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Synthesis and study of crown ether-appended boron dipyrrin chemosensors for cation detection

James D. Blakemore, Raghu Chitta and Francis D'Souza*

Department of Chemistry, Wichita State University, 1845 Fairmount, Wichita, KS 67260-0051, USA

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Abstract—Boron dipyrrin (BDP) bearing crown ethers of varying cavity sizes, namely, 15-crown-5, 18-crown-6, and 21-crown-7, at the *meso*-position are synthesized and employed as chemosensors for cation detection in solution. In the absence of metal cations, the emission of the BDP moiety is found to be quenched to some extent by an intramolecular charge transfer (ICT) process from the donor oxygen atoms to the acceptor BDP unit. Coordination of metal ions to the oxygen donor atoms in the crown ether cavity inhibits intramolecular charge transfer to the BDP acceptor, leading to cation-induced fluorescence enhancement. The fluorescence enhancement is systematically probed as a function of crown ether cavity and metal ion sizes to achieve metal ion selectivity.

Crown ethers[1] are known to coordinate a variety of metal ions into their polyether cavity. As such, they have been utilized for constructing amperometry,[2] potentiometry,[3] fluorescence,[4] and surface techniques[5] based sensors for selective detection of cationic, anionic, and also neutral analytes.[6] Among these, fluorophores functionalized with crown ethers are of particular importance due to the sensitivity of the resulting chemosensors and the ease with which the change in the optical signal is monitored with respect to metal ion binding. Hence, the design and synthesis of chemosensors for sensitive and selective detection of specified analytes has become one of the major goals in fluorometric analysis.[7]

Among the different fluorophores available for constructing chemosensors, boron dipyrrin (BDP), commercially known as BODIPY for this family of dyes from Molecular Probes, Inc., is an useful fluorophore because of its advantageous characteristics, which include sharp absorption and fluorescence bands, large molar extinction coefficients ($\varepsilon > 70{,}000\ \mathrm{M^{-1}\ cm^{-1}}$), high fluorescence quantum yields (ϕ_f up to 0.8), high photostability, and excitation at relatively long wavelengths (ca. 500 nm).[8] Importantly, BDP is amenable to structural modification, enabling the fine tuning of its spectroscopic properties by the introduction of suitable substituents. As a result, BDP derivatives are currently used as laser dyes, as fluorescent tags for bio-molecules, and as components in electron transfer probes of radical ion generated electric fields.[9] Additionally, several fluorescent chemosensors have been reported based on modified boron dipyrrins,[10] including some with crown ethers.[11–16]

In case of BDP-crown ether chemosensors, the fluorophore unit acts as an electron acceptor, while the electron-rich crown ether acts as an electron donor. More specifically, the photophysical properties of an aza crown- and benzo crown-substituted BDP that forms 1:1 complexes with alkali and alkaline-earth metals have been studied.[12] In these complexes, the sensing is based upon changes in fluorescence caused by charge transfer (CT) upon coordination of the crown ether to the analyte. In particular, coordination of metal ions (Na^+ or K^+ or Mg^{2+}) to the aza-15-crown-5 and benzo-15-crown-5 moieties inhibits the intramolecular charge transfer process between the electron rich nitrogen or oxygen atoms to the BDP moiety, thereby leading to a cation-induced fluorescence enhancement without significant spectral shifts.[12,13] A sodium-selective fluorescent sensor was developed by Yamada et al., in which the biaryl boron dipyrrin was linked with an oligoethyleneglycol bridge.[14] Recently, a highly potassium-selective ratiometric BDP-based probe functionalized with

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Keywords: Boron dipyrrin; Chemosensor; Cation-induced fluorescence enhancement; Cation detection selectivity.

* Corresponding author. Tel.: +1 316 978 7380; fax: +1 316 978 3431; e-mail: Francis.DSouza@wichita.edu

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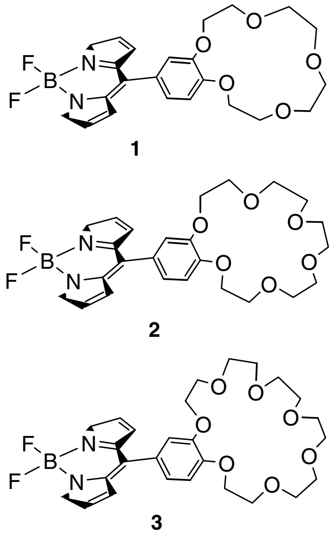
an aza-18-crown-6 moiety on the pyrrole ring was reported.[15] Upon binding to potassium ions, significant fluorescence enhancement accompanied by a 20 nm hypsochromic shift was achieved. The highly potassium-selective nature of the probe was attributed to the transition of stronger to weaker electronic coupling between the nitrogen atom of the aza-crown ether ring and the pyrrole ring of BDP. A highly selective and sensitive fluorescent detection of Ag(I) ions was achieved by coupling the concept of resonance energy transfer (FRET) to intramolecular charge transfer (ICT) in a BDP dimer. Here, the emission of the red-emitting dye was monitored upon excitation of the green-emitting dye, which was followed by the fluorescence enhancement (due to ICT inhibition) upon Ag(I) binding to the *N*-phenyl-9-aza-3,6,12,15-tetrathiaheptadecane receptor moiety.[16a] Similar principles of fluorescence enhancement have been extended for the selective detection of Hg(II) ions.[16b]

As seen in the preceding discussion, the reported systems in the literature have proven the utility of BDP-crown based chemosensors. However, most of the reported systems utilized crown ether of one cavity size paired with BDP and have not independently studied the effects of varying the crown ether cavity size on their overall emission behavior in the presence and absence of metal cations. This has been accomplished in the present study, in which BDP-based chemosensors with cavity diameters varied in the analogous series of benzo-15-crown-5, benzo-18-crown-6, and benzo-21-crown-7 have been synthesized. This expands the possibilities for use of these sensors, as well as demonstrates the effective selectivity afforded by the various crown ether sizes. In addition, and most unique to this study, the benzo-21-crown-7 functionalized with BDP reported here has never been presented in the literature as a supramolecular entity paired with BDP for ion sensing applications.

The structure of the synthesized BDP-crown ether chemosensors for metal cations is shown in Scheme 1.



Scheme 1. Structure of the boron dipyrrin-crown ether chemosensors utilized in the present study.

These were synthesized by the condensation of the corresponding aldehyde with pyrrole to make dipyrromethane substituted at the *meso*-position with the respective benzo-crown ether entity (see Supplementary data for synthetic details).[17,18] Subsequent treatment of these dipyrromethanes with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), triethylamine, and BF_3-etherate afforded the crude compounds as a black reaction mixture. Evaporation of the solvent and purification of these crude products by column chromatography on silica gel afforded the target molecules as orange crystals.[19]

The UV–visible spectra of these compounds in polar solvents (e.g., methanol) revealed a distinct absorption band at 497 nm and a shoulder at 472 nm, characteristic of the BDP chromophores.[20] No apparent absorption in the wavelength region covering 300–700 nm corresponding to the crown ether entities was observed. Addition of metal ions did not induce any observable spectral changes (see Fig. 1). Importantly, no charge transfer band (CT) corresponding to the ground state interactions between the crown ether and BDP moieties was observed. This may be attributed to a twist angle ($\theta = {\sim}78^\circ$) between the phenyl ring and the BDP fluorophore.[21]

Upon excitation at 475 nm, compounds **1**, **2**, and **3** displayed an emission band around 514 nm corresponding to the BDP fluorophore. As mentioned earlier, in the absence of coordinating metal ions, the fluorescence of the BDP moiety in these probes is quenched to some extent due to an intramolecular charge transfer (ICT) process from the donor oxygen atoms to the acceptor BDP unit. Coordination of metal ions to the oxygen donor atoms in the crown ether cavity inhibits the ICT to the BDP acceptor leading to a cation-induced fluorescence enhancement.[12] As a result, addition of metal ions that coordinate to the crown ether entity resulted in fluorescence enhancement. Interestingly, addition of metal ions that do not bind to the crown ether cavity (owing to the size differences) exhibited a small bimolecular quenching effect. It may be mentioned here that the addition of

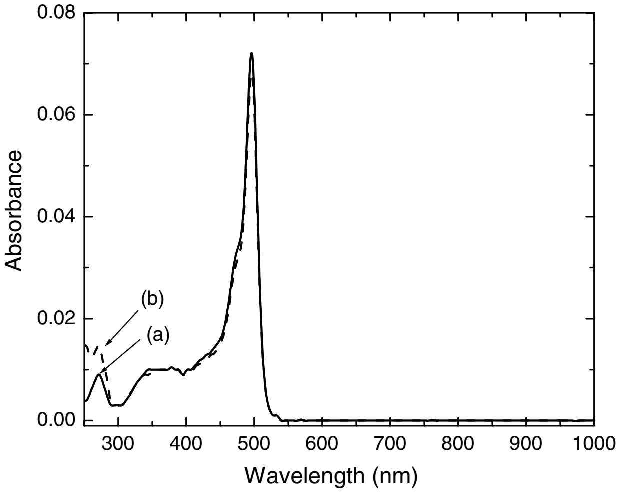


Figure 1. UV–visible spectrum of (a) **2** and (b) **2** in the presence of excess K^+ in methanol.

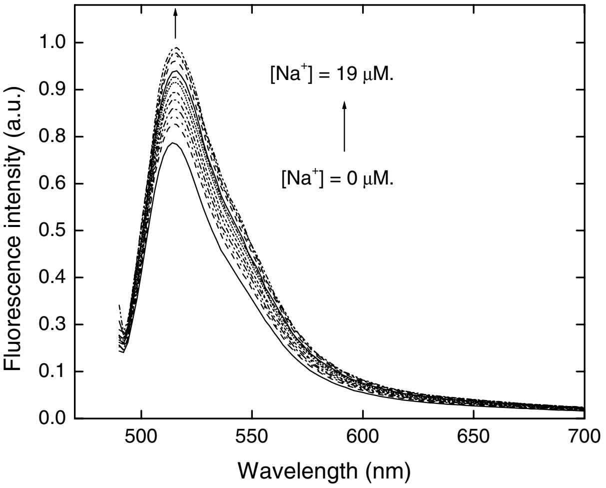


Figure 2. Emission spectra of compound **1** (3×10^{-6} M) on increasing additions of Na$^+$ in methanol. Excitation wavelength = 475 nm.

trifluoroacetic acid (up to 10 equiv) to a methanol solution containing either of probes **1**–**3** changed the absorption and emission intensities less than 2% of the original values.

In order to determine the complexation behavior and to evaluate the selectivity of these probes toward various metal ions, compounds **1**, **2**, and **3** were titrated with different alkali, alkaline-earth, and diamagnetic transition metal ions (viz., Mg^{2+}, Zn^{2+}, Li$^+$, Ca^{2+}, Na$^+$, Ag$^+$, Ba^{2+}, K$^+$, Rb$^+$, and Cs$^+$) varying in their ionic sizes. The fluorescence change at 514 nm was monitored for all these titrations. The fluorescence enhancement of **1** was well pronounced only in the case of Na$^+$ (see Fig. 2). Under these conditions, the change in the fluorescence quantum yield, Φ_f, was from 0.004 to 0.005 upon Na$^+$ binding to **1**. Figure 3 illustrates three-dimensional bar graphs showing the emission intensity ratio I/I_0 of the 514 nm emission band as a function of increasing concentrations of the employed metal ions. Except for Na$^+$, for all of the employed metal ions there was a small quenching effect at the monitoring wavelength, thus demonstrating Na$^+$ selectivity of **1** (Fig. 3). Using the Benesi–Hildebrand plot,[22] the binding constant of Na$^+$ with **1** in methanol was determined to be 8.1×10^4 M^{-1} (Table 1), which agreed well with the literature value of Na$^+$ binding to 15-crown-5.[23] The stability constants of all the other metal ions with **1** were too small to be determined using fluorescence data.

Table 1. Binding constants calculated from the Benesi–Hildebrand plots of the fluorescence data for the metal ion bound BDP crown ether probes in methanol

BDP crown ether[a]	Metal ion	K_a[b] (M^{-1})
1	Na$^+$	8.2×10^4
2	K$^+$	9.7×10^5
	Ba^{2+}	9.2×10^4
	Rb$^+$	5.0×10^4
3	Cs$^+$	8.6×10^4
	Ba^{2+}	1.6×10^4
	Rb$^+$	6.6×10^3

[a] See Scheme 1 for structures of the BDP probes.
[b] Error = ±10%.

Interestingly, among the series of the employed metal ions to bind **2**, fluorescence enhancement was observed in the case of K$^+$, Ba^{2+}, and Rb$^+$ (Fig. 4). However, the maximum fluorescence enhancement, and largest

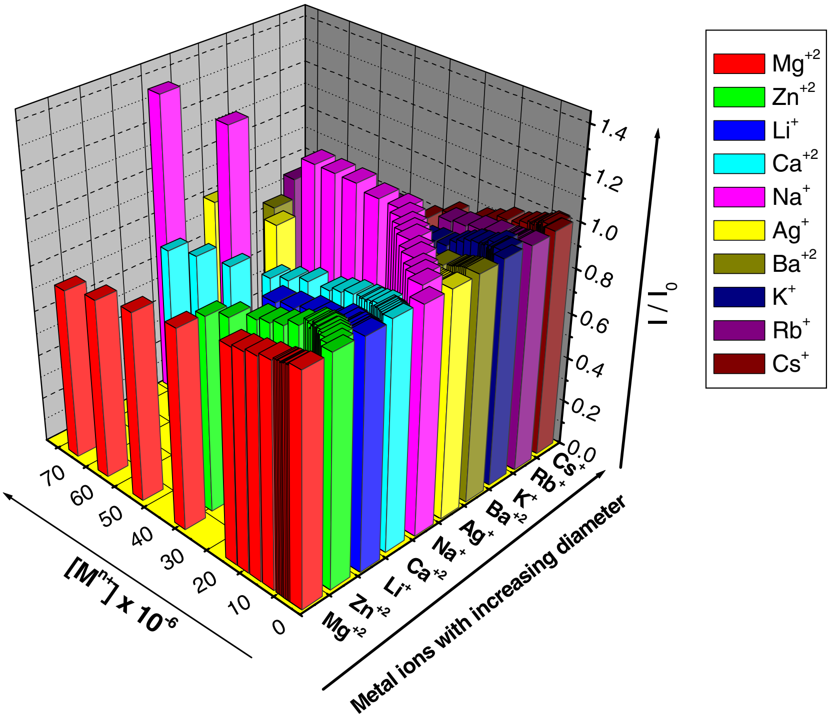


Figure 3. Fluorescence response of **1** upon increasing additions of metal ions in methanol. Fluorescence intensity was monitored at 514 nm (I_0 and I represent the fluorescence intensity in the absence and presence of metal ions).

binding constant, $9.7 \times 10^5\ \mathrm{M}^{-1}$, was achieved only in the case of K^+. This may be attributed to the selective and efficient binding of K^+ with the benzo-18-crown-6 ether moiety. The change in the fluorescence quantum yield, Φ_f, was from 0.004 to 0.006 upon K^+ binding to **2**. The large fluorescence enhancement and high binding constant obtained by employing low K^+ metal ion concentration shows the sensitivity and selectivity of probe **2** for K^+ ion.

As predicted, fluorescence enhancement was observed when metal ions of larger ionic radii, such as Ba^{2+}, Cs^+, and Rb^+, were allowed to interact with **3** bearing a larger crown ether cavity (Fig. 5). The divalent metal

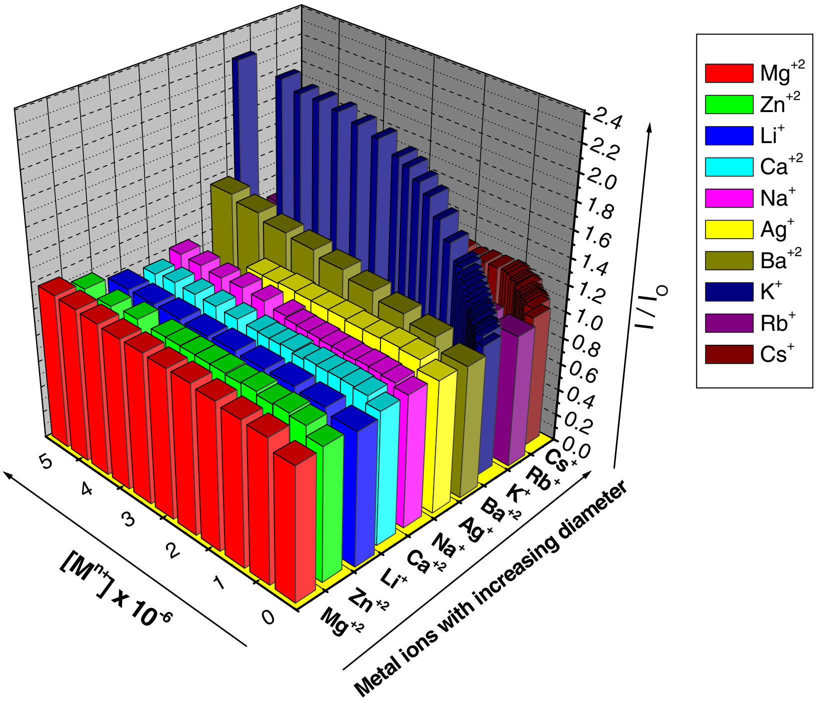


Figure 4. Fluorescence response of **2** upon increasing additions of metal ions in methanol. Fluorescence intensity was monitored at 514 nm (I_0 and I represent the fluorescence intensity in the absence and presence of metal ions).

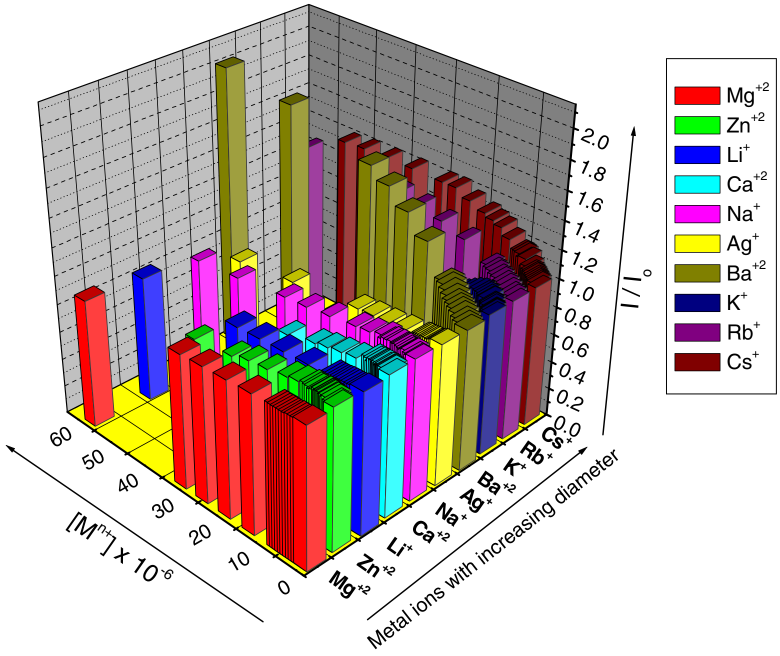


Figure 5. Fluorescence response of **3** upon increasing additions of metal ions in methanol. Fluorescence intensity was monitored at 514 nm (I_0 and I represent the fluorescence intensity in the absence and presence of metal ions).

ion, Ba^{2+}, with a relatively small ionic radius of 2.70 Å[24] revealed maximum emission enhancement. However, the calculated binding constant was the highest for Cs^{+} having a larger ionic radius of 3.34 Å[24] (Table 1). This exceptional behavior of Ba^{2+}, having a moderate stability but the largest fluorescence enhancement, can be attributed to the stronger affinity of the doubly charged Ba^{2+} for the donor oxygen atoms of the crown ether cavity. The change in the fluorescence quantum yield, Φ_f, was from 0.005 to 0.006 upon Cs^{+} binding, and 0.005 to 0.007 upon Ba^{2+} binding to **3**.

The fluorescence enhancement seen in spectral form for the chemosensors titrated with their preferred cations encouraged us to investigate the possibility of a change in visual appearance of the chemosensor solution upon addition of metal cations. With this in mind, equimolar solutions of **2** were taken into two separate cuvettes, and K^{+} (10 equiv) was added to one of the cuvettes. When UV light impinges upon the cuvettes, the fluorescence enhancement of the solution containing an excess of K^{+} is clearly visible to the naked eye as shown in the table of contents figure.

In summary, this work illustrates the application of boron dipyrrin bearing crown ethers of varying cavity sizes as chemosensors for metal ions in solution. The donor ability of crown ethers and acceptor capacity of the boron dipyrrin moiety were utilized to design the chemosensors by adopting the cation-induced fluorescence enhancement mechanism. The present study revealed that among the employed metal ions, Na^{+} is the only one that induced fluorescence enhancement upon binding to **1**. Probe **2** showed maximum fluorescence enhancement upon K^{+} binding. Probe **3** revealed cation-induced fluorescence enhancements for metal ions of larger sizes, viz., Ba^{2+}, Cs^{+}, and Rb^{+}, with a maximum enhancement for the doubly charged Ba^{2+}.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.067.

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