. The presence of tertiary amine moieties within the macrocyclic ring causes a much more dramatic reduction in fluorescence efficiencies of the naphthalene chromophore. A comparison of the fluorescence data for the propyl-tethered naphthalamine **15c** and allyl-tethered naphthalamide **10c** shows that the in-ring tertiary amine donor causes a >5-fold decrease in the fluorescence efficiency. Another factor that might contribute to the differences seen in the fluorescence efficiencies of the naphthalamine versus naphthalamide crowns is the nature of the naphthalene chromophore. The latter substances contain carbonyl conjugated naphthalene rings, which should have different singlet lifetimes as compared to unconjugated analogs. Finally, fluorescence is highly inefficient from the naphthalene chromophore in

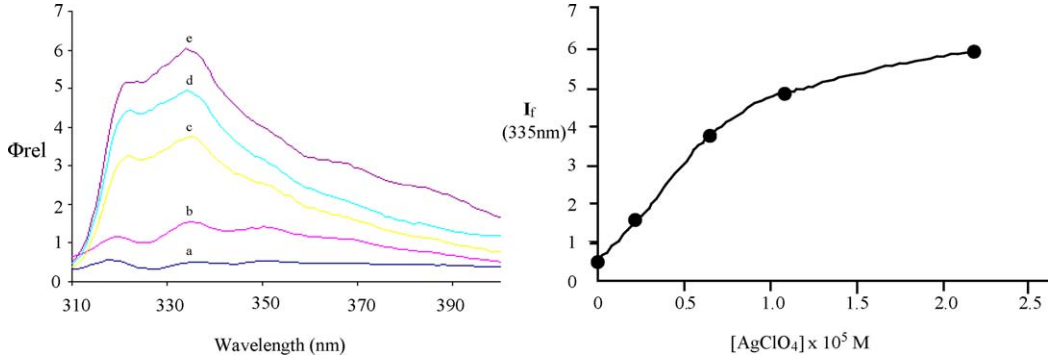


Fig. 4. Fluorescence spectra of **14b** in MeCN (8.0×10^{-6} M, 25 °C) containing $AgClO_4$: (a) 0, (b) 2.2×10^{-6}, (c) 6.6×10^{-6}, (d) 1.1×10^{-5}, (e) 2.2×10^{-5} M) and a replot of the data.

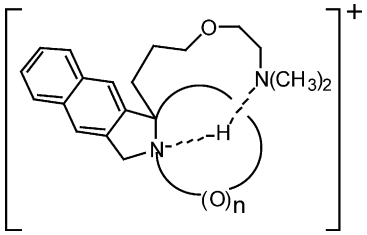


Fig. 5. Pictorial representation of monoprotonated **14b**.

lariat-type crowns **14b** and **c**, which possess both in-ring and side chain tertiary amine SET-donor groups.

An interesting observation was made while performing experiments to demonstrate that the reduction in fluorescence efficiencies of **13b** and **14b** is due to SET quenching by the amine moieties. As anticipated, addition of perchloric acid to a MeCN solution of aminoethoxy-tethered crown **13b** results in a regular increase in its fluorescence efficiency (Fig. 1a). This effect reaches a maximum after ca. 1 mole-equivalent of acid is added. At that point, when the tertiary amine group is completely protonated, the fluorescence efficiency is nearly identical to that of the allyl-naphthalamide crown **10b**. Similar phenomena are observed in studies with the lariat-type crown **14b**. Again, addition of perchloric acid results in a regular increase in fluorescence efficiency. However, the effect reaches a maximum after 1 mole-equivalent of acid is added despite the fact that **14b** contains two tertiary amine groups, both of which serve as SET quenchers of the excited naphthalene chromophore (see above). These results suggest that both of the amine moieties are interacting with the added proton. Thus, it appears that protonation of one of the nitrogens in this crown generates an ammonium ion that is stabilized by hydrogen bonding to the other amine group (Fig. 5) (and perhaps ring or side chain oxygens) [12] and this blocks SET quenching by both amine groups.

As discussed above, lariat-type crown ethers **13**–**15** that contain tertiary nitrogens in either the side chains or macrocyclic rings strongly complex with alkali metal cations. In addition, the side chain and in-ring amine groups serve as SET-quenchers of the fluorescence from the naphthalene chromophores in these crowns. In this context, the observation that alkali metal cations have no effect on the fluorescence efficiencies of **13**–**15** is quite remarkable and not easily explained. Adding to this unexpected behavior are observations which demonstrate that divalent Mg and Cu and monovalent Ag cations cause dramatic enhancements in the fluorescence efficiencies of the aminoethoxy-tethered naphthalamide and naphthalamine crowns **13b** and **14b**. Thus, it appears that binding of these ions blocks SET quenching by the side chain and in-ring amine donors.

Clearly, much work remains to be done in order to derive a detailed understanding of the observations made in the current investigation. However, at this point it is possible to conclude that the SET-promoted photocyclization process serves as the cornerstone of a concise method for the preparation of novel lariat-type crown ethers. In addition, the crown ethers formed in this manner serve as strong complexing agents for metal cations and effective fluorescence sensors for divalent Mg and Cu and monovalent Ag ions.

4. Experimental

4.1. General

All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification. All compounds were isolated as oils unless otherwise noted and shown to be >90% pure by ^{1}H and/or ^{13}C NMR. ^{1}H and ^{13}C NMR spectra were recorded on $CDCl_3$ solutions unless otherwise specified and chemical shifts are reported in ppm relative to residual $CHCl_3$ at 7.24 ppm (for ^{1}H NMR) and 77.0 ppm (for ^{13}C NMR). ^{13}C NMR resonance assignments were aided by the use of the DEPT technique to determine numbers of attached hydrogens. Mass spectra were recorded by using fast atomic bombardment (FAB) or electrospray (ES) techniques. Infrared absorption bands are recorded in units of cm^{-1}.

*4.2. N-((ω-Trimethylsilylmethoxy)polyethylenoxy)-2,3-naphthalimides **8a–c***

Independent solutions of potassium 2,3-naphthalimide (0.6 g, 2.5 mmol), the known [9] ω-trimethylsilylmethoxy)polyethyeneoxy iodides (n = 3, 1.29 g, 3.3 mmol; n = 4, 1.43 g, 3.3 mmol; n = 5, 1.58 g, 3.3 mmol), and hexadecyltributyl-phosphonium bromide (0.10 g, 0.2 mmol) in 7 mL of DMF were stirred at 80 °C for 4 h, cooled to 25 °C and diluted with CH_2Cl_2. The CH_2Cl_2solutions were washed with water, dried and concentrated in vacuo affording residues which were subjected to column chromatography (silica gel, 2:1 EA–hexane) to yield the naphthalimide derivative **8a** (0.99 g, 85%), **8b** (0.89 g, 70%) and **8c** (1.04 g, 75%).

8a: ^{1}H NMR 0.07 (s, 9H), 3.02 (s, 2H), 3.42–3.67 (m, 12H), 3.70 (t, 2H, J = 5.7 Hz), 3.85 (t, 2H, J = 5.7 Hz), 7.54–7.57 (m, 2H), 7.87–7.91 (m, 2H), 8.13 (s, 2H); ^{13}C NMR 3.3, 37.2, 65.1, 67.6, 69.9, 70.1, 70.3, 70.4, 74.4, 124.2, 127.5, 128.8, 129.9, 135.0, 167.5; HRMS (FAB) m/z: 460.2169 (M +1) (calcd for $C_{24}H_{34}NO_6Si$, 460.2155).

8b: ^{1}H NMR 0.01 (s, 9H), 3.12 (s, 2H), 3.50–3.65 (m, 16H), 3.77 (t, 3H, J = 5.7 Hz), 3.95 (t, 2H, J = 5.8 Hz), 7.88–7.69 (m, 2H), 8.02–8.06 (m, 2H), 8.32 (s, 2H); ^{13}C NMR 2.9, 37.6, 65.5, 68.0, 70.2, 70.5, 70.7, 74.8, 124.7, 128.0, 129.2, 130.4, 135.5, 168.0; HRMS (ES) m/z: 526.2218 (M + Na) (calcd for $C_{26}H_{37}NO_7SiNa$, 526.2231).

8c: ^{1}H NMR 0.01 (s, 9H), 3.12 (s, 2H), 3.53–3.63 (m, 20H), 3.76 (t, J = 6.0Hz), 3.95 (t, J = 5.8 Hz), 7.66–7.68 (m, 2H), 8.02–8.04 (m, 2H), 8.31 (s.2H); ^{13}C NMR 3.2, 37.3, 65.2, 67.6, 69.9, 70.2, 70.3, 70.4, 74.5, 76.5, 124.3, 127.6,

128.9, 130.0, 135.2, 167.6; HRMS (FAB) *m/z*: 548.2674 (*M* + 1) (calcd for $C_{28}H_{42}NO_8Si$, 548.2680).

5. Photocyclization reactions of the *N*-(ω-trimethylsilylmethoxy-polyethylenoxy)-2,3-naphthalimides 8a–c

5.1. Preparation of crown ethers 9a–c

Independent nitrogen purged solutions of **8a** (1 g, 2.2 mmol), **8b** (1 g, 2.0 mmol) and **8c** (1 g, 1.8 mmol) in 100 mL methanol were irradiated by using Pyrex glass filtered light for 1 h. Concentration of the photolysates in vacuo gave residues, which were subjected to column chromatography (silica gel, 10:1 EA–MeOH) yielding crown ethers **9a** (conversion 85%, 0.64 g, 76%), **9b** (conversion 90%, 0.61 g, 71%) and **9c** (conversion 88%, 0.65 g, 75%).

9a: ^{1}H NMR 3.48–3.76 (m, 15H), 3.83 and 4.05 (two d, 2H, *J* = 10.4 Hz), 3.88–4.02 (m, 1H), 5.40 (s, 1H), 7.41 (m, 1H), 7.80–7.83 (m, 2H), 7.97 (s, 1H), 8.08 (s, 1H); ^{13}C NMR 40.0, 70.1, 70.1, 70.2, 70.4, 70.6, 71.0, 71.4, 75.4, 88.6, 122.3, 123.4, 126.7, 127.6, 128.7, 129.0, 129.5, 133.7, 135.4, 141.0. 167.7; HRMS (FAB) *m/z*: 386.1598 (*M* + 1) (calcd for $C_{21}H_{24}NO_6$, 386.1604).

9b: ^{1}H NMR 3.53–3.76 (m, 20H), 4.00 and 4.08 (two d, 2H, *J* = 10.5 Hz), 5.74 (s, 1H), 7.48–7.55 (m, 2H), 7.90 (m, 2H), 8.01 (s, 1H), 8.25 (s, 1H); ^{13}C NMR 39.5, 69.9, 70.1, 70.2, 70.3, 70.6, 70.8, 71.7, 74.0, 88.8, 121.5, 123.3, 126.5, 127.5, 128.5, 129.2, 129.4, 133.6, 135.4, 141.0, 167.7; HRMS (FAB) *m/z*: 432.2026 (*M* + 1) (calcd for $C_{23}H_{30}NO_7$, 432.2022).

9c: ^{1}H NMR 3.47–3.74 (m, 24H), 4.04 and 4.15 (two d, 2H, *J* = 10.7 Hz), 5.75 (s, 1H), 7.47–7.53 (m, 2H), 7.88–7.95 (m, 2H), 8.08 (s, 1H), 8.23 (s, 1H); ^{13}C NMR 39.2, 69.7, 69.7, 70.0, 70.2, 70.4, 70.4, 70.5, 70.6, 71.3, 73.3, 88.6, 121.6, 123.2, 126.3, 127.3, 128.4, 129.0, 129.3, 133.4, 135.2, 141.1, 167.6; HRMS (FAB) *m/z*: 476.2285 (*M* + 1) (calcd for $C_{25}H_{34}NO_8$, 476.2284).

5.2. Allyl side chain crown ethers 10a–c

To independent solutions of **9a** (1.54 g, 3.97 mmol), **9b** (1.77 g, 3.88 mmol) and **9c** (1.9 g, 4.0 mmol) in 10 mL CH_2Cl_2 at −78 °C were added allyltrimethylsilane (1.5 mL) followed BF_3–OEt_2 (1.5 mL of a 1.0 M solution in ether, 1.5 mmol). The reaction mixtures were stirred at 25 °C for 12 h, diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with water, dried and concentrated in vacuo to afford residues, which were subjected to column chromatography (silica gel, 10:1 EA–CH_3OH) to yield **10a** (1.23 g, 75%), **10b** (1.48 g, 84%) and **10c** (1.54 g, 77%).

10a: ^{1}H NMR 2.85–2.94 (m, 2H), 3.54–3.74 (m, 15H), 3.91–3.97 (m, 3H), 4.78–4.83 (m, 1H), 4.90–4.95 (m, 1H), 4.95–5.10 (m, 1H), 7.47–7.57 (m, 2H), 7.88–7.99 (m, 3H), 8.29 (s, 1H); ^{13}C NMR 37.6, 41.1, 67.8, 68.2, 69.8, 70.1, 70.2, 70.5, 70.9, 71.5, 76.8, 119.1, 121.3, 123.2, 126.2, 127.3, 128.2, 129.3, 130.0, 131.3, 133.0, 135.0, 142.1, 168.8; HRMS (FAB) *m/z*: 412.2139 (*M* + 1) (calcd for $C_{24}H_{29}NO_5$, 412.2124).

10b: ^{1}H NMR 2.84–2.95 (m, 2H), 3.51–3.94 (m, 22H), 4.76– 4.80 (m, 1H), 4.85–4.93 (m, 1H), 5.06–5.21 (m, 1H), 7.44–7.50 (m, 2H), 7.82 (s, 1H), 7.86–7.93 (m, 2H), 8.25 (s, 1H); ^{13}C NMR 37.8, 41.0, 68.1, 68.9, 70.5, 70.7, 70.8, 70.9, 71.0, 71.1, 71.4, 76.5, 119.3, 121.2, 123.4, 126.4, 127.5, 128.3, 129.5, 130.3, 131.5, 133.2, 135.1, 141.9, 168.8; HRMS (FAB) *m/z*: 456.23910.

10c: ^{1}H NMR 2.86–2.95 (m, 2H), 3.54–3.93 (m, 26H), 4.76–4.80 (m, 1H), 4.85–4.94 (m, 1H), 5.13–5.17 (m, 1H), 7.51–7.57 (m, 2H), 7.85 (s, 1H), 7.88 and 7.7.97 (two d, 2H, *J* = 8 Hz), 8.29 (s, 1H); ^{13}C NMR 38.0, 41.0, 68.3, 68.8, 70.7, 70.8, 71.0, 71.5, 76.4, 119.4, 121.3, 123.5, 126.5, 127.6, 128.4, 129.7, 130.4, 131.6, 133.3, 135.2, 142.0, 169.0; HRMS (FAB) *m/z*: 500.2662 (*M* + 1) (calcd for $C_{28}H_{38}NO_7$, 500.2648).

5.3. 3-Hydroxypropyl side chain crown ethers 11a–c

To independent solutions of **10a** (0.82 g, 2 mmol), **10b** (0.91 g, 2 mmol) and **10c** (1.0 g, 2 mmol) in 5 mL THF at 0 °C were added 9-BBN–H (10 mL, 0.5 M in THF, 5 mmol). The mixtures were stirred at 25 °C for 12 h and diluted with 5 mL ethanol, 6 mL 6 M NaOH and 4 mL 30% H_2O_2. The resulting solutions were stirred at reflux for 1 h, cooled to 25 °C and concentrated in vacuo. The residues were dissolved in CH_2Cl_2 giving solutions which were washed with water, dried and concentrated in vacuo to give residues which were subjected to column chromatography (silica gel, 5:1 EA–CH_3OH) to afford **11a** (0.69 g, 80%), **11b** (0.8 g, 84%) and **11c** (0.88 g, 85%).

11a: ^{1}H NMR 0.72–0.85 (m, 1H), 1.05–1.21 (m, 1H), 2.20–2.28 (m, 2H), 3.45–3.97 (m, 20H), 7.51–7.55 (m, 2H), 7.85–7.75 (m, 2H), 7.97–7.98 (m, 1H), 8.31 (s, 1H); ^{13}C NMR 25.9, 29.3, 40.8, 62.1, 68.0, 68.3, 69.8, 70.2, 70.6, 70.8, 71.4, 76.5, 120.9, 123.2, 126.2, 127.4, 128.2, 129.3, 130.0, 133.0, 135.1, 142.4, 168.9; HRMS (FAB) *m/z*: 430.2221 (*M* + 1) (calcd for $C_{24}H_{32}NO_6$, 430.2230).

11b: ^{1}H NMR 0.69–0.80 (m, 1H), 0.99–1.15 (m, 1H), 2.11–2.17 (m, 1H), 2.25–2.39 (m, 1H), 3.34–3.82 (m, 24H), 7.39–7.46 (m, 2H), 7.76 (s, 1H), 7.79 and 7.86 (two d, 2H, *J* = 8 Hz), 8.20 (s, 1H); ^{13}C NMR 25.9, 29.5, 40.6, 61.9, 68.4, 70.5, 70.5, 70.8, 70.9, 76.5, 120.7, 123.3, 126.3, 127.5, 128.2, 129.4, 130.2, 133.0, 135.1, 142.1, 169.0; HRMS (FAB) *m/z*: 474.2497 (*M* + 1) (calcd for $C_{26}H_{36}NO_7$, 474.2280).

11c: ^{1}H NMR 0.81 (m, 1H), 1.15 (m, 1H), 1.99–2.14 (m, 2H), 3.42–3.98 (m, 28H), 7.46–7.52 (m, 2H), 7.80 (s, 1H), 7.85 and 7.93 (two d, 2H, *J* = 8 Hz), 8.27 (s, 1H); ^{13}C NMR 26.0, 29.6, 40.7, 62.1, 68.5, 68.9, 70.3, 70.6, 70.7, 70.8, 70.9, 71.2, 76.6, 120.7, 123.4, 126.4, 127.6, 128.3, 129.5, 130.4,

133.2, 135.2, 142.3, 169.1; HRMS (FAB) *m*/*z*: 518.2748 (*M* + 1) (calcd for $C_{28}H_{40}NO_8$, 518.2754).

5.4. 3-Methanesulfonyl-hydroxypropyl side chain crown ethers **12a–c**

Independent solutions of alcohol **11a** (0.43 g, 1 mmol), **11b** (0.47 g, 1 mmol) and **11c** (0.52 g, 1 mmol), triethylamine (0.42 mL, 3 mmol) and methanesulfonyl chloride (0.16 mL, 2 mmol) at 0 °C in 5 mL CH_2Cl_2 were stirred at 25 °C for 12 h, diluted with CH_2Cl_2, washed with water, dried and concentrated in vacuo to give residues which were subjected to column chromatography (silica gel, 7:1 EA–CH_3OH) to give **12a** (0.46 g, 90%), **12b** (0.51 g, 92%) and **12c** (0.57 g, 96%).

12a: ^{1}H NMR 0.91 (m, 1H), 1.24 (m, 1H), 2.26–2.29 (m, 2H), 2.85 (s, 3H), 3.08 (s, 2H), 3.55–3.58 (m, 1H), 3.63–3.70 (m, 16H), 3.90–3.93 (m, 3H), 7.47–7.55 (m, 2H), 7.88–7.89 (m, 2H), 7.94 (d, 1H, *J* = 8.0 Hz), 8.28 (s, 1H); ^{13}C NMR 22.6, 28.9, 37.1, 40.8, 67.5, 69.7, 70.1, 70.5, 70.8, 76.4, 121.1, 123.4, 126.3, 127.5, 128.2, 129.3, 129.8, 133.0, 135.0, 141.7, 168.7; HRMS (FAB) *m*/*z*: 508.2010 (*M* + 1) (calcd for $C_{25}H_{34}NO_8S$, 508.2005).

12b: ^{1}H NMR 0.90–1.00 (m, 1H), 1.21–1.37 (m, 1H), 2.20–2.38 (m, 2H), 2.89 (s, 3H), 3.57–3.96 (m, 22H), 4.04 (t, 2H, *J* = 6.2 Hz), 7.52–7.58 (m, 2H), 7.84 (s, 1H), 7.89 and 7.98 (two d, 2H, *J* = 7.5 Hz), 8.31 (s, 1H); ^{13}C NMR 22.6, 29.0, 37.0, 40.6, 67.8, 68.7, 69.4, 70.3, 70.4, 70.5, 70.7, 70.7, 71.1, 76.5, 77.0, 77.5, 120.6. 123.4, 126.3, 127.5, 128.1, 129.3, 129.9, 133.0, 135.0, 141.4, 168.7; HRMS (FAB) *m*/*z*: 552.2265 (*M* + 1) (calcd for $C_{27}H_{38}NO_9S$, 552.2267).

12c: ^{1}H NMR 0.95–1.08 (m, 1H), 1.21–1.45 (m, 1H), 2.18–2.35 (m, 2H), 2.89 (s, 3H), 3.58–3.90 (m, 26H), 4.05 (t, 2H, *J* = 6.3 Hz), 7.52–7.58 (m, 2H), 7.84 (s, 1H), 7.89 and 7.97 (two d, 2H, *J* = 7.5 Hz), 8.31 (s, 1H); ^{13}C NMR 22.8, 29.2, 37.3, 40.8, 68.1, 68.9, 69.7, 70.4, 70.5, 70.7, 71.2, 76.6, 120.8, 123.6, 126.6, 127.8, 128.3, 129.5, 130.2, 133.3, 135.2, 141.7, 169.0; HRMS (FAB) *m*/*z*: 596.2513 (*M* + 1) (calcd for $C_{29}H_{42}NO_{10}S$, 596.2318).

5.5. Dimethylaminoethoxypropyl side chain crown ethers **13a–c**

Mixtures of *N*,*N*-dimethylethanol amine (0.1 mL, 1 mmol) in 7 mL DMF and NaH (25 mg, 1 mmol) were stirred at 25 °C for 2 h. The methansulfonates **12a** (0.18 g, 0.35 mmol), **12b** (0.18 g, 0.33 mmol) and **12c** (0.30 g, 0.5 mmol) were independently added and the resulting mixtures were stirred at 25 °C for 5 h, diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with saturated $NaHCO_3$, dried and concentrated in vacuo to afford residues, which were subjected to column chromatography (silica gel, 10:2:1 EA–CH_3OH–Et_3N) to give **13a** (0.083 g, 51%), **13b** (0.11 g, 59%) and **13c** (0.19 g, 64%).

13a: ^{1}H NMR 0.65–85 (m, 1H), 0.95–1.15 (m, 1H), 2.17 (s, 6H), 2.38 (t, 2H, *J* = 5.7Hz), 3.15 (t, 2H, *J* = 6.4Hz), 3.35 (t, 2H, *J* = 5.8Hz), 3.45–3.88 (m, 20H), 7.44–7.50 (m, 2H), 7.82–7.90 (m, 3H), 8.25 (s, 1H); ^{13}C NMR 23.0, 29.6, 40.9, 45.8, 58.7, 68.1, 68.3, 68.6, 69.9, 70.3, 70.4, 70.7, 71.0, 71.6, 76.7, 77.2, 77.4, 77.7, 121.1, 123.4, 126.3, 127.5, 128.3, 129.5, 130.2, 133.2, 135.2, 142.5, 169.0; HRMS (FAB) *m*/*z*: 501.2983 (*M* + 1) (calcd for $C_{28}H_{41}N_2O_6$, 501.2965).

13b: ^{1}H NMR 0.72–0.90 (m, 1H), 1.04–1.21 (m, 1H), 2.14 (s, 6H), 2.31–2.36 (m, 1H), 3.15–3.31 (m, 3H), 3.5–3.95 (m, 26H), 7.45–7.51 (m, 2H), 7.78 (s, 1H), 7.84 and 7.92 (two d, 2H, *J* = 5.5 Hz), 8.25 (s, 1H); ^{13}C NMR 14.7, 22.8, 29.5, 40.4, 45.8, 58.7, 68.2, 68.5, 68.7, 70.4, 70.5, 70.6, 70.8, 70.9, 71.2, 76.5, 76.7, 77.0, 77.5, 120.6, 123.2, 126.2, 127.3, 128.1, 129.3, 130.2, 133.0, 135.0, 142.0, 168.8; HRMS (ES) *m*/*z*: 567.3032 (*M* + Na) (calcd for $C_{30}H_{44}N_2O_7Na$, 567.3041).

13c: ^{1}H NMR 0.70–0.85 (m, 1H), 1.05–1.15 (m, 1H), 1.28 (t, 1H, *J* = 7.0 Hz), 2.11–2.20 (m, 1H), 2.21 (s, 6H), 2.43 (t, 2H, *J* = 5.5 Hz), 3.20 (t, 2H, *J* = 6.5 Hz), 2.43 (t, 2H, *J* = 5.5 Hz), 3.50–3.86 (m, 26H), 7.45–7.52 (m, 2H), 7.78 (s, 1H), 7.83 and 7.92 (two d, 2H, *J* = 8 Hz), 8.25 (s, 1H); ^{13}C NMR 23.0, 29.7, 40.5, 46.0, 58.9, 68.4–71.3 (m, 15C), 120.7, 123.4, 126.3, 127.5, 128.2, 129.5, 130.4, 133.2, 135.1, 142.2, 169.0; HRMS (ES) *m*/*z*: 597.3503 (*M* + Na) (calcd for $C_{32}H_{50}N_2O_7Na$, 597.3510).

5.6. Aza-crown ethers **14b** and **c** and **15b** and **c**

Independent solutions of amides **12b** (43 mg, 0.078 mmol), **12c** (37 mg, 0.062 mmol), **13b** (40 mg, 0.072 mmol) and **13c** (39 mg, 0.065 mmol) and lithium aluminum hydride (3 equivalent) in 5 mL THF stirred at reflux for 3 h, cooled to 0 °C and diluted with solutions (3 mL) of 5 N LiOH. The mixtures were filtered and the filtrates were diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried and concentrated in vacuo to afford residues which were subjected to column chromatography (10:2:1, EA–MeOH–Et_3N) to give the respective aza-crown ethers **15b** (23 mg, 63%), **15c** (15 mg, 47%), **14b** (18 mg, 45%) and **14c** (18 mg, 46%).

14b: ^{1}H NMR 1.15–1.25 (m, 1H), 1.51–1.60 (m, 1H), 1.81 (t, 2H, *J* = 7.9 Hz), 2.40 (s, 6H), 2.41 (t, 2H, *J* = 5.6 Hz), 3.3–3.75 (m, 26H), 4.2–4.3 (m, 2H), 7.36–7.38 (m, 2H), 7.49 (s, 1H), 7.58 (s, 1H), 7.74–7.77 (m, 2H); ^{13}C NMR 24.0, 29.3, 45.8, 47.9, 57.5, 58.8, 68.6, 70.4–71.6 (11 C), 78.4, 119.9, 120.1, 124.9, 125.1, 127.6, 127.9, 132.8, 133.2, 139.7, 143.5; HRMS (ES) *m*/*z*: 553.3214 (*M* + Na) (calcd for $C_{30}H_{46}N_2O_6Na$, 553.3248).

14c: ^{1}H NMR 1.10–1.25 (m, 1H), 1.40–1.70 (m, 1H), 1.81 (t, 2H, *J* = 7.9 Hz), 2.25 (s, 6H), 2.47 (t, 2H, *J* = 5.6 Hz), 3.01–3.25 (m, 2H), 3.26–72 (m, 24H), 4.25 (s, 2H), 7.33–7.37 (m, 2H), 7.47 (s, 1H), 7.57 (s, 1H), 7.73–7.76 (m, 2H); ^{13}C NMR 24.1, 29.5, 45.7, 47.9, 57.7, 58.7, 68.4, 70.6, 70.9, 71.1, 71.2, 71.4, 71.8, 78.4, 120.1, 120.3, 125.1, 125.3, 127.8, 128.0, 133.0, 133.4, 139.9, 143.7; HRMS (ES) *m*/*z*: 597.3503 (*M* + Na) (calcd for $C_{32}H_{50}N_2O_7Na$, 597.3510).

15b: ^{1}H NMR 0.80 (t, 3H, *J* = 7.1 Hz), 0.85–1.05 (m, 2H), 1.21–1.27 (m, 2H), 1.74–1.84 (m, 2H), 3.07–3.10 (m, 1H), 3.28–3.3.38 (m, 1H), 3.44–3.76 (m, 20H), 4.18 and

4.30 (two d, 2H, $J = 13$ Hz), 7.35–7.40 (m, 2H), 7.50 (s, 1H), 7.60 (s, 1H), 7.75–7.80 (m, 2H); ^{13}C NMR 14.8, 17.3, 35.8, 48.4, 57.8, 70.5, 70.6, 70.7, 71.0, 71.1, 71.3, 71.4, 78.8, 120.1, 120.3, 125.1, 125.3, 127.8, 128.1, 133.0, 133.4, 140.0, 144.2; HRMS (ES) *m*/*z*: 466.2583 (*M* + Na) (calcd for $C_{26}H_{37}NO_5Na$, 466.2564).

15c: ^{1}H NMR 0.80 (t, 3H, $J = 7.0$ Hz), 0.81–1.05 (m, 2H), 1.20–1.40 (m, 2H), 1.75–1.80 (m, 2H), 3.05–3.25 (m, 2H), 3.30–3.75 (m, 24H), 4.26 (s, 2H), 7.34–7.38 (m, 2H), 7.49 (s, 1H), 7.58 (s, 1H), 7.73–7.66 (m, 2H); ^{13}C NMR 14.7, 17.1, 35.6, 48.0, 57.7, 70.5, 70.6, 70.7, 71.0, 71.0, 71.1, 71.4, 78.4, 119.9, 120.1, 125.0, 125.2, 127.7, 127.9, 132.9, 133.2, 139.8, 144.0; HRMS (ES) *m*/*z*: 510.2823 (*M* + Na) (calcd for $C_{28}H_{41}NO_6Na$, 510.2826).

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