Tetrahedron 64 (2008) 5268–5278

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Lariat-crown ether based fluorescence sensors for heavy metal ions

Hajime Maeda [a], David L. Tierney [a], Patrick S. Mariano [a,*], Mainak Banerjee [b], Dae Won Cho [b], Ung Chan Yoon [b,*]

[a] Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, NM 87131, USA
[b] Department of Chemistry and Chemistry Institute for Functional Materials, Pusan National University, Busan 609-735, Republic of Korea

ARTICLE INFO

Article history:
Received 19 February 2008
Received in revised form 10 March 2008
Accepted 11 March 2008
Available online 14 March 2008

ABSTRACT

Exploratory investigations were conducted to probe several aspects of a new strategy for the design of metal ion fluorescence sensors. The results of the investigation show that lariat-crown ethers that contain amine and thioether side chains, and a naphthalene chromophore can be efficiently prepared by using sequences that rely on key single electron transfer promoted photocyclization reactions. Members of this novel family of lariat-crown ethers serve as selective fluorescence sensors for the divalent metal cation of Mg, Hg, and Pb. The response of the sensors to the divalent metal ion is modulated by the nature of the heteroatom(s) incorporated into the side chains. Specifically, lariat-crown ethers that contain tertiary amine groups in their side chains display an off–on type response to Mg(II), Hg(II), and Pb(II). In contrast, thioether side chain containing lariat-crown ethers behave differently in that their fluorescence intensities decrease in the presence of increasing concentrations of these divalent metal cations. These responses can be understood on the basis of selective divalent metal ion induced disruption of intramolecular single electron transfer (SET)-quenching (for side chain amine containing lariat-crown ethers) and the enhancement of intersystem crossing (for side chain thioether containing lariat-crown ethers) of the singlet excited state of the naphthalene fluorophore.

1. Introduction

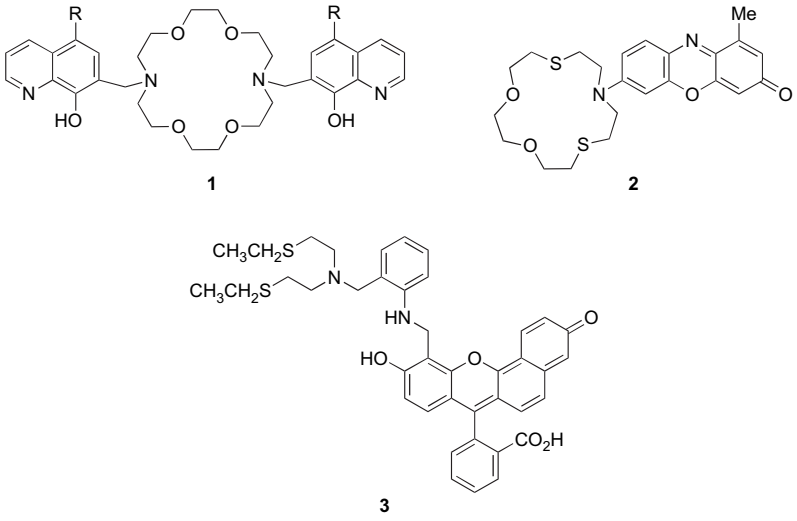
Owing to the ever-growing concern about the effects of environmental contaminants on human health, studies focusing on fluorometric and colorometric detection of heavy metal ions have continued into the 21st century. Perhaps of greatest interest has been the development of sensors that detect Hg(II)[1] in a highly selective and sensitive manner. A variety of fluorescence sensors for these species, based on polymeric, macromolecular, and small molecule scaffolds have been described. Noteworthy in this regard are the recent Hg(II) detection systems developed by (1) Lippard[2] that rely on turn-on fluorescence of naphthafluorescein derivatives, (2) Vicens[3] that are based in the enhancement of fluorescence resonance energy transfer (FRET) of calyx[4]arenes, and (3) Chang[4] that utilizes cyclam derivatives containing benzoxadiazole and pyrene fluorophores.

Beginning with the pioneering work of Sousa[5] and his co-workers in the 1970s, a wide-ranging effort has been given to the development of crown ether based fluorescence sensors for the detection of metal cations.[6] Novel fluorescence sensors for Hg(II) based on crown ether frameworks have come from recent independent studies by Prodi and Savage,[7] and Martinez-Manez and Rurack.[8] The two systems, **1** and **2**, developed by these respective groups, display contrastingly different responses to Hg(II). In the case of the phenoxazinone-tethered dithia, dioxa-monoaza-crown **2**,[8] fluorescence is quenched upon addition of Hg(II), whereas the fluorescence intensity of the 8-hydroxyquinoline containing diaza-crown **1** (R=NO_2)[7] is markedly enhanced in the presence of this divalent metal cation. The behavior of **2** is opposite to that of Lippard's[2] non-crown sensor **3**, containing aza-thia-side chains linked to a seminaphthafluorescein chromophore, which displays a significant enhancement in emission efficiency upon addition of Hg(II). Moreover, the fluorescence of the chloro- and unsubstituted analogs of **1** (R=Cl or H) is dramatically increased by addition of Mg(II), making these sensors highly suitable for use in the detection of this biologically important divalent cation in living cells.[9]

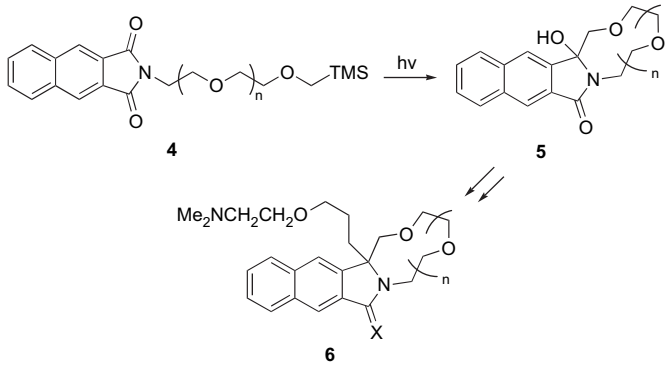
In a previous report,[10] we described an efficient photochemical approach to the synthesis of naphthalene containing, lariat-type crown ethers and the results of a brief evaluation of their use as fluorescence sensors for metal cations. As described in the earlier report, the general route for preparation of these sensors takes advantage of the ready synthesis and SET-promoted photomacrocyclization reactions of silylether terminated, polyethylenoxy-tethered 2,3-naphthalimides **4** (Scheme 1).[11] Sequences

* Corresponding authors.
E-mail addresses: mariano@unm.edu (P.S. Mariano), ucyoon@pusan.ac.kr (U.C. Yoon).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.03.031



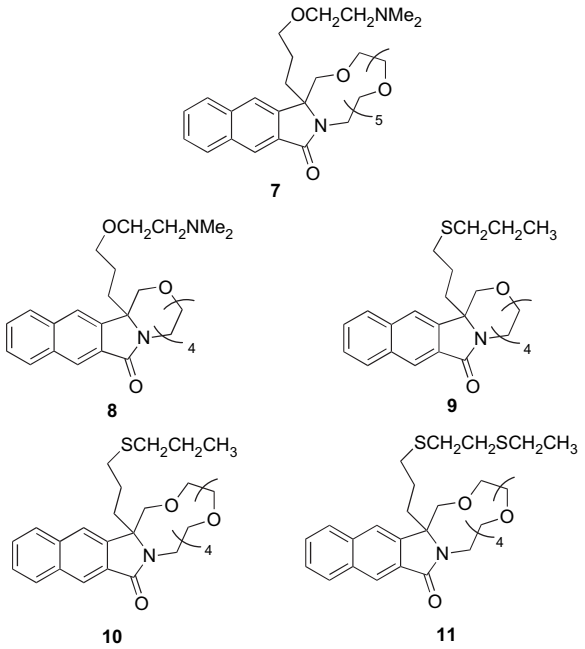
based on this chemistry lead to efficient generation of the crown ethers **5**, which are then transformed to the lariat-crowns **6** by side chain installation and functionality manipulation procedures.[10]



Scheme 1.

As demonstrated in the previous effort,[10] lariat-crown ethers of general structure **6** have alkali metal cation binding affinities that match those of 18-crown-6 and its monoaza analog. Owing to the presence of naphthalene chromophores and side chain, tertiary amine electron-donor sites, these substances also serve as fluorescence sensors for certain metal cations. While alkali metal cations do not perturb the emission efficiencies of these substances (e.g., **7**), Mg(II) and Ag(I) salts promote large enhancements in their fluorescence quantum yields.[10] The effects, associated with formation of 1:1 complexes between the crowns and these metals, have been attributed to the disruption of single electron transfer (SET)-quenching of the naphthalene singlet excited state via complexation involving the side chain, electron donating tertiary amine moiety.

Intrigued by these preliminary observations, we have carried out more detailed studies aimed at exploring the divalent metal cation fluorescence sensing properties of crown ethers related to **6**. In the investigations described below, we have probed the fluorescence properties of tertiary amine-tethered crown **7** and a non-crown analog **8** in order to determine the role played by the crown ring in Mg(II) sensing. In addition, the effects of the heavy metal cations Hg(II) and Pb(II) on the fluorescence efficiencies of **7** and **8** were elucidated. Finally, to evaluate the effects of incorporation of thioether side chains into the crown scaffolds on fluorescence responses to Hg(II) and Pb(II), the emission properties of thioether lariat-crown ethers **10** and **11** along with the non-crown analog **9** were investigated.

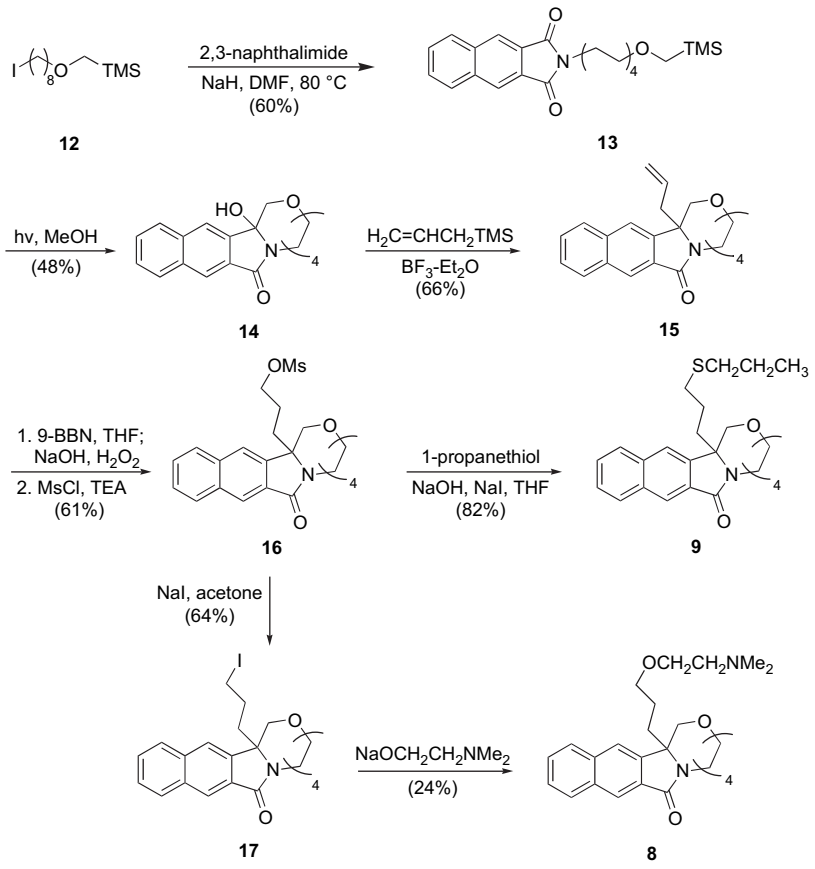


2. Results

2.1. Synthesis of crown ethers and non-crown analogs 8–11

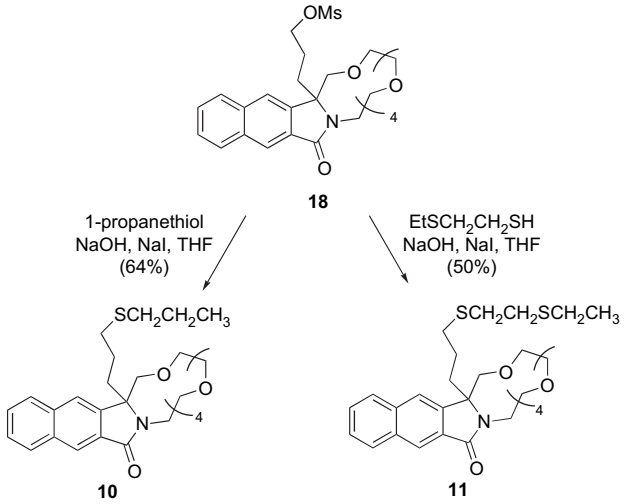
The synthetic pathway employed to prepare the tertiary amine-tethered, macrocyclic naphthalimide **8**, a non-crown analog of **7**, is shown in Scheme 2. The sequence relies on the strategy developed earlier[10] for preparation of related crown ethers. Accordingly, the silylether terminated, polymethylene-tethered 2,3-naphthalimide **13**, generated by reaction of the known[12] iodoalkyl silylmethyl ether **12** with sodium naphthalimide, was subjected to SET-promoted photomacrocyclization promoted by irradiation in methanol. This process produces the macrocyclic amidol **14**, which is transformed to the propenyl analog **15** by Lewis acid promoted reaction with trimethylallylsilane. Side chain manipulation (via mesylate **16**) yields the iodide **17**, which serves as the precursor of **8**.

The thioether-tethered crown ethers **10** and **11** were synthesized starting with the mesylate **18**, prepared in our earlier effort in this area[10] (Scheme 3). Respective reactions of **18** with the thiolate anions generated from propanethiol and mono-*S*-ethylethanedithiol



Scheme 2.

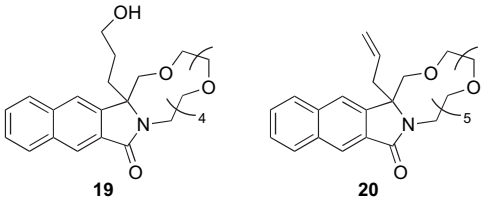
gave **10** and **11** in moderate yields. In a similar manner, the thioether-tethered non-crown analog **9** was produced by reaction of mesylate **16** with propanethiol (Scheme 2).



Scheme 3.

2.2. Fluorescence properties of the crown ethers and non-crown analogs, responses to Mg(II)

Owing to the presence of the 2,3-naphthalamide chromophore, the crown ethers **7**, **10**, and **11** as well as the non-crown analogs **8** and **9** are fluorescent substances (Fig. 1). Non-degassed acetonitrile solutions of these compounds display structured emission in the 340–410 nm range when excited at 290 nm. As expected, the amine- and thioether-tethered naphthalamides are more weakly fluorescent than related crown ethers (e.g., **19** and **20**) that do not possess strong electron-donor groups in their side chains. This phenomenon is associated with fluorescence quenching via reversible SET between the amine and thioether donors and naphthalamide singlet excited states of **7**–**11**.



The fluorescence emission efficiencies of **7**–**11** are not affected by the addition of alkali metal (Na, K, Rb, and Cs) perchlorates. This is exemplified by observations made in studies with the amine- and bis-thioether-tethered crown ethers **7** and **11**. As can be seen from the fluorescence spectra shown in Figure 2, addition of $NaClO_4$ to acetonitrile solutions of these substances does not alter their emission intensities. Thus, even though these crown ethers are moderately strong alkali metal cation complexing agents,[13] binding of monovalent cations does not block quenching of the naphthalamide singlet excited state by SET from the side chain *N*- and *S*-heteroatom donors.

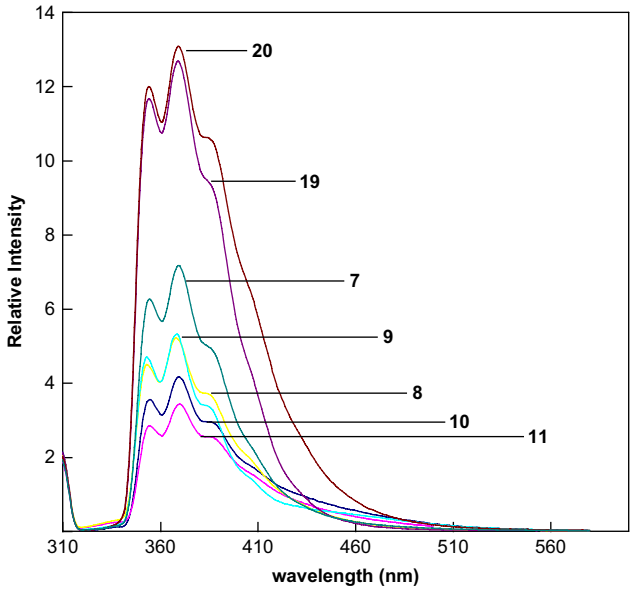


Figure 1. Fluorescence spectra of non-degassed acetonitrile solutions of 1×10^{-5} M amine- and thioether-tethered macrocyclic naphthalamides **7**–**11** and hydroxypropyl- and allyl-analogs **19** and **20**; excitation wavelength 290 nm.

In contrast, certain divalent metal cations cause a wide range of effects on the fluorescence efficiencies of the tethered crown ethers and their non-crown analogs. As noted in our earlier studies in this area,[10] addition of $Mg(ClO_4)_2$ to the amine-tethered crown ether **7** causes a dramatic enhancement of its fluorescence (Fig. 3A). A plot of emission intensity versus $Mg(ClO_4)_2$ concentration (Fig. 3A, insert 1) shows that the rise in intensity reaches a maximum when 1 equiv of Mg(II) is present. Thus, the fluorescence enhancement is associated with formation of a 1:1 Mg(II) complex with **7**. Interestingly, the stoichiometry corresponding to the effect of $Mg(ClO_4)_2$ on the fluorescence intensity of **7** is altered when $KClO_4$ is present. As shown in the insert of Figure 3B, in the presence of a 2 equiv excess of $KClO_4$, maximum fluorescence emission is now associated with formation of a 1:2 complex between Mg(II) and **7**.

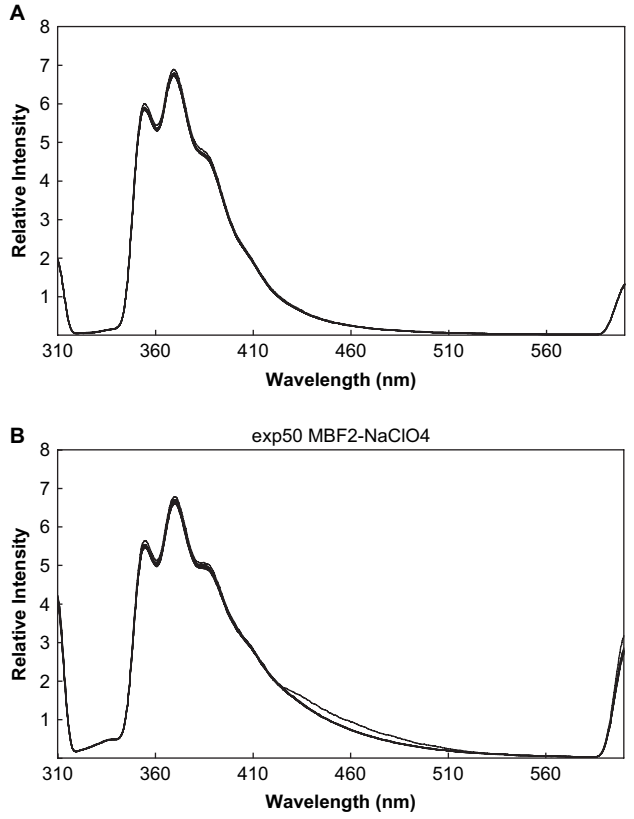


Figure 2. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M amine-tethered crown ether **7** (A) and thioether-tethered crown ether **11** (B) containing 0–2.0×10^{-5} M $NaClO_4$ (increasing in increments of 0.2×10^{-5} M).

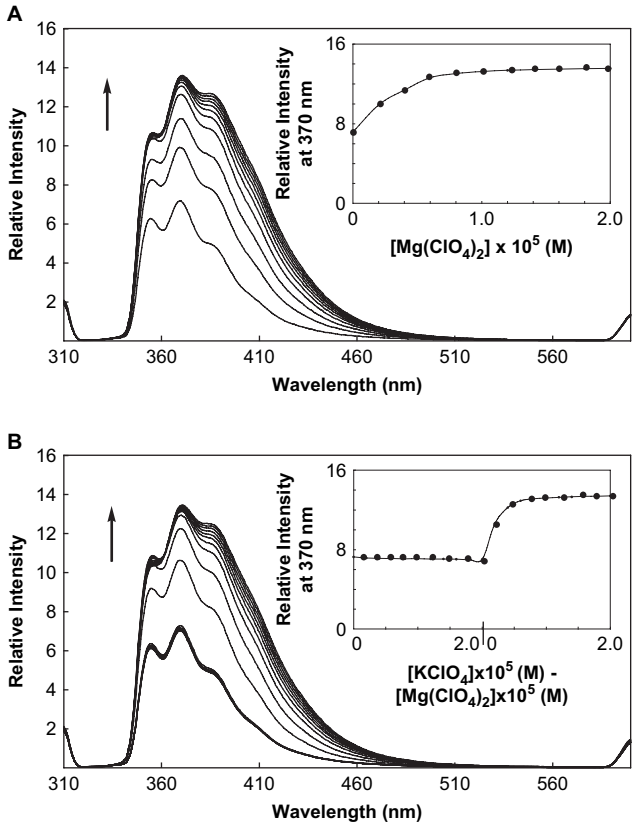


Figure 3. (A) Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M amine-tethered crown ether **7** containing 2.0×10^{-5} M $Mg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrow represents the direction of increasing $Mg(ClO_4)_2$ concentration. The insert is a plot of relative fluorescence intensities at 370 nm versus concentration of $Mg(ClO_4)_2$. (B) Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M amine-tethered crown ether **7** containing 0–2.0×10^{-5} M $KClO_4$ (increasing in increments of 0.2×10^{-5} M) and 0–2.0×10^{-5} M $Mg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrow represents the direction of increasing $Mg(ClO_4)_2$ concentration. The insert is a plot of relative fluorescence intensities at 370 nm versus concentrations of $KClO_4$ (0–2.0×10^{-5} M) and $Mg(ClO_4)_2$ (0–2.0×10^{-5} M).

The non-crown, amine-tethered analog **8** displays similar fluorescence behavior. Like with **7**, addition of $Mg(ClO_4)_2$ to an acetonitrile solution of **8** brings about a large increase in its fluorescence intensity (Fig. 4A). However, in this case plots of emission intensity versus $Mg(ClO_4)_2$ concentration show that the enhancement is due to the generation of a 1:2 complex between Mg(II) and **8** (insert of Fig. 4A) and that the stoichiometry is unaffected by the presence of $KClO_4$ (Fig. 4B and insert).

It is important to point out that the fluorescence changes stimulated by Mg(II), described above, are not the result of alterations of the absorption wavelengths or extinction coefficients of the naphthalamide chromophores in **7** and **8**. This is shown by the observation that the absorption spectra of acetonitrile solutions of these substances remain virtually unchanged upon addition of $Mg(ClO_4)_2$ in the concentration ranges used in the fluorescence studies described above. The fluorescence response of amine-tethered crown ether **7** and its non-crown analog **8** to $Mg(ClO_4)_2$ is

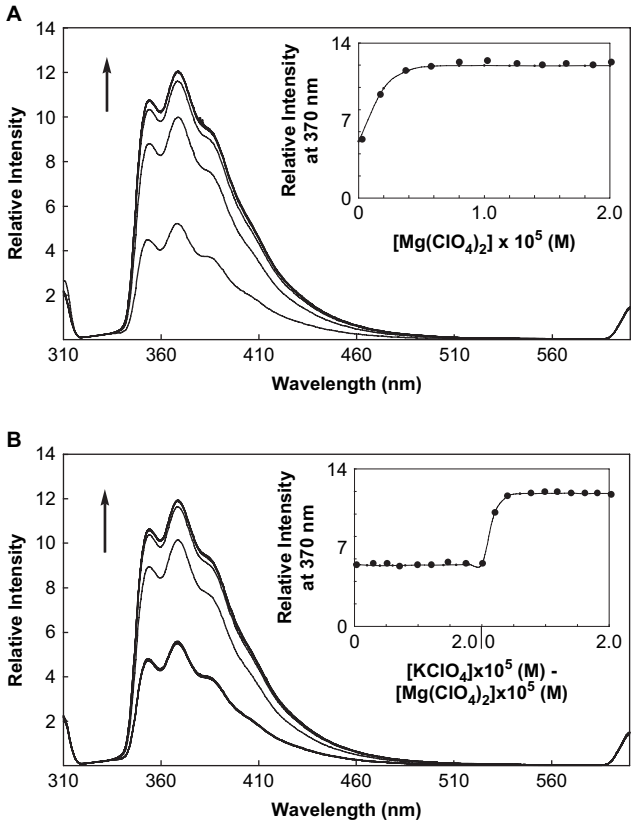


Figure 4. (A) Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M amine-tethered non-crown analog **8** containing 2.0×10^{-5} M $Mg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrow represents the direction of increasing $Mg(ClO_4)_2$ concentration. The insert is a plot of relative fluorescence intensities at 370 nm versus concentration of $Mg(ClO_4)_2$. (B) Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M amine-tethered non-crown analog **8** containing $0–2.0\times10^{-5}$ M $KClO_4$ (increasing in increments of 0.2×10^{-5} M) and $0–2.0\times10^{-5}$ M $Mg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrow represents the direction of increasing $Mg(ClO_4)_2$ concentration. The insert is a plot of relative fluorescence intensities at 370 nm versus concentrations of $KClO_4$ ($0–2.0\times10^{-5}$ M) and $Mg(ClO_4)_2$ ($0–2.0\times10^{-5}$ M).

unique in the series of substances probed in the current effort. For example, addition of this divalent metal cation to acetonitrile solutions of the thioether-tethered naphthalamide **9**–**11** causes only a slight decrease (for **10** and **11**) or no change (for **9**) in fluorescence intensities (Fig. 5).

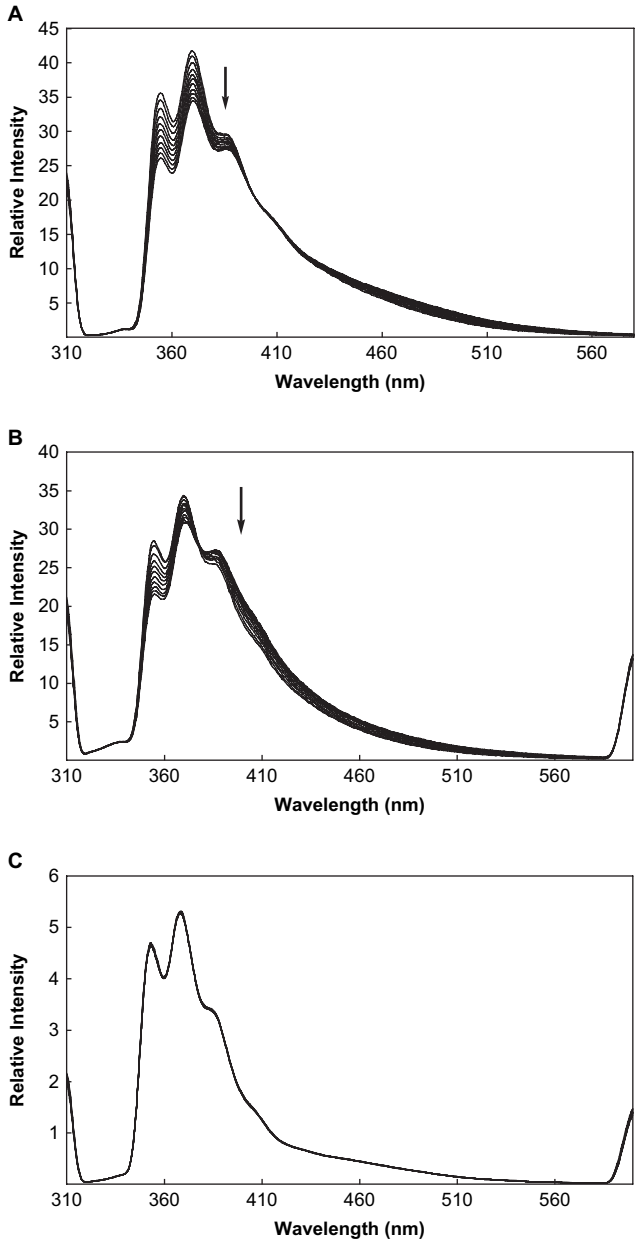


Figure 5. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M thioether-tethered macrocyclic naphthalamides **10** (A), **11** (B), and **9** (C) containing 2.0×10^{-5} M $Mg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrows represent the direction of increasing $Mg(ClO_4)_2$ concentration.

2.3. Responses to Hg(II) and Pb(II)

In a manner similar to those promoted by Mg(II), the fluorescence intensities of the amine-tethered crown **7** and its analog **8** are dramatically increased upon addition of $Hg(ClO_4)_2$ (Figs. 6 and 7). In addition, the responses are associated with the respective formation of a 1:1 and 1:2 complex between Hg(II) and **7** and **8** (inserts in Figs. 6 and 7). The fact that the absorption spectra of **7** and **8** are nearly unperturbed by $Hg(ClO_4)_2$ demonstrates that the observed fluorescence changes are not due to alterations of absorption wavelengths or extinction coefficients. Thus, the amine-tethered macrocyclic naphthalamides **7** and **8**, both serve as 'turn-on' type fluorescence sensors for Hg(II).

Quite different behavior is displayed by the thioether-tethered crown ethers **10** and **11** and the non-crown analog **9**. Addition of $Hg(ClO_4)_2$ to acetonitrile solutions of **9**–**11** brings about a large decrease in their fluorescence intensities (Fig. 8). In each case, fluorescence is maximally quenched when a 1:1 stoichiometric ratio of $Hg(ClO_4)$ and the naphthalamide is reached (inserts in Fig. 8). In an analogous fashion, $Pb(ClO_4)_2$ causes a similar 'turn-off' type, 1:1 stoichiometric effect on the fluorescence emission of the thioether-tethered crown ethers **10** and **11** (Fig. 9). Surprisingly, Pb(II) has no effect on the fluorescence of **9** (Fig. 9).

To determine if the quenching effects of Hg(II) and Pb(II) are a consequence of the presence of thioether moieties in the side chains of **9**–**11**, fluorescence studies were carried out with the model naphthalamides **19** and **20**.[10] As can be seen from the spectra displayed in Figure 10, addition of $Hg(ClO_4)_2$ to acetonitrile solutions of the hydroxypropyl- and allyl-tethered crown ethers **19** and **20** does not promote quenching of the naphthalamide fluorescence. In contrast, addition of $Pb(ClO_4)_2$ causes a large decrease in the fluorescence efficiencies of **19** and **20**, which in each case is associated with formation of a 1:1 Pb(II)–crown ether complex (Fig. 11). The decrease in the fluorescence caused by addition of Pb(II) is

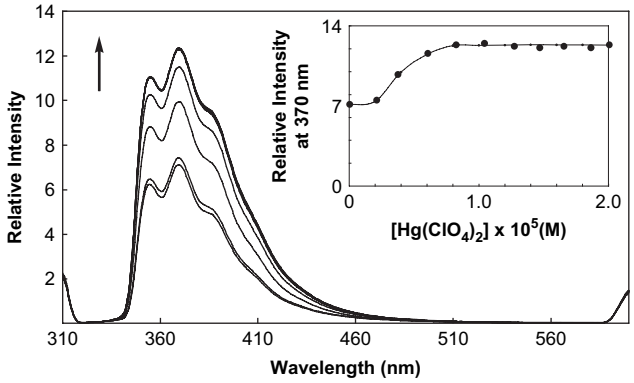


Figure 6. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M amine-tethered crown ether **7** containing 2.0×10^{-5} M $Hg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrow represents the direction of increasing $Hg(ClO_4)_2$ concentration. The insert is a plot of relative fluorescence intensities at 370 nm versus concentration of $Hg(ClO_4)_2$.

observed to be larger for the hydroxypropyl-crown ether **19** than the allyl analog **20**.

Although not thoroughly, the effects of other common divalent metal cations on the fluorescence efficiencies of the macrocyclic naphthalamides were probed. In general, fluorescence emission from each of the thioether-tethered macrocycles **9**–**11** is unaffected by the addition of $Zn(ClO_4)_2$ (Fig. 12) or $Cu(ClO_4)_2$ (Fig. 13).

3. Discussion

Observations made in the studies described above highlight some of the unique features of lariat-crown ether based metal ion fluorescence sensors. One important attribute is the ease with which these sensors are constructed by using concise sequences that rely on SET-promoted photocyclization reactions of readily prepared trimethylsilyl-terminated, polyether-linked naphthalimides. Although the naphthalene chromophore in the sensors produced from these starting materials was selected for the initial studies designed to test concepts, sensors containing a variety of fluorophores with more favorable fluorescence properties (e.g., longer wavelength absorption, higher fluorescence quantum efficiencies, lifetimes, etc.) can be prepared by using the same general strategy.

Another feature of the observations described above concerns the fluorescence response of the lariat-crown ethers to divalent metal cations. The effect of M(II) (M=Mg, Pb, and Hg) on the

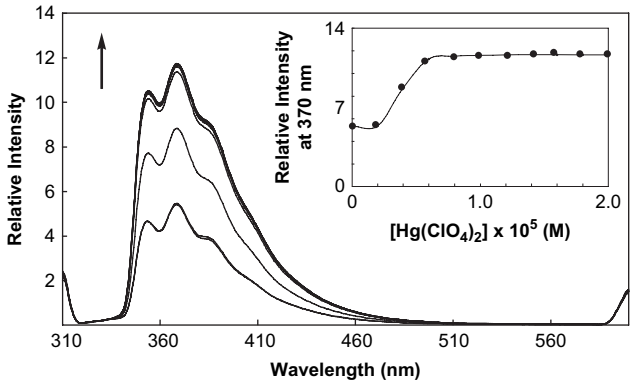


Figure 7. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M amine-tethered non-crown analog **8** containing 2.0×10^{-5} M $Hg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrow represents the direction of increasing $Hg(ClO_4)_2$ concentration. The insert is a plot of relative fluorescence intensities at 370 nm versus concentration of $Hg(ClO_4)_2$.

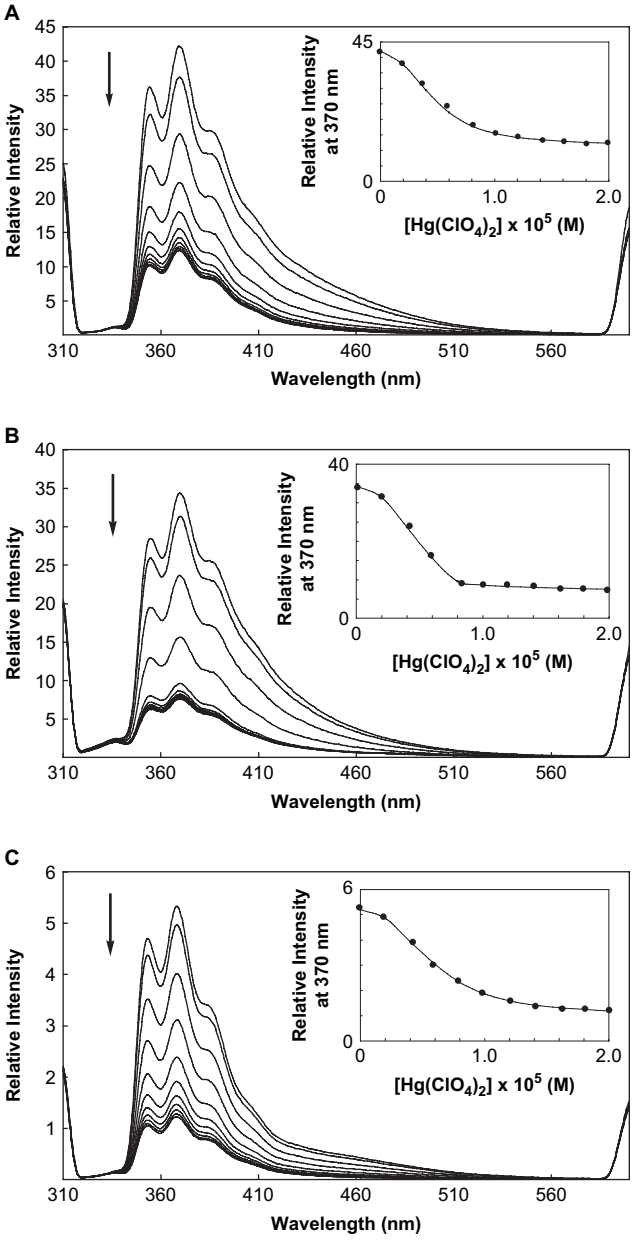


Figure 8. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M thioether-tethered macrocyclic naphthalamides **10** (A), **11** (B), and **9** (C) containing 2.0×10^{-5} M $Hg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrows represent the direction of increasing $Hg(ClO_4)_2$ concentration. The inserts are plots of relative fluorescence intensities at 370 nm versus concentration of $Hg(ClO_4)_2$.

fluorescence properties displayed by these substances can be rationalized in terms of the properties of the various cations. K(I) and Mg(II) are hard Lewis acids, preferring hard N/O donors and a high coordination number (typically 6), and they show little affinity for soft sulfur donors in solution. Pb(II) is a borderline hard/soft acid, only slightly favoring N/O ligands over soft S donors, typically displaying coordination numbers of four or six. Hg(II) is a soft, highly thiophilic Lewis acid that prefers low coordination numbers from two to four. Pb(II) and Hg(II) are very similar in size (ionic radii=1.19 and 1.16 Å, respectively); Mg(II) is significantly smaller at 0.72 Å, and K(I) is the largest of the cations employed in these studies, at 1.38 Å. Thus, although the 18-crown-6 core is best suited to the sequestration of alkali metal ions, it also serves to complex divalent, alkaline earth ions with high affinity. Inclusion of the tertiary amine and ether functions in the side chain of **7**

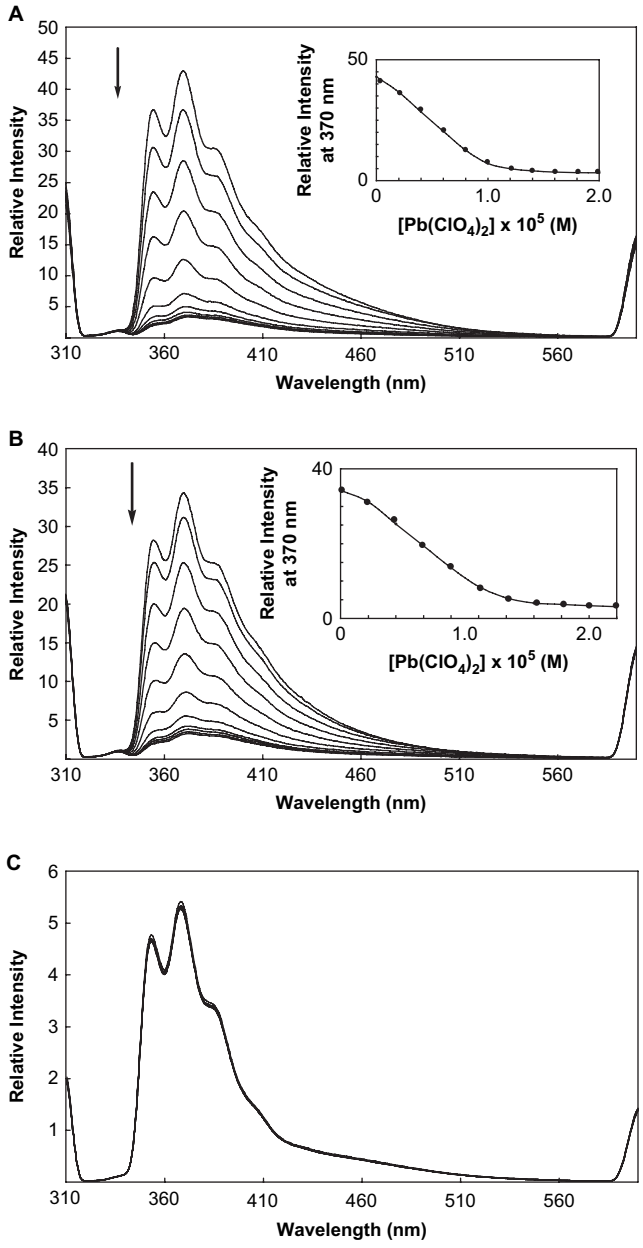


Figure 9. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M thioether-tethered macrocyclic naphthalamides **10** (A), **11** (B), and **9** (C) containing 2.0×10^{-5} M $Pb(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrows represent the direction of increasing $Pb(ClO_4)_2$ concentration. The inserts are plots of relative fluorescence intensities at 370 nm versus concentration of $Pb(ClO_4)_2$.

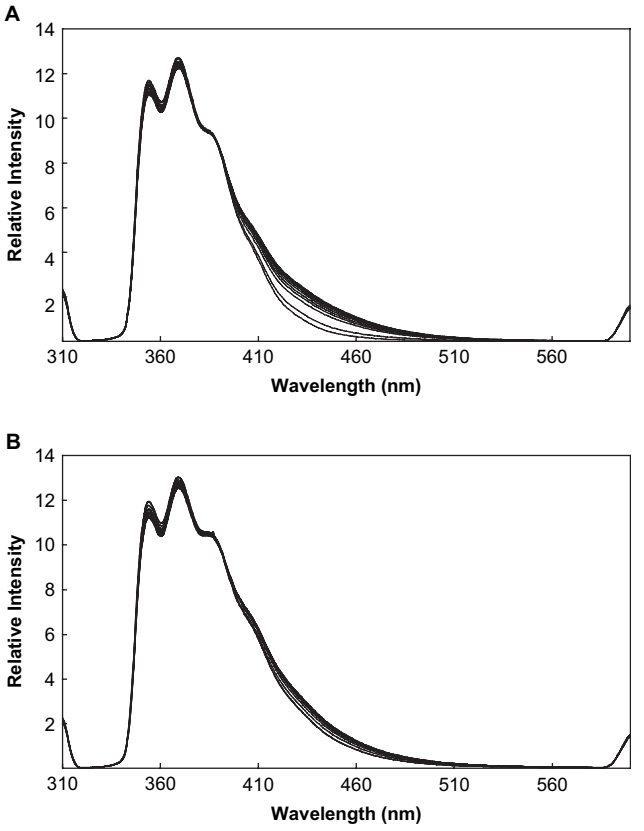


Figure 10. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M hydroxypropyl-tethered crown ether **19** (A) and allyl-tethered analog **20** (B) containing 2.0×10^{-5} M $Hg(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M).

strengthens this interaction, favoring formation of a tight 1:1 complex. Removing the free electron pair of nitrogen in the amine function through complexation results in a loss of SET-quenching of the naphthalamide singlet excited state. The non-crown analog **8** contains only a single oxygen atom in the ring along with the side chain amine nitrogen and ether oxygen as potential donors to metals. Given the requirement of a high coordination number for Mg(II), the formation of a 1:2 complex is to be expected. A similar argument can be used to explain the observed formation of a 1:2 Mg(II) complex with **7** in the presence of K(I). The latter monovalent ion likely competes favorably for the oxygen donor sites in the crown, leaving only the side chain donor atoms to complex the Mg(II). While the present studies cannot rule out participation of the solvent acetonitrile in formation of metal ion complexes, the lack of available π-orbitals on the cation suggests that this is unlikely.

In contrast to their amine-tethered counterparts, the fluorescence of thioether appended lariat-crown ethers is not greatly affected by the presence of Mg(II). The soft sulfur donors are poor ligands for the relatively hard Mg(II) ion. While the sulfur atoms might still participate in forming complexes, in the absence of strong interaction with the Mg(II), complexation is not expected to inhibit SET-quenching of the naphthalamide singlet excited state.

Most fluorescent sensors developed for the detection of Hg(II) display a decrease in fluorescence intensity with increasing concentrations of this heavy divalent metal ion. In these cases fluorophore singlet quenching is a consequence of the relatively large spin-orbit coupling constant of Hg.[14] This type of behavior is observed for both the thioether appended crown and non-crown analogs, **9**–**11**. Here, quenching of the naphthalamide fluorescence in the presence of Hg(II) rises by a combination of the high covalency of the Hg–S bond and heavy atom induced singlet-to-triplet intersystem crossing. Interestingly, the crown and non-crown analogs in this group show similar behavior, both forming 1:1 complexes. This observation indicates that the Hg–S interaction is dominant in determining both fluorescence and fluorescence properties.

The lariat-crown and non-crown ethers **7** and **8**, containing amine tethers have fluorescence responses to Hg(II) that are similar to those seen with Mg(II), with the non-crown **8** again favoring formation of a 1:2 complex. This result suggests that complex formation with Hg(II) requires participation by ring or side chain oxygen donors. The lack of competitive binding of K(I) to **7** likely

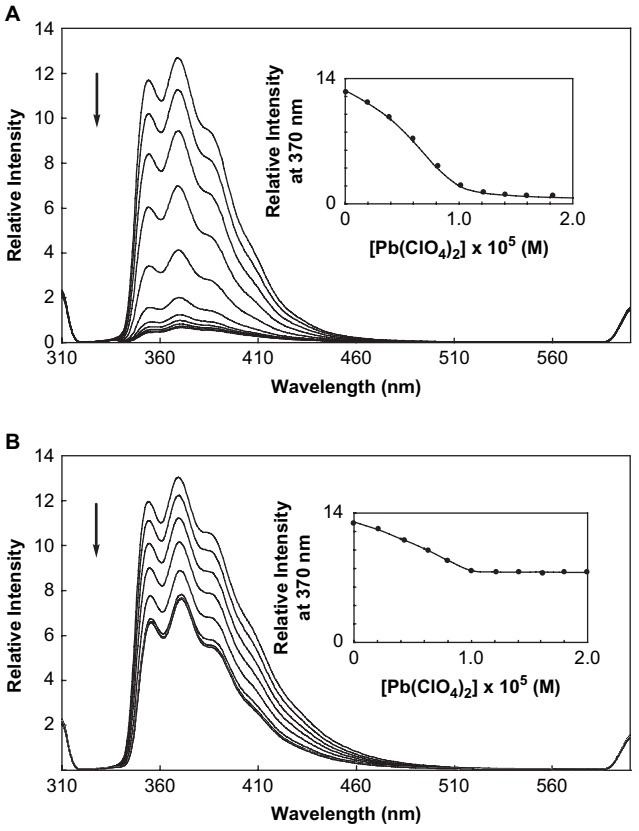


Figure 11. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M hydroxypropyl-tethered crown ether **19** (A) and allyl-tethered analog **20** (B) containing 2.0×10^{-5} M $Pb(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M). The arrows represent the direction of increasing $Pb(ClO_4)_2$ concentration. The inserts are plots of relative fluorescence intensities at 370 nm versus concentration of $Pb(ClO_4)_2$.

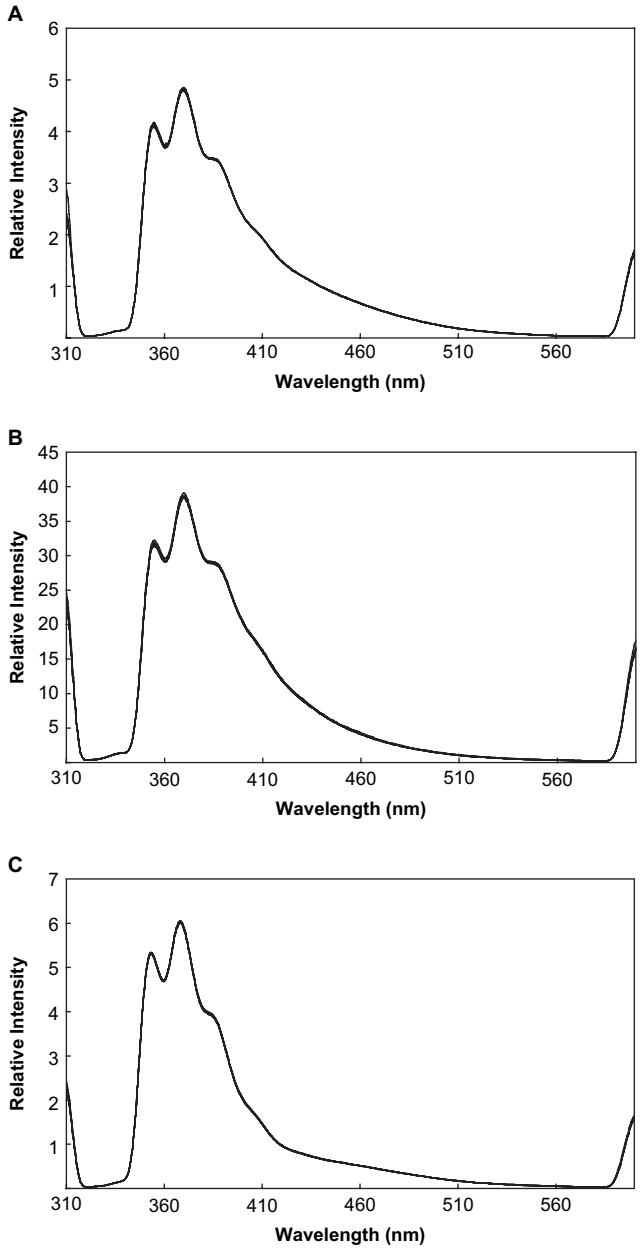


Figure 12. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M thioether-tethered macrocyclic naphthalamides **10** (A), **11** (B), and **9** (C) containing 2.0×10^{-5} M $Zn(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M).

results from a steric effect associated with the much larger Hg(II) ion. This is consistent with the lack of a Hg(II) effect on the allyl and alcohol side chains of the crown ethers **19** and **20**.

The thiophilicity of Pb(II) leads to similar fluorescence responses of the thioether-tethered substances **10** and **11** as seen with Hg(II). The lack of a similar effect with the non-crown **9** suggests that a significant interaction with the donor oxygen atoms of the crown ether is present in the Pb(II) complexes of **10** and **11**. This proposal is further supported by the observation of significant quenching of fluorescence seen in the Pb(II) adducts of the allyl and alcohol appended crowns, **19** and **20** and by the more significant quenching of fluorescence in alcohol appended crown **20**, which has one more oxygen in its side chain.

In summary, this effort has led to the development of a novel family of lariat-crown ethers that serve as fluorescence sensors for the divalent metal cation of Mg, Hg, and Pb. Response of the sensors to the divalent metal ion is modulated by the nature of heteroatom(s) incorporated into the side chains. Specifically, lariat-crown ethers that contain tertiary amine groups in their side chains display an off–on type response to Mg(II), Hg(II), and Pb(II). Thioether side chain containing lariat-crown ethers behave differently in that their fluorescence intensities decrease in the presence of increasing concentrations of these divalent metal cations. These responses can be understood on the basis of a metal ion induced disruption of intramolecular SET-quenching (for side chain amine containing lariat-crown ethers) and the enhancement of intersystem crossing (for side chain thioether containing lariat-crown ethers) of the singlet excited state of the fluorophore.

4. Experimental

4.1. General

Each reaction was run under a dry nitrogen atmosphere. All reagents were obtained from commercial sources and used without further purification and solvents were dried using standard procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ solutions, unless specified otherwise, and chemical shifts are reported in parts per million relative to $CHCl_3$ (7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C), which was used as a chemical shift internal standard for samples in $CDCl_3$. For spectra recorded on acetone-d_6 solutions, chemical shifts are reported in parts per million relative to acetone-d_5 (2.05 ppm for ^{1}H and 29.92 ppm for ^{13}C). For spectra recorded using methanol-d_4, chemical shifts are reported in parts per million relative to methanol-d_3 (3.31 ppm for ^{1}H and 49.15 ppm

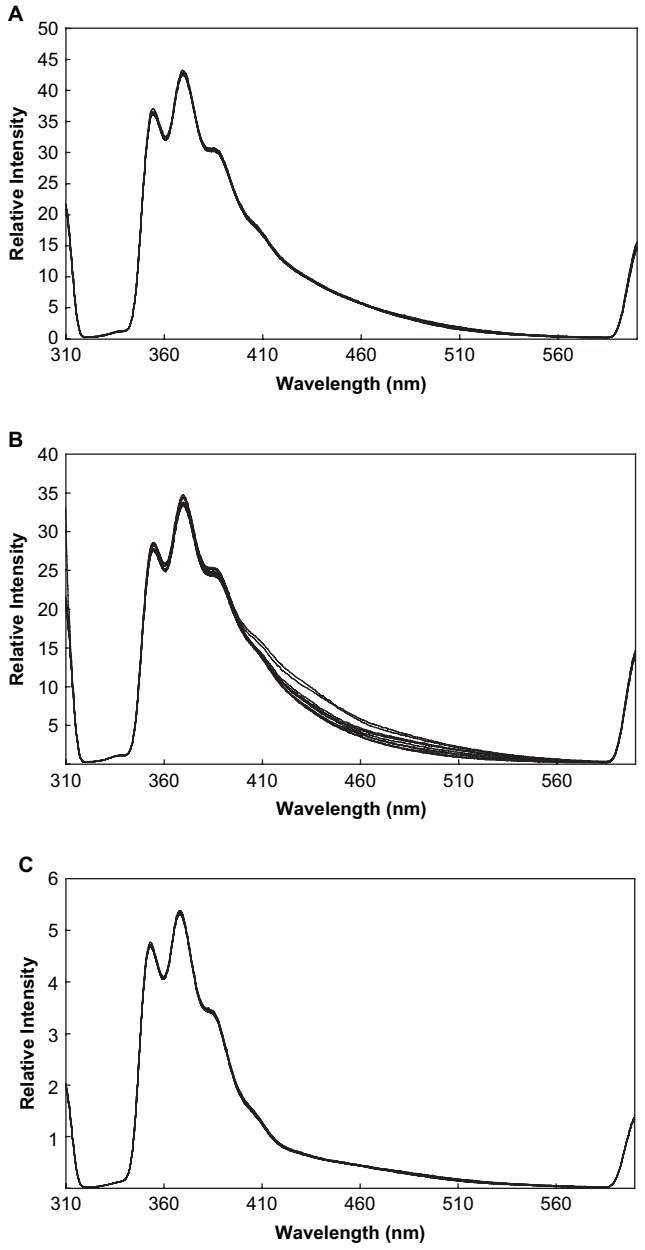


Figure 13. Fluorescence spectra (excitation wavelength 290 nm) of non-degassed acetonitrile solutions of 1×10^{-5} M thioether-tethered macrocyclic naphthalamides **10** (A), **11** (B), and **9** (C) containing 2.0×10^{-5} M $Cu(ClO_4)_2$ (increasing in increments of 0.2×10^{-5} M).

for ^{13}C). ^{13}C NMR resonance assignments were aided by the use of the DEPT-135 technique to determine numbers of attached hydrogens. HRMS data were obtained by using electrospray ionization or fast atom bombardment. All compounds were isolated as oils unless otherwise specified and the purity of each was determined to be >90% by ^1H and ^{13}C NMR analysis. Column chromatography was performed using 230–400 mesh silica gel.

*4.1.1. N-(8-Trimethylsilylmethoxyoctanyl)-2,3-naphthalimide (**13**)*

A suspension of NaH (629 mg, 60% in oil, 15.7 mmol) containing 2,3-naphthalimide (1.55 g, 7.86 mmol) in DMF (10 mL) was stirred at 60 °C for 1 h. The iodide **12**[12] (3.5 g, 10.22 mmol) was then added and the resulting mixture was stirred at 80 °C for 6 h, diluted with water, and extracted with ethyl acetate. The extracts were washed with water, brine, dried, and concentrated in vacuo giving a residue, which was subjected to silica gel column chromatographed (20:1 hexane–ethyl acetate) to afford the naphthalimide **13** (1.91 g, 60%) as white waxy solid (mp 34–35 °C). ^1H NMR ($CDCl_3$) 0.02 (s, 9H), 1.28–1.34 (br s, 8H), 1.48–1.54 (m, 2H), 1.67–1.74 (m, 2H), 3.05 (s, 2H), 3.34 (t, 2H, *J*=6.6 Hz), 3.72 (t, 2H, *J*=7.2 Hz), 7.66–7.69 (m, 2H), 8.03 (d, 1H, *J*=6.0 Hz), 8.04 (d, 1H, *J*=6.0 Hz), 8.30 (s, 2H); ^{13}C NMR ($CDCl_3$) −3.2 (3C), 25.8, 26.6, 28.3, 28.9, 29.1, 29.2, 37.9, 64.3, 75.0, 123.9 (2C), 127.5 (2C), 128.6 (2C), 129.8 (2C), 134.9 (2C), 167.5 (2C); HRMS *m*/*z* (M+1): 412.2290, calcd for $C_{24}H_{34}NO_3Si$: 412.2308.

*4.1.2. Photocyclization of N-(8-trimethylsilylmethoxyoctanyl)-2,3-naphthalimide (**13**)*

A nitrogen purged solution of naphthalimide **13** (300 mg, 0.73 mmol) in 100 mL of methanol was irradiated by using Pyrex glass filtered light for 1 h (48% conversion). Concentration of the photolysate in vacuo gave a residue, which was subjected to silica gel column chromatography (5:1 hexane–ethyl acetate) to afford the macrocyclic ether **14** (98 mg, 40%, based on 48% conversion) as white solid, mp 165–168 °C. ^1H NMR ($CDCl_3$) 1.24–1.53 (m, 11H), 1.84–1.89 (m, 1H), 3.33–3.64 (m, 4H), 3.86 (abq, 2H, *J*=9.6 Hz), 4.37 (br s, 1H, exchangeable), 7.47 (t, 1H, *J*=8.0 Hz), 7.57 (t, 1H, *J*=8.0 Hz), 7.81 (d, 1H, *J*=8.0 Hz), 7.92 (d, 1H, *J*=8.0 Hz), 7.93 (s, 1H), 8.02 (s, 1H); ^{13}C NMR (DMSO-d_6) 19.5, 20.6, 22.9, 25.5, 26.5, 27.0, 37.4, 67.5, 73.4, 89.3, 121.5, 122.9, 127.3, 128.3, 129.1, 130.0, 130.5, 133.9, 135.5, 143.0, 167.8; HRMS *m*/*z* (M+1): 340.1914, calcd for $C_{21}H_{26}NO_3$: 340.1913.

*4.1.3. C-Allyl-macrocyclic ether (**15**)*

To a stirred solution of macrocyclic amidol **14** (440 mg, 1.30 mmol) in 5 mL of CH_2Cl_2 at −78 °C was added allyltrimethylsilane (0.52 mL, 3.26 mmol) followed $BF_3\cdot OEt_2$ (0.91 mL of a 1.0 M solution in ether, 0.91 mmol). The mixture was stirred at 0 °C for 3 h, diluted with water, dried, and concentrated in vacuo to afford the residue, which was subjected to silica gel column chromatography (7:1 hexane–ethyl acetate) to yield the *C*-allyl-macrocyclic ether **15** (324 mg, 66%) as white solid, mp 120–122 °C. ^1H NMR ($CDCl_3$) 1.25–1.31 (m, 2H), 1.41–1.54 (m, 6H), 1.62–1.81 (m, 3H), 2.08–2.20 (m, 1H), 2.73 (dd, 1H, *J*=6.0, 14.4 Hz), 3.01 (dd, 1H, *J*=10.8, 14.4 Hz), 3.30 (t like, 1H, *J*=10.8 Hz), 3.40 (dt, 1H, *J*=2.4, 8.5 Hz), 3.55–3.63 (m, 2H), 3.70–3.83 (m, 2H), 4.82 (d, 1H, *J*=7.5 Hz), 4.96 (d, 1H, *J*=14.0 Hz), 5.01–5.21 (m, 1H), 7.52–7.62 (m, 2H), 7.76 (s, 1H), 7.91 (d, 1H, *J*=7.2 Hz), 8.01 (d, 1H, *J*=7.2 Hz), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$) 22.45, 22.49, 23.6, 23.9, 24.7, 26.2, 37.7, 39.8, 68.2, 70.7, 76.3, 119.3, 120.2, 123.3, 126.3, 127.3, 128.0, 129.4, 130.6, 131.1, 133.2, 134.8, 141.1, 168.3; HRMS *m*/*z* (M+1): 324.2277, calcd for $C_{24}H_{30}NO_2$: 364.2277.

*4.1.4. Macrocyclic ether C-propylmethanesulfonate (**16**)*

To a stirred solution of *C*-allyl-macrocyclic ether **15** (250 mg, 0.66 mmol) in 1 mL of THF at 0 °C was added 9-BBN (4 mL, 1.98 mmol). The mixture was stirred at 25 °C for 12 h and diluted with 1 mL of ethanol, 2 mL of 6 M NaOH, and 1.3 mL of H_2O_2. The resulting solution was stirred at reflux for 1 h, cooled to 25 °C, and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water, brine, dried, and concentrated in vacuo to give the crude alcohol, which was used without purification.

A solution of alcohol (280 mg), triethylamine (0.28 mL, 1.99 mmol), and MsCl (0.1 mL, 1.32 mmol) in CH_2Cl_2 (5 mL) was stirred at 25 °C for 12 h, diluted with CH_2Cl_2, washed with water and brine, dried, and concentrated in vacuo to afford the residue, which was subjected to silica gel column chromatography (1:1 hexane–ethyl acetate) to yield *C*-propylmethanesulfonate **16** (190 mg, 61% for two steps) as colorless oil. ^1H NMR ($CDCl_3$) 0.88–1.01 (m, 1H), 1.23–1.35 (m, 5H), 1.43–1.55 (m, 4H), 1.59–1.80 (m, 3H), 1.96–2.05 (m, 1H), 2.07–2.18 (m, 1H), 2.52–2.62 (m, 1H),

2.90 (s, 3H), 3.21 (br t, 1H, J=11.4 Hz), 3.36–3.42 (m, 1H), 3.56–3.60 (m, 2H), 3.71–3.80 (m, 2H), 4.01–4.06 (m, 2H), 7.52–7.63 (m, 2H), 7.75 (s, 1H), 7.91 (d, 1H, J=7.2 Hz), 8.02 (d, 1H, J=7.2 Hz), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) 22.4, 22.5, 22.6, 23.6, 23.7, 24.8, 26.3, 29.3, 37.2, 39.7, 68.1, 69.5, 70.7, 77.2, 120.0, 123.7, 126.6, 127.7, 128.1, 129.5, 130.5, 133.3, 135.0, 140.9, 168.4; HRMS m/z (M+1): 460.2155, calcd for $C_{25}H_{34}NO_5S$: 460.2158.

4.1.5. Thioether-tethered macrocyclic ether (**9**)

A suspension of NaOH (76 mg, 1.9 mmol) containing 1-propanethiol in anhydrous THF (5 mL) was stirred at 50 °C for 1 h. The methanesulfonate **16** (90 mg, 0.19 mmol) was added dropwise followed by NaI (14 mg, 0.09 mmol). The resulting mixture was stirred at 55–60 °C for 1 h, concentrated in vacuo, giving a residue, which was diluted with ethyl acetate, washed with water and brine, dried, and concentrated in vacuo to afford a residue, which was subjected to silica column chromatography (5:1 hexane–ethyl acetate) to yield the thioether **9** (70 mg, 82%) as colorless oil. ^{1}H NMR ($CDCl_3$) 0.82 (s, 3H), 1.11–1.21 (m, 1H), 1.22–1.30 (m, 2H), 1.35–1.51 (m, 3H), 1.56–1.73 (m, 8H), 1.96–2.34 (m, 7H), 2.50 (dt, 1H, J=4.5, 12.2 Hz), 3.23 (br t, 1H, J=11.4 Hz), 3.38 (dt, 1H, J=2.4, 8.2 Hz), 3.53–3.59 (m, 2H), 3.72–3.79 (m, 2H), 7.51–7.60 (m, 2H), 7.74 (s, 1H), 7.90 (d, 1H, J=7.2 Hz), 8.01 (d, 1H, J=7.2 Hz), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 22.1, 22.3, 22.7, 22.8, 23.4, 23.5, 24.8, 26.3, 31.7, 31.9, 33.8, 39.6, 68.5, 70.4, 76.95, 119.8, 123.4, 126.3, 127.4, 128.0, 129.4, 130.5, 133.2, 134.9, 141.5, 168.4; HRMS m/z: 440.2610, calcd for $C_{27}H_{38}NO_2S$: 440.2623.

4.1.6. Macrocyclic ether C-propyliodide (**17**)

A solution of the methanesulfonate **16** (80 mg, 0.17 mmol) and sodium iodide (254 mg, 1.7 mol) in acetone (30 mL) was stirred at reflux for 6 h. Concentration in vacuo gave a residue, which was diluted with water and extracted with ethyl acetate. The extracts were washed with water and brine, dried, and concentrated giving a residue, which was subjected to silica gel column chromatography (4:1 hexane–ethyl acetate) to afford the iodide **17** (55 mg, 64%) as colorless oil. ^{1}H NMR ($CDCl_3$) 0.98–1.11 (m, 1H), 1.23–1.36 (m, 4H), 1.40–1.57 (m, 5H), 1.61–1.79 (m, 3H), 1.95–2.05 (m, 1H), 2.07–2.18 (m, 1H), 2.51–2.60 (m, 1H), 3.00 (dt, 2H, J=1.8, 6.6 Hz), 3.25 (br t, 1H, J=10.8 Hz), 3.40 (dt, 1H, J=2.7, 8.7 Hz), 3.56–3.62 (m, 2H), 3.71–3.80 (m, 2H), 7.53–7.63 (m, 2H), 7.75 (s, 1H), 7.92 (d, 1H, J=8.0 Hz), 8.02 (d, 1H, J=8.0 Hz), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) 6.42, 22.3, 22.6, 23.5 (2C), 24.8, 26.29, 26.34, 33.9, 39.7, 68.0, 70.5, 77.2, 119.9, 123.5, 126.4, 127.5, 128.1, 129.5, 130.4, 133.2, 134.9, 141.1, 168.3; HRMS m/z (M+1): 492.1399, calcd for $C_{24}H_{31}INO_2Si$: 492.1400.

4.1.7. N,N-Dimethylamine-tethered macrocyclic ether (**8**)

A mixture of *N*,*N*-dimethylethanolamine (0.2 mL) and sodium (35 mg, 1.52 mmol) was stirred until the sodium metal dissolved. Iodide **17** (75 mg, 0.15 mmol) in 0.1 mL of THF was added and the mixture was stirred for 16 h at room temperature. Concentration in vacuo gave a residue, which was diluted with water and extracted with ethyl acetate. The extracts were washed with water and brine, dried, and concentrated in vacuo giving a residue, which was subjected to silica gel column chromatography (10:1 $CHCl_3$–MeOH) to afford **8** (16 mg, 24%) as yellow oil. ^{1}H NMR ($CDCl_3$) 0.83–0.88 (m, 1H), 1.03–1.18 (m, 2H), 1.24–1.30 (m, 3H), 1.35–1.52 (m, 4H), 1.55–1.72 (m, 3H), 1.91–2.04 (m, 1H), 2.07–2.16 (m, 2H), 2.36 (s, 6H), 2.36–2.51 (m, 1H), 2.60 (br s, 1H), 3.18–3.28 (m, 3H), 3.35–3.47 (m, 3H), 3.54–3.59 (m, 2H), 3.70–3.81 (m, 2H), 7.51–7.62 (m, 2H), 7.75 (s, 1H), 7.90 (d, 1H, J=7.2 Hz), 8.01 (d, 1H, J=7.2 Hz), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$) 22.4 (2C), 22.8 (2C), 23.59 (2C), 23.64 (2C), 24.9, 26.4, 29.7, 29.9, 39.7, 68.7, 70.5, 70.7, 77.2, 120.0, 123.5, 126.3, 127.5, 128.1, 129.3, 130.8, 133.3, 135.0, 141.6, 168.5; HRMS m/z: 453.3124, calcd for $C_{28}H_{41}N_2O_3$: 453.3117.

4.1.8. Thioether-tethered crown (**10**)

A mixture of 1-propanethiol (0.21 mL, 2.35 mmol) and finely powdered NaOH (94 mg, 2.35 mmol) in dry THF (8 mL) was stirred at 50 °C for 1 h. A THF (2 mL) solution of the known[10] methanesulfonate **18** (130 mg, 0.235 mmol) was added and stirring at 50 °C was continued for 4 h. Concentration in vacuo gave a residue, which was diluted with ethyl acetate, washed with water and brine, dried, and concentrated in vacuo giving a residue, which was subjected to silica gel column chromatography (2% MeOH in ethyl acetate) to afford **10** (80 mg, 64%) as an oil. ^{1}H NMR ($CDCl_3$) 0.83 (t, 3H, J=7.2 Hz), 1.09–1.25 (m, 2H), 1.36–1.49 (m, 2H), 2.21–2.28 (m, 4H), 2.29–2.36 (m, 2H), 3.52–3.86 (m, 21H), 3.90–3.99 (m, 1H), 7.51–7.62 (m, 2H), 7.85 (s, 1H), 7.91 (d, 1H, J=7.2 Hz), 8.00 (d, 1H, J=7.2 Hz), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 22.4, 22.7, 31.8, 31.9, 33.8, 40.5, 68.2, 68.6, 70.4, 70.6, 70.7, 70.8, 70.9, 71.0, 71.2, 76.8, 77.2, 120.6, 123.4, 126.2, 127.4, 128.1, 129.6, 130.2, 133.1, 135.0, 142.0, 168.6; HRMS m/z: 532.2753, calcd for $C_{29}H_{42}NO_6S$: 532.2733.

4.1.9. Bis-thioether-tethered crown (**11**)

A mixture of 2-mercaptoethyl ethyl sulfide (135 mg, 1.1 mmol) and finely powdered NaOH (44 mg, 1.1 mmol) in dry THF (5 mL) was stirred at 50 °C for 1 h. A THF (1 mL) solution of the known[10] methanesulfonate **18** (62 mg, 0.11 mmol) and NaI (8 mg, 0.055 mmol) was added and the mixture was stirred at 50 °C for 2 h. Concentration in vacuo gave a residue, which was diluted with ethyl acetate, washed with water and brine, dried, and concentrated in vacuo giving a residue, which was subjected to silica gel column chromatography (ethyl acetate) to afford **11** (36 mg, 56%) as an oil. ^{1}H NMR ($CDCl_3$) 0.79–0.86 (m, 2H), 1.12 (t, 3H, J=7.2 Hz), 1.17–1.25 (m, 2H), 2.09–2.54 (m, 8H), 3.46–3.85 (m, 21H), 3.90–3.97 (m, 1H), 7.49–7.59 (m, 2H), 7.84 (s, 1H), 7.90 (d, 1H, J=7.8 Hz), 7.98 (d, 1H, J=7.8 Hz), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$) 14.6, 22.5, 25.8, 31.4, 31.85, 31.92, 40.6, 68.2, 68.6, 70.4, 70.54, 70.56, 70.65, 70.76, 70.82, 70.9, 71.3, 76.8, 77.2, 120.6, 123.4, 126.3, 127.5, 128.2, 129.4, 130.1, 133.1, 135.1, 141.9, 168.9; HRMS m/z: 578.2369, calcd for $C_{30}H_{44}NO_6S_2$: 578.2610.

Acknowledgements

This research was supported by (for U.C.Y.) the Korea Research Foundation (MOEHRD, Basic Research Promotion Fund RO5-2004-000-10557-0) and (for P.S.M.) the National Science Foundation (CHE-0550133).

References and notes

1. Harris, H. H.; Pickering, I. J.; George, G. N. *Science* **2003**, *301*, 1203; Bolger, P. M.; Schwetz, B. A. *N. Engl. J. Med.* **2002**, *347*, 1733; Guallar, E.; Sanz-Gallardo, M. I.; van't Veer, P.; Bode, P.; Aro, A.; Gómez-Aracena, J.; Kark, J. D.; Riemersma, R. A.; Martín-Moreno, J. M.; Kok, F. J. *N. Engl. J. Med.* **2002**, *347*, 1747; Yoshizawa, K.; Rimm, E. B.; Morris, J. S.; Spate, V. L.; Hsieh, C.-C.; Spiegelman, D.; Stampfer, M. J.; Willett, W. C. *N. Engl. J. Med.* **2002**, *347*, 1755.
2. Nolan, E. M.; Racine, M. E.; Lippard, S. J. *Inorg. Chem.* **2006**, *45*, 2742; Nolan, E. M.; Lippard, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 5910.
3. Othman, A. B.; Lee, J. W.; Wu, J.-S.; Kim, J. S.; Abidi, R.; Thuery, P.; Strub, J. M.; Dorsselear, A. V.; Vicens, J. *J. Org. Chem.* **2007**, *72*, 7634.
4. Kim, S. H.; Kim, J. S.; Chang, S.-K. *Org. Lett.* **2006**, *8*, 371.
5. Sousa, L. R.; Larson, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 307; Larson, J. M.; Sousa, L. R. *J. Am. Chem. Soc.* **1978**, *100*, 1943.
6. de Sylva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515; Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev.* **2004**, *104*, 2723; Chae, M.-Y.; Cherian, X. M.; Czarnik, A. W. *J. Org. Chem.* **1993**, *58*, 5797.
7. Prodi, L.; Bargossi, C.; Montalti, M.; Zaccheroni, N.; Su, N.; Bradshaw, J. S.; Izatt, R. M.; Savage, P. B. *J. Am. Chem. Soc.* **2000**, *122*, 6769.
8. Descalzo, A. B.; Martinez-Manez, R.; Radeglia, R.; Rurack, K.; Soto, J. *J. Am. Chem. Soc.* **2003**, *125*, 3418.
9. Farruggia, G.; Iotti, S.; Prodi, L.; Montalti, M.; Zaccheroni, N.; Savage, P. B.; Trapani, V.; Sale, P.; Wolf, F. I. *J. Am. Chem. Soc.* **2006**, *128*, 344.
10. Wang, R.; Zhao, Z.; Mariano, P. S.; Choi, K. H.; Kim, S. H.; Yoon, U. C. *J. Photochem. Photobiol., A: Chem.* **2005**, *175*, 232.

11. Yoon, U. C.; Kwan, H. C.; Hyung, T. G.; Choi, K. H.; Oh, S. W.; Yang, S.; Zhao, Z.; Mariano, P. S. *J. Am. Chem. Soc.* **2004**, *126*, 1110; Yoon, U. C.; Oh, S. W.; Lee, J. H.; Park, J. H.; Kang, K. T.; Mariano, P. S. *J. Org. Chem.* **2001**, *66*, 939; Yoon, U. C.; Jin, Y. X.; Oh, S. W.; Park, C. H.; Park, J. H.; Campana, J. H.; Cai, X.; Duesler, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 10664.
12. Yoon, U. C.; Oh, J. H.; Kim, J. S.; Lee, J. G.; Kang, K. T.; Mariano, P. S. *Bull. Korean Chem. Soc.* **1992**, *13*, 166.
13. Maeda, H.; Mariano, P. S.; Yoon, U. C., unpublished results.
14. Masuhara, H.; Shioyama, H.; Saito, T.; Hamada, K.; Yasoshima, S.; Mataga, N. *J. Phys. Chem.* **1984**, *88*, 5868.