

Note

Aza-crown ether tethered with benzothiazole: Synthesis and optical spectral studies

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Synthesis of a new fluoroionophore **2** encompassing aza-phenyl-crown and benzothiazole is described. The UV-Vis spectra of **2** are not altered with change in solvent polarity indicating the absence of solvatochromism. However, the fluorescence spectra are progressively red shifted in more polar solvents on account of increasing charge transfer character of the excited state. In the presence of trifluoroacetic acid (TFAA), protonation of benzothiazole nitrogen results in the red shift of the absorption spectra. Contrary to expectation, the emission spectra suffers blue shift in the presence of TFAA. Presumably, the emission for the case $2+H^+$ occurs from higher vibrational energy levels which accounts for the blue shift. Unfortunately, selected alkali or alkaline earth metals ions examined for metal sensing applications have failed to induce significant perturbations either in the absorption or emission spectra. This may be attributed to poor electronic communication between the crown-bound metal ions and the benzothiazole fluorophore due to steric encumbrance between the *ortho*-substituted benzothiazole chromophore and the phenyl aza-crown moiety.

Keywords: Aza-crown fluoroionophore, optical spectral studies, intramolecular charge transfer, protonation, metal-ion complexation.

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Sensing of metal ions is of great interest and importance in fields as diverse as medical diagnostics, biology, analytical science, environment science and material chemistry¹⁻⁴. Of the various methods available for metal detection, the fluorescence emission technique is one of the most attractive methods for signalling because of its high sensitivity⁵. The basic design concept involved in developing chemo- and fluoroionophores relies on connecting a selective binding domain, called receptor with a signalling component, an antenna to deliver either enhanced emission (an 'on' state) or signal quenching (an 'off' state) response. While crown ethers have been widely employed as metal ion receptors,

coumarin, anthracene, pyrene and quinoline derivatives have been used as fluorescent probes. A number of fluoroionophores derived from benzothiazole moiety have also been designed to detect hard alkali/alkaline earth metal as well as transition metal ions⁶⁻¹¹. In particular, aza-crown linked to benzothiazole moiety either directly or *via* a saturated spacer has been successful in producing high "on state" systems that operate on the basis of photo-induced electron transfer mechanism. Mitewa and coworkers¹² have synthesized 4-(benzothiazolyl)-phenylaza-15-crown-5 **1** and investigated its potential for the selective detection and quantification of Ba^{++} and Ca^{++} ions. The system **1** functions on the basis of intramolecular charge transfer mechanism. Curiously, its isomer, namely 2-(benzothiazolyl)phenylaza-15-crown-5 **2** has not yet been reported in the literature.

In continuation of previous work done on fluoroionophoric systems¹¹, the current investigations focus on the synthesis and optical properties of **2** without and with added metal ions. Being a donor-acceptor type system, the photophysical properties of **2** are expected to be governed by intramolecular charge transfer (c.t.) processes. However, unlike **1**, it is anticipated that *ortho*-substituted benzothiazole chromophore in **2** might provide an extra binding site to the "crown complexed" metal ion *via* nitrogen ligation as illustrated in **Figure 1**. Such an interaction might lead to changes in the c.t. character of the system so as to produce detectable perturbations in the optical properties. The synthesis of **2** is depicted in **Scheme I**. Initially, 2-fluorobenzaldehyde **3** and *o*-aminothiophenol **4** were refluxed in alcohol for 8 hr using an open-air condenser. The reaction mixture was then diluted with water and allowed to cool in ice. The crude solid was filtered, washed with water and air dried. Repeated crystallization from an excess of hot petroleum ether gave (2-fluorophenyl)-benzothiazole **5**, m.p. 67-9°C in 80% yield.

Monoaza-15-crown-5 **6**, prepared using the literature procedure¹³ was coupled with **5** in dry N-methylpyrrolidone containing an excess of anhyd. K_2CO_3 . The reaction mixture was stirred and refluxed under N_2 for 10 hr. The reaction mixture was then diluted with water and extractively worked up in chloroform. The crude product was purified by SiO_2

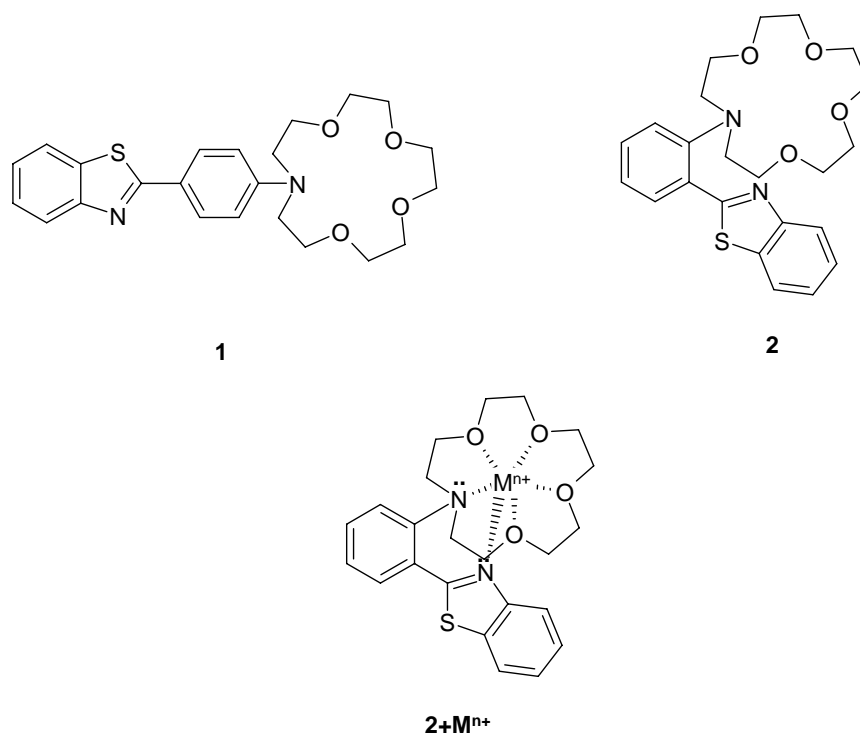


Figure 1

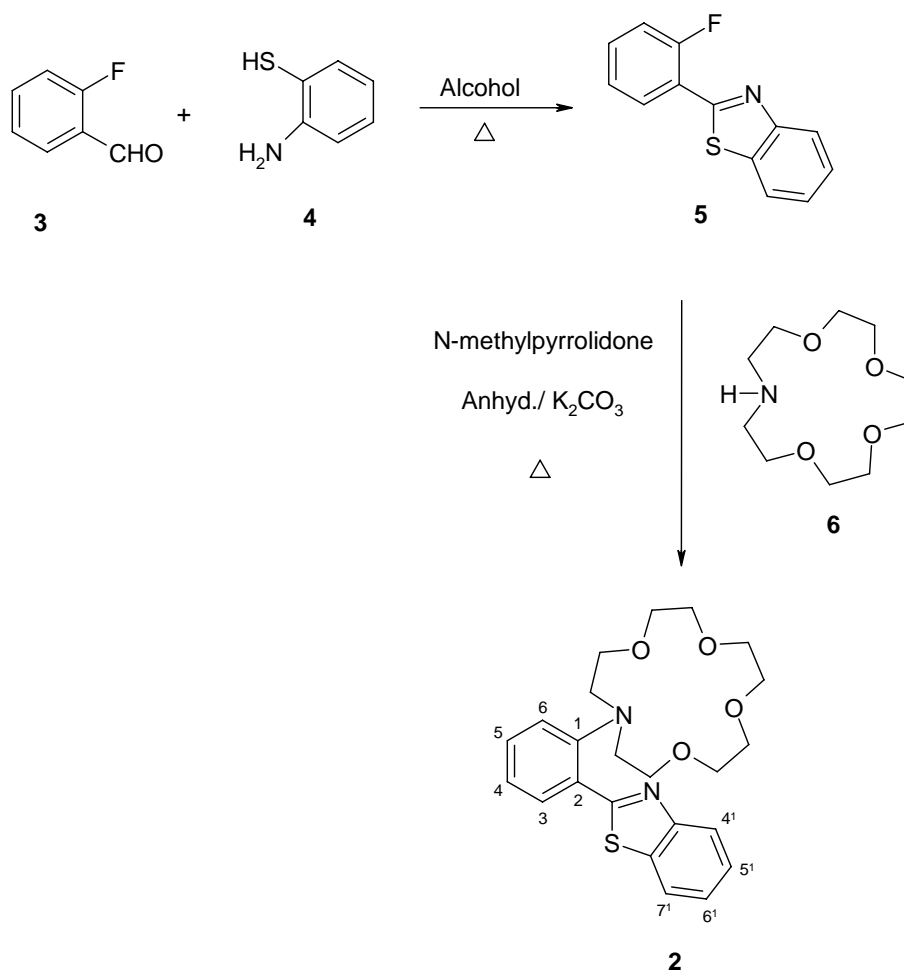
column chromatography to furnish a pale yellow oil in 19% yield. The product was identified as the required benzothiazole aza-crown **2** on the basis of elemental analysis ($C_{23}H_{28}O_4N_2S$; M^+ at m/z 428) and its high resolution (500 MHz) NMR spectrum. The 1H NMR proton assignments are based on chemical shifts, spin multiplicities and whether the protons are attached to the π -deficient benzothiazole ring or the π -rich azaphenyl ring. The methylene protons (20 H) appeared as a complex multiplet in the region δ 3.63–3.75. A doublet at δ 8.4 and a triplet at δ 7.43 are assigned, respectively to H4' and H5', whereas a doublet located at δ 8.04 is for the H7' which is coupled to H6' in the form of a triplet centered at δ 7.36. The azaphenyl H6 and H3 appear as doublet each at δ 7.95 and δ 7.57, respectively. The remaining H4 and H5 are seen as triplet each at δ 7.39 and δ 7.43, respectively.

UV-Vis and Fluorescence studies on **2**

The optical spectroscopic parameters under different conditions are summarized in **Table I**. The absorption maxima measured in different solvents are essentially insensitive to the polarity of the solvent; the λ_{max} being observed in a narrow range of 296 to 299 nm. The absence of solvatochromism indicates

that neither the ground state nor the excited states are appreciably perturbed by the polarity of the solvents. However, the fluorescence spectra obtained on excitation using λ_{ex} 298 nm are significantly altered with respect to polarity changes. Increase in the solvent polarity led to progressive increase in the λ_{em} from 441 nm in nonpolar cyclohexane to 476 nm in highly polar methanol, with the highest Stokes shift of 180 nm being recorded in the latter solvent. Evidently, the emissive local excited state acquires increasing c.t. character with increase in solvent polarity¹⁴. The resulting intramolecular c.t. excited states are stabilized in polar solvents and hence the emission occurs from the vibrationally relaxed levels to account for higher Stokes shifts in polar solvents^{15,16}.

Addition of trifluoroacetic acid (TFAA) to a solution of **2** in different solvents caused the absorption maxima to shift to longer wavelength with increments in the λ_{max} in the range of 12 to 14 nm, depending on the nature of the solvent. The red shifts in the presence of TFAA can be rationalized by assuming preferential protonation of benzothiazole nitrogen. The resulting benzothiazolium salt, being more π -deficient than the neutral benzothiazole ring, brings about slightly greater charge transfer from the π -rich azaphenyl ring to the highly π -deficient



Scheme I

Table I — UV-Vis and emission data of compound **2**

Solvent	Cyclohexane	Chloroform	Acetonitrile	Methanol
$\lambda_{ab}(nm)$	298	298	298	296
$\epsilon_{max} \times 10^3$	11.76	26.10	19.10	22.30
$\lambda_{em}(nm)$	441	462	474	476
Intensity	244	256	136	129
Stokes shift (Δ, nm)	143	164	176	180
Solvent + TFAA				
$\lambda_{ab}(nm)$	312	312	309	308
$\epsilon_{max} \times 10^3$	11.20	28.40	21.60	28.60
$\lambda_{em}(nm)$	419	409	430	437
Intensity	13	58	69	37
Stokes shift (Δ, nm)	107	97	121	129

benzothiazolium ring and hence the red shift in the absorption band¹⁴.

Although, the emission bands of **2** in the presence of trifluoroacetic acid (TFAA) are red shifted (increasing Stokes shifts) with increase in the solvent

polarity, these bands, contrary to expectation were found to be blue shifted (from 419 to 437 nm) compared to that observed without added TFAA (from 441 to 476 nm). Indeed, we had anticipated the emissions also to be red shifted in accord with the red

shifts observed in the absorption spectra of neutral **2**. The lower values of Stokes shifts (97 to 129 nm) for **2** in the presence of TFAA compared to that observed for the neutral **2** (143 to 180 nm) could be rationalized as a consequence of the emission taking place from relatively higher vibrational levels of the excited state of $2+H^+$. Under the situation where the reorganization of the solvent molecules to stabilize the polar c.t. excited state of $2+H^+$ is relatively slower compared to the rate of emission, then the emission occurring from higher vibrational energy levels or partially relaxed Frank Condon states is not entirely unexpected¹⁷. The lower emission intensity $2+H^+$ compared to neutral **2** could be attributed at least in part to intramolecular electron transfer from the donor, aza-crown nitrogen, to the electron acceptor, benzothiazolium ring thereby leading to partial quenching effects.

We have also investigated the effects of metal ions on the absorption and emission properties to evaluate the potential of **2** in the metal sensing applications. The results are summarised in **Table II**. Addition of $LiClO_4$ in up to 100 fold concentration to an acetonitrile solution of **2** had practically no effect on absorption or emission properties, thereby indicating weak or no complexation of lithium ions with **2**. Although Na^+ and K^+ up to 10 fold concentration with respect to that of **2** produced no detectable effects on the optical properties, on the other hand, at 100 fold concentration, these cations induced a small blue shift by 4 and 3 nm, respectively. The blue shift in the λ_{ab} is consistent with decrease in the c.t. character upon metal ion binding within the aza-crown domain¹⁸. Although emission intensity was not significantly altered in the presence of Na^+ and K^+ at 10 fold concentration, however at 100 fold concentration with respect to **2**, there was observed a slight decrease in the emission intensity relative to the free aza-crown **2**.

Table II — UV-Vis and emission data of **2** in presence of metal ions

System	λ_{abs} (nm) ^a	$\epsilon_{max} \times 10^4$	$\lambda_{em}(nm)^b$	Intensity
2	298	1.25	474	224
2 + Li^+	298	1.26	476	222
2 + Na^+	294	1.18	475	206
2 + K^+	295	1.31	474	203
2 + Ba^{++}	297	1.27	474	212
2 + Ca^{++}	298	1.25	473	216
2 + Mg^{++}	298	1.25	476	219

^a Conc. of **2** and metal ions are 1×10^{-5} and 1×10^{-3} M, respectively.

^b excitation wavelength λ_{ex} is 298 nm.

In the case of divalent cations Ba^{2+} , Ca^{2+} and Mg^{2+} , no detectable perturbations were observed in the UV-Vis spectra, but the emission spectra were accompanied with only a marginal decrease in the emission intensity. Evidently, the optical changes in the presence of selected alkali and alkaline earth metal ions are too small to be meaningful for metal sensing applications. It is likely that steric encumbrance between the *ortho*-substituted benzothiazole chromophore and the phenyl aza-crown moiety could cause significant twists between these two components to prevent effective electronic communication between the crown-bound metal ions and the benzothiazole fluorophore¹¹. In contrast, in the case of known *para* analog **1** in which the biaryl twist is minimal, the molecule exhibits substantial optical response in the presence of Ba^{2+} and Ca^{2+} ions¹².

In conclusion, the synthesis of a new fluoroionophore **2** encompassing monoaza-15-crown-5 and benzothiazole components has been carried out. The molecule exhibits c.t. interaction in the excited state as revealed by red shifts in the emission bands in polar solvents. The ground state protonation of benzothiazole nitrogen in presence of TFAA is responsible for the red shift in the absorption spectra. However, the emission spectra undergo blue shift in the presence of TFAA. This is explained on the basis of the fact that emission for the case $2+H^+$ in contrast to **2** occurs from higher vibrational energy levels. Unfortunately, the particular alkali or alkaline earth metals ions selected for metal sensing applications failed to induce significant perturbations either in the absorption or emission spectra. Investigation of optical properties of **2** with heavy metal ions such as Ag^I , Hg^{II} and Cu^{II} are currently in progress.

Experimental Section

Metal perchlorates were prepared as described in the literature¹⁹ and dried under vacuum prior to use. The chemicals and spectral grade solvents were purchased from S.D. Fine Chemicals (India) and used as received. Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. 1H NMR spectra were recorded on a Bruker-AMX-500 spectrometer with TMS as an internal standard. UV-Vis spectra were recorded on Shimadzu UV-2100 UV-Vis spectrophotometer and fluorescence spectra were recorded on a Shimadzu RF-5301 PC spectrofluorimeter.

Preparation of (2-fluorophenyl)benzothiazole 5.

2-Fluorobenzaldehyde **3** (1.1 mL, 10 mmoles) and *ortho*-aminothiophenol **4** (1.1 mL, 10 mmoles) were refluxed in 75 mL alcohol for 8 hr. On completion, the reaction mixture was diluted with ice-cold water and filtered. On recrystallization from pet. ether, the white, solid product was obtained in desirable purity. Yield 80% (1.83 g), m.p. 67-8°C; IR(KBr): 1610, 1580, 1570, 1500, 1450, 1430, 1310, 1280, 1200, 1100, 1020, 980, 970 cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_8\text{FNS}$: C, 68.12; H, 3.49; F, 8.29; N, 6.11; S, 13.97. Found: C, 68.29; H, 3.15; F, 8.33; N, 5.80; S, 13.81%.

Synthesis of *ortho*-benzothiazole aza-15 crown-5 **2**.

Ortho-fluorobenzothiazole **5** (0.46 g, 2 mmoles) and aza crown **6** (0.44 g, 2 mmoles) were taken in 5 mL of *N*-methylpyrrolidone. Anhyd. K_2CO_3 (0.69 g, 5 mmoles) was then added to the reaction mixture and stirred at reflux under N_2 atmosphere for 10 hr. On completion, the reaction mixture was poured into 100mL water and extracted twice with CHCl_3 . The organic layer was thoroughly washed with water, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography using CHCl_3 : CH_3OH (98: 2) as eluent. The compound **2** was obtained as pale yellow oil. Yield 19% (0.16 g). IR(Nujol): 3100, 2900, 2700, 1680, 1600, 1580, 1500, 1450, 1430, 1320, 1280, 1240, 1210, 1110, 970, 760 cm^{-1} ; ^1H NMR (CDCl_3): δ 8.36 (1H, d), 8.04 (1H, d), 7.89 (1H, d), 7.34-7.55 (4H, m), 7.22-7.24 (1H, m). Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{O}_4\text{N}_2\text{S}$: C, 64.49; H, 6.54; N, 6.54; S, 7.48. Found: C, 64.73; H, 6.74; N, 6.87; S, 7.55%.

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References

- 1 Czarnik A W, Fluorescence Chemosensors for Ions and Molecules Recognition, *ACS Symposium Series*, 358, (American Chemical Society, Washington DC), **1993**.
- 2 DeSilva A P, Gunaratne N Q N, Gunnlaugsson T, Huxley A J M, McCoy C P, Rademacher J T & Rice T E, *Chem Rev*, 97, **1997**, 1515.
- 3 Spichiger U S K, *Chemical Sensors and Biosensors for Medical and Biological Applications*, (Wiley-VCH, Weinheim, Germany), **1998**.
- 4 Valeur B & Leray I, *Coord Chem Rev*, 205, **2000**, 3.
- 5 Lakowicz J R, *Principle of Fluorescence Spectroscopy*, 2nd edition, (Plenum Press, New York) **1999**.
- 6 Tanigawa I, Tsuemoto K, Kaneda T & Misumi S, *Tetrahedron Lett*, 25, **1984**, 5327.
- 7 Lednew I K, Hester R F & Moore N J, *J Am Chem Soc*, 119, **1997**, 356.
- 8 Alifimov M W, Gromov S P, Braun A, Sears D F Jr & Saltiel J, *J Am Chem Soc*, 121, **1999**, 4992.
- 9 Matsumoto K, Hashimoto M, Toda M & Tsukube H, *J Chem Soc, Perkin Trans 1*, **1995**, 2497.
- 10 Nakashima K, Nagaoka Y, Nakatsuji S, Kaneda T, Tanigawa I, Hirose K, Misumi S & Akiyama S, *Bull Chem Soc Jpn*, 60, **1987**, 3219.
- 11 Mashraqui S H, Kumar S & Vashi D, J Inclusion Phenomenon, *Mol Recog Chem*, 48, **2004**, 125.
- 12 Mateeva N, Enchev V, Antonov T, Deligeorgiev T & Mitewa M, *J Inclusion Phenomenon*, 20, **1999**, 323.
- 13 Maeda H, Furuyoshi S, Nakatsuji Y & Okahara M, *Bull Chem Soc Jpn*, 56, **1983**, 212.
- 14 Krishnamurthy G & Dogra S K, *J Org Chem*, 64, **1999**, 6566.
- 15 Rurack K, Bricks J L, Reck G, Radeaglia R & Resch-Genger U, *J Phys Chem*, 104, **2000**, 3087.
- 16 Bourson J & Valeur B, *J Phys Chem*, 92, **1989**, 6233.
- 17 Grabowski Z R, Rotkiewicz K & Rettig W, *Chem Rev*, 103, **2003**, 4031.
- 18 Shin E J, *Chem Lett*, 31, **2002**, 686.
- 19 Bartsch R A, Yang I W, Jeon E G, Walkowiak W & Charewicz W A, *J Coord Chem*, 27, **1992**, 75.