REVIEW ARTICLE

The chemistry of constrained crown ring systems and fluorescence sensor applications

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Abstract Using anthraquinone as a useful synthetic scaffold and the ability of anthraquinone to form stable intermediate reduction products (i.e. anthrones and anthranols), we have synthesized a wide variety of constrained crown ring systems where the receptor includes several types and patterns of Lewis bases that can tune receptor selectivity for different metal cations. Constrained crown ring systems are defined as macrocycles that contain an intraannular heteroatom, in addition to the normal peripheral Lewis bases that compose the outer ring of the macrocycle. These fluorescence sensors predominantly utilizes the internal charge transfer mechanism to promote fluorescence, but has also led to the development of new photophysical mechanisms, i.e. metal-mediated tautomerization, to selectively detect Zn(II) ion in solution. We are currently pursuing a number of synthetic avenues to incorporate new functional groups and lumophores such that a myiad of different photophysical mechanisms under optimal conditions can be employed to improve solubility, sensitivity and take advantage of the cross pollination of electrochemistry and fluorescence spectroscopy with these sensors which incorporate closely integrated electrochemical, fluorescence and receptor subunits.
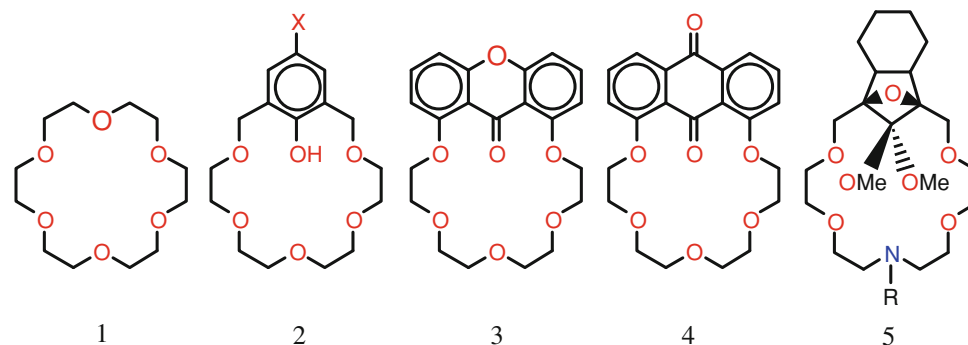
Keywords Anthraquinone · Constrained crown ether · Fluorescence sensors · ICT

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Introduction

18-Crown-6, **1**, initially investigated by Pederson [1], is the quintessential cyclic crown ether that promotes solubility and stability of ionic species in nonpolar solvents. Compounds **2**–**4** contain similar 18-crown cyclic motifs, with the exception that an intraannular substituent has been introduced within the cavity. We classify these compounds as *constrained crown ring systems,* macrocycles that contain an intraannular heteroatom, in addition to the normal peripheral atoms that compose the outer ring of the macrocycle. Here, the cavity size is reduced by the presence of the heteroatom, and the macrocycle generally contains a scaffold that limits the flexibility of part of the receptor. Molecules of this structural type originated with **2** and were explored for their photoinduced electron transfer potential (employing reversible quinone/hydroquinone redox chemistry) as models for photosynthesis [2–8]. Compound **3**, containing an intraannular carbonyl oxygen from the xanthone scaffold, has been employed as a luminescence sensor for the detection of alkaline earth metals [9–12], and, similar to **2**, the anthraquinone derivative, **4**, exhibits anodic shifts in the quinone reduction potentials when electropositive cations are complexed within the macrocycle, resulting in an electrochemical sensor [13–16]. In addition, compound **4** has been derivatized with dithio-Ylids [17], reduced to the corresponding anthracene system [18], and a cyclic anthraquinone analog containing two triazole rings has been reported as a fluorescence sensor selective for Al(III) [19]. Recently, Khan has synthesized compound **5**, which contains two methoxy groups within the ring, and the chemistry of the ring has been expanded to include a nitrogen heteroatom where additional functionality can be added [20]. We know of only two examples of constrained systems where smaller rings contain an

intraannular heteroatom, one involving dibenzocrowns with proton-ionizable pendent groups, used for the extraction of aqueous alkali metals into organic solvent [21], and the other involving the substitution of polyether chains at the 1,3-positions of a sugar molecule [22, 23].

This sensor was originally classified as a $n-\pi^* \rightarrow \pi-\pi^*$ inversion sensor, where upon coordination of the electropositive cation with one of the lone pairs of the carbonyl group, the non-radiative $n-\pi^*$ relaxation pathway is raised above the energy of the radiative $\pi-\pi^*$ pathway,

Here we review the reaction chemistry of the parent macrocycle **4** that yields a variety of different adducts all associated with the fluorescence detection of many different metal cations of clinical and environmental concern (Scheme 1). **4** is made in 40–50 % yield via a one-step reaction by nucleophilic aromatic substitution of 1,8-dichloroanthraquinone with the appropriate glycol [13].

Fluorescent acid sensors

As described in an series of earlier articles, we helped pioneer the use of constrained crown ring systems as fluorescence sensors starting in the late 1990s [24–28]. The parent macrocycle **4** was found to fluorescence brightly in the presence of strong mineral acids in acetonitrile. With the addition of acid, a yellow-orange emission is produced in the relative order $HClO_4 > H_2SO_4 > HNO_3$. Since the leveling effect of acids in this organic solvent is less pronounced than in aqueous media, compound **4** is essentially an anion sensor, where the strength of the conjugate base dictates the amount of acid available. Binding constants and static versus dynamic quenching constants for various acids have been measured for several different related open bipodands and closed macrocycles.

Crystallography of the perchlorate adduct revealed that hydronium ion is bound within the cavity of the macrocycle (Fig. 1), producing the same emission in the solid-state. The hydronium ion's three-fold symmetry matches very well with the three fold symmetry of the macrocycle that includes the carbonyl oxygen and two ether oxygen atoms. Hydrogen bond lengths of ~ 2.5 Å signify the formation of low-barrier hydrogen bonds (LBHB) within the adduct, and the hydronium ion adopts a trigonal pyramidal structure as expected.

resulting in enhanced emission [29]. The authors contend that sensor **4** is also a member of the more familiar internal charge transfer (ICT) family of photophysical mechanisms [29, 30]. ICT sensors always have the receptor (the crown ring in this case) integrated with the lumophore (the anthraquinone), which is the case with **4**. The push–pull of electrons between donors and acceptors within ICT sensors governs the emission wavelength that results. In compound **4**, coordination of the carbonyl group (the acceptor) to an electropositive center results in the expected red shift in absorbance, and the phenyl ethers then constitute the electron donor groups within the molecule. The corresponding increase in quantum yield is also governed by increased stiffening of the molecule upon adduct formation, particularly since the internal carbonyl C=O stretch would be restricted, limiting potential vibrational modes of the anthraquinone lumophore, thus reducing non-radiative relaxation.

Fluorescent transition-metal ion sensors

The ICT photophysical mechanism is even more apparent with the introduction of different metal cations, particularly those of environmental concern, such as cadmium, mercury, and lead cations. Lead, when bound within the cavity of **4**, also interacts with the carbonyl oxygen (Fig. 1), and a large enhancement in luminescence at 515 nm (green emission) is observed (Fig. 2) [31]. Sulfur-substituted analogues of **4** also demonstrate luminescence enhancement and excellent selectivity for different heavy metal cations results. Cadmium(II) is selective for the cyclic disulfur derivative **6** (orange emission, center), and mercury(II) is selective for the cyclic trisulfur derivative **7**
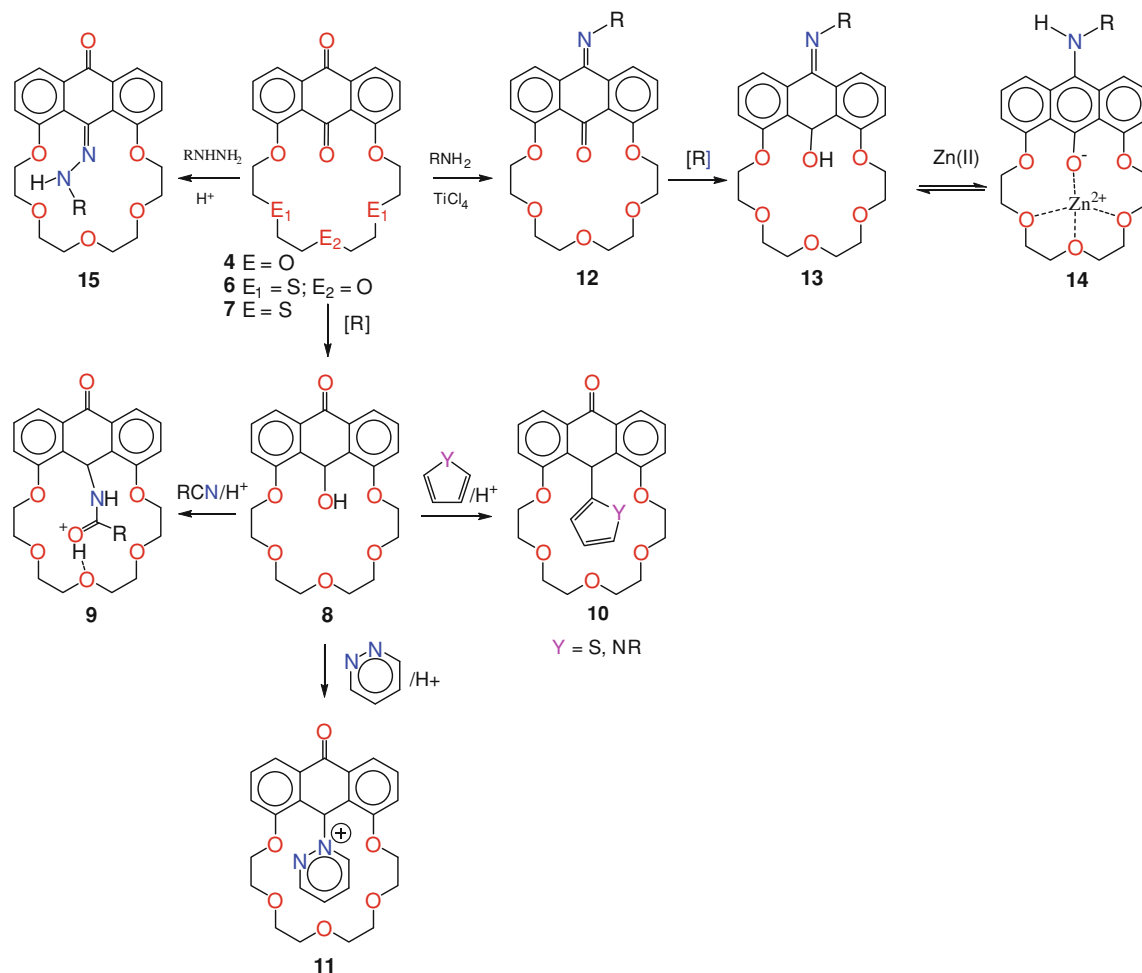
Scheme 1 Reaction sequence of the parent constrained crown ether macrocycle **4**

(yellow emission, top) [32]. These examples demonstrate that constrained macrocyclic ring systems exhibit excellent selectivity for cations of environmental concern.

Reduction and reactivity

Using the rich reduction chemistry available for anthraquinones, we have selectively reduced the intraannular carbonyl in **4** to produce the 2° alcohol, **8** (Scheme 1) [33]. The addition of strong acid and a nucleophilic nitrile group forms secondary amides that leaves the amide oxygen protonated, forming a LBHB with the central ether oxygen (compound **9** in Scheme 1 and the crystal structure shown in Fig. 3) [33]. Acid protonates the alcohol in **8**, generating a carbocation that is then attacked by the nucleophilic nitrile to generate the amide via the Ritter amide synthesis [34].

A wide variety of nitriles can be used, including alkyl, acrylo, and dinitriles. Aromatic nitriles, which have low nucleophilicity due to resonance between the nitrile group

and the aromatic ring, are unreactive. The LBHB essentially blocks the macrocyclic pore, and neutralization produces a free amide that undergoes a large amplitude change in geometry to unblock the pore (Fig. 3). We have shown that unprotonated adducts do coordinate metal cations as well, including coordination with the amide oxygen atom. Formation of adducts using other nucleophiles, such as pyridines, phosphines, and primary amides, has also been demonstrated (compound **11**, Scheme 1) [35]. Through a combination of X-ray crystallographic and competition studies, a nucleophilic reactivity series has been developed that parallels what is already known about nucleophilicity. Reaction of diimines, analogues of compound **11**, form ammonium adducts, which could potentially add an additional Lewis base for coordination to metal cations; however addition of metals was found to dissociate ammonium adducts, due to the relatively weak C–N coordinate-covalent bond.

The pi-electrons of activated aromatic compounds, such as thiophene and pyrrole groups, can also act as
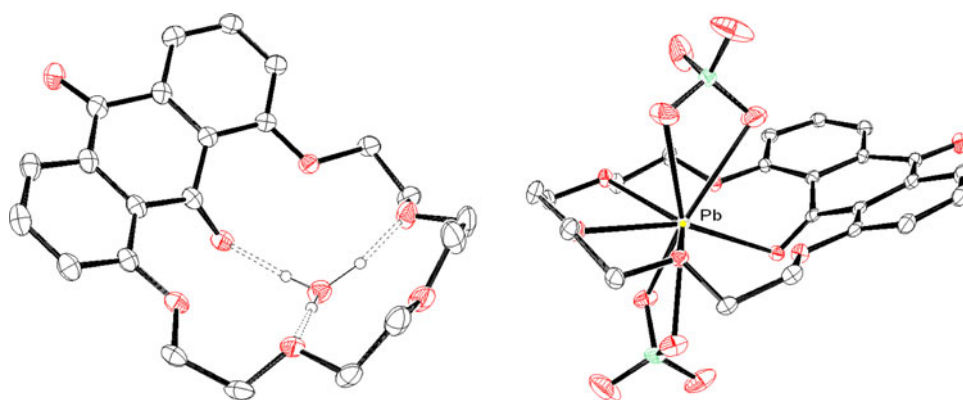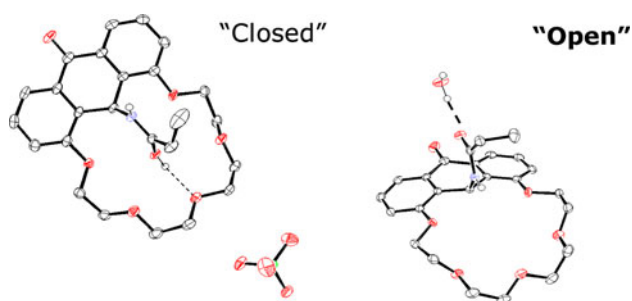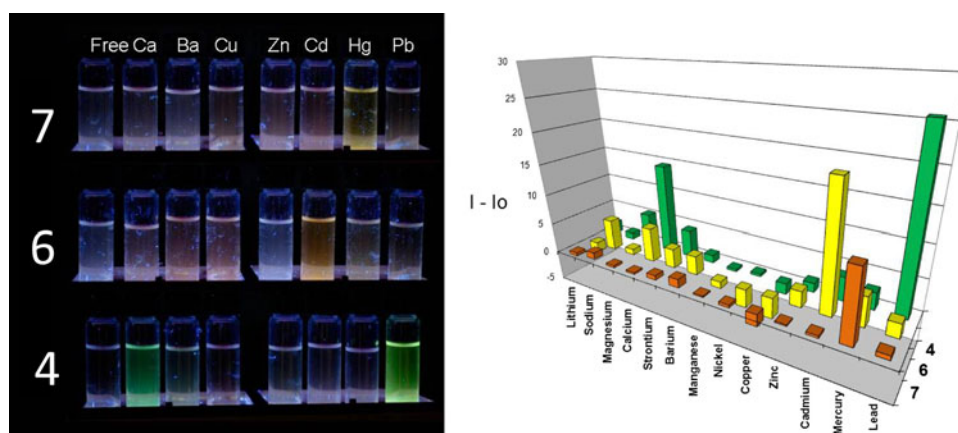
Fig. 3 Protonated (*left*) and deprotonated (*right*) ethyl amide adducts undergo a large amplitude change in geometry to either block and unblock the macrocyclic pore

nucleophiles and undergo substitution at the alpha carbons of the five-membered ring. We have successfully made thiophene adducts of **8** with thiophene, bithiophene, terthiophene, and other substituted thiophenes (analogues of compound **10**, Scheme 1) [36]. Single macrocyclic endcaps can be added to bithiophene or terthiophene to make monocapped adducts, or two macrocyclic endcaps can be added at both the available alpha carbons. We have determined that addition of Hg(II) cation to either the mono and dicapped terthiophene adducts produce an intense red

colorimetric change; attributed to charge transfer when the thiophilic Hg(II) ion associates with the terthiophene. In addition, two monomeric terthiophene adducts can be linked together to make a longer dicapped adduct using the stronger oxidants Fe(III) or Cu(II), producing the sexithiophene oligomer with two macrocyclic endcaps in a single step. Due to the endcaps, this adduct is very soluble (uncommon for higher thiophene oligomers) and possesses an intense green luminescence.

Generation of imine analogues

Reaction of **4** with aromatic amines in the presence of TiCl$_4$, based on similar chemistry of Hall [37–43], produces the site-selective formation of ketimines, where the imine forms only at the external carbonyl group (Compound **12**, Scheme 1) [44]. A wide variety of ketimines have been synthesized, but none exhibit similar luminescence compared to the parent macrocycle **4**. This can be been attributed to the isomerization of the CN functionality that rapidly deactivates the excited state non-radiatively [45]. However we have synthesized a bridging diimine, starting from 1,2-diaminobenzene, that is selective for the fluorescence detection of barium (II) ion. Complexation by

Scheme 2
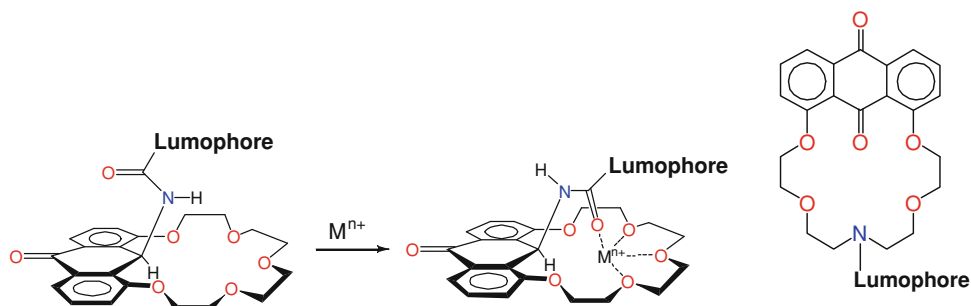
the metal center ostensibly links the two macrocycles together, limiting C=N isomerization and enhancing luminescence.

As with **4**, the carbonyl group in compound **12** can be selectively reduced (NaBH$_4$ in ethanol) to yield the 2° alcohol (Compound **13**, Scheme 1), leaving the imine group unreduced. What is most interesting is that **13** undergoes a tautomeric shift upon the addition of Zn(II) ion to produce the corresponding enamine [46]. Tautomerization is specific for Zn(II) addition, which produces a 50-100 fold increase in luminescence characteristic with the growth of an anthracene emission manifold in 50 % acetonitrile/water. Hydrogen bonding solvents also promote imine-enamine tautomerization, which explains why reduction of the imine is not observed. Compound **4**, having a higher energy barrier than imine-enamine tautomerization, does not undergo the corresponding metal-mediated keto-enol tautomerization.

Lastly, in contrast to the previous imine chemistry, reactions of hydrazines with compound **4**, produce exclusively hydrazones at the *internal* carbonyl group (Compound 15, Scheme 1) [47]. The structure of resulting hydrazones have been confirmed by X-ray crystallography and contradicts the reported literature [48]. In contrast to the fluorescent acid sensor work originally presented, reaction of **15** with a strong base produces intense luminescence and interesting carbanion substitution chemistry, which complements the earlier carbocation work. The more reactive carbonyl group is always the internal carbonyl as evidence by reduction (compound **8**) and the reaction with hydrazines (compound **15**). Imine formation at the external carbonyl is most likely because the internal carbonyl is blocked by potential coordination of the catalyst within the macrocyclic ring. The close proximity of the electron donating anthraquinone phenyl ether groups also supports the reactivity of the internal carbonyl group.

Outlook

As with most macrocyclic ring systems, constrained crown ring systems maintain excellent selectivity for the complexation and detection of metal cations. Beyond this, numerous chemical means for modifying the macrocycles in our system have been demonstrated, as illustrated by the diverse set of examples outlined above. Disadvantages still remain however, including reasonably low quantum yields for the observed ICT process (~ 5 %), and the limited solubility of these molecules in water. The different reactivities of our constrained ring system, however, do offer exciting opportunities to offset these limitations and help tune selectivity and sensitivity through the addition of other functional groups and lumophores. The formation of secondary amides (analogues of compound **9**) allow the introduction of another lumophore to the macrocycle (Scheme 2, left) for instance. A lumophore can be chosen or designed that imparts water solubility and has a high quantum yield. Coordination of the amide carbonyl group to a metal cation, as has already been demonstrated [33], increases the dimensionality of the macrocycle, thus changing selectivity, and would behave as an ICT type sensor, since the pi-system of the lumophore is extended through the amide carbonyl group.

In the above examples, reduction of the anthraquinone and reaction with corresponding nucleophiles does not retain the anthraquinone lumophore however. An option to keep the anthraquinone lumophore involves the introduction of an aza functionality within the crown ring, where an additional lumophore can be appended due to the increased valency of the nitrogen atom (Scheme 2, right). Again lumophores can be chosen that impart water solubility and high quantum yield, even extending fluorescence into the infrared region of the electromagnetic spectrum. A diverse array of either ICT type or photoinduced electron transfer (PET) type lumophores could be added. Perhaps most intriguing is the fact that two lumophores coexist within the lumophore, leading to potential interesting ratiometric sensing applications and interactions. Because the anthraquinone in our constrained crown ring system is also an energy acceptor, quantum yields for the ICT process can potentially be dramatically increased by the judicious choice of a second lumophore where fluorescence resonance energy transfer (FRET) between the lumophore and the quinone is employed. In our estimation, application of

FRET to increase low quantum yields seems underutilized in the field of luminescence sensors.

Lastly, a number of reports detail the synthesis of chemical sensors that pair both an electrochemically active subunit (e.g., ferrocene or quinone functionalities) and a fluorescent subunit (e.g., polyarenes and rhodamine dyes) with a receptor. These systems are often called "multimode" or "multichannel" sensors, although the two subunits in these sensors generally have very little to do with one another, other than perhaps one being used as a structural scaffold [49–58], or involve investigations into new spectroelectrochemistry techniques [59–62]. If the receptor happens to be in close proximity to the redox active site, anodic or cathodic shifts in the reduction/oxidation potentials of the electroactive subunit may result—producing an electrochemical sensor. If the receptor happens to be in close proximity to the lumophore, changes in emission may occur—producing a fluorescence sensor. To our knowledge, never have the simultaneous control of the electrochemical channel and the coordination of guests been used to control the fluorescence output of the sensor.

A few investigations have looked at what effect simple oxidation/reduction of the electroactive subunit has on the output of the lumophore. The oldest investigation is by Lehn and colleagues, who report the covalent attachment of a quinone to $Ru(phen)_3^{2+}$, where reduction of the quinone to the hydroquinone enhances the luminescence of the metal-to-ligand charge transfer band (MLCT) [63]. Other quinones have been attached to dansyl and perylene fluorophores to the same effect [64–66]. The oxidation of ferrocene covalently bound to pyrene, a luminescent tris(diimine)iridium complex, or a naphthalimide unit also enhances emission [67–69]. Tetrathiafulvene (TTF) dyads similarly utilize the $TTF^{+\cdot}/TTF^0$ redox couple to control emission quenching [70]. In a few additional cases, the redox state of a receptor-bound transition metal cation is sufficient to modulate the emission intensity of the ligands of a covalently appended fluorophore upon oxidation/reduction of the metal center [71–73]. Resch-Genger and Hennrich have also demonstrated changes in luminescence for a cyclic thiodiazole ring that converts to an open thiocarbonylamidine group after chemical reduction, where the selectivity for metal cations changes with the corresponding structural change in the receptor [74, 75].

All of these examples are classic energy transfer (ET) quenching systems, where the output of the fluorophore is solely dependent on the redox state of the intramolecular quencher, but none of these examples can be classified as a true "electrochemosensor"—a molecular system where the emission is modulated by both the electrochemical state and the presence of a guest molecule or ion trapped within the receptor. We believe that constrained crown ring systems hold great promise in this area, since the electroactive

quinone, in this case, is integrated within the receptor. The potential for the reduction of the quinone is modulated by the cation bound within the selective receptor, and will produce new emission bands for either the hydroquinone dianion or any other appended lumophore, since the quinone ET process has been removed. We are currently exploring all of these exciting new avenues related to constrained crown ring systems.

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