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Lithium Responsive Fluorophores Derived from Monoaza-12-crown-4 and Coumarin. The Influence of a Methoxy Side-arm on Photophysical Properties

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Abstract: The syntheses of fluorescent macrocycles in which monoaza-12-crown-4 is attached through nitrogen to the 7-position of a coumarin are described. Complexation with the lithium ion in MeCN solution results in large hypsochromic shifts in absorption maxima. Li^+ binding shifts the fluorescence maximum to shorter wavelengths with an enhancement in intensity only if a methoxy side-arm is present.

In recent years there have been a number of reports of chromogenic reagents that respond to alkali and alkaline earth metal ions.[1] Typically, these chromoionophores are based on a donor-acceptor chromogen[2] and are designed such that the complexed metal ion can perturb the π-system of the chromophore resulting in spectral shifts. Fluorescent compounds capable of responding to these ions in organic phases (fluoroionophores)[3] or in aqueous solution (indicators)[4] are being actively studied. Notably, a 7-aminocoumarin derivative has been attached through an intervening methylene group to azacrown ethers and the resulting donor-acceptor fluorophores shown to undergo shifts in absorption and emission spectra in the presence of metal ions.[5] For our applications, namely lithium selective extraction agents and water soluble indicators, less basic molecules are required in order to minimize proton interference. We have synthesized fluorophores **1** and **2** in which the azacrown nitrogen is less basic because it is directly attached to the 7-position of coumarin. In MeCN solution **1** and **2** respond selectively to the lithium ion by undergoing large hypsochromic shifts in their electronic absorption spectra. Whereas the lithium complex of **1** does not fluoresce, fluorophore **2** forms a lithium complex with a fluorescence maximum at shorter wavelengths and a higher quantum yield than uncomplexed **2**.

Reaction of 1,11 diiodo-3,6,9-trioxaundecane,[6] **3**, with 3-benzyloxyaniline or 2,5-dimethoxyaniline gave the N-arylmonoaza-12-crown-4 derivatives **4a** and **4b**[7] respectively which were formylated by treatment with DMF and $POCl_3$ to give the corresponding aldehydes **5a** and **5b** (Scheme 1). Benzyl ether **5a** was hydrogenolyzed at low pressure to give salicylaldehyde derivative **6a** which condensed readily with diethyl malonate in the presence of piperidine to give azacrown coumarin derivative **1**. Treatment of **5b** with $AlCl_3$ in dichloromethane resulted in selective demethylation of the methoxy group ortho to the aldehyde group giving **6b** which was treated with diethyl malonate to give coumarin **2**.

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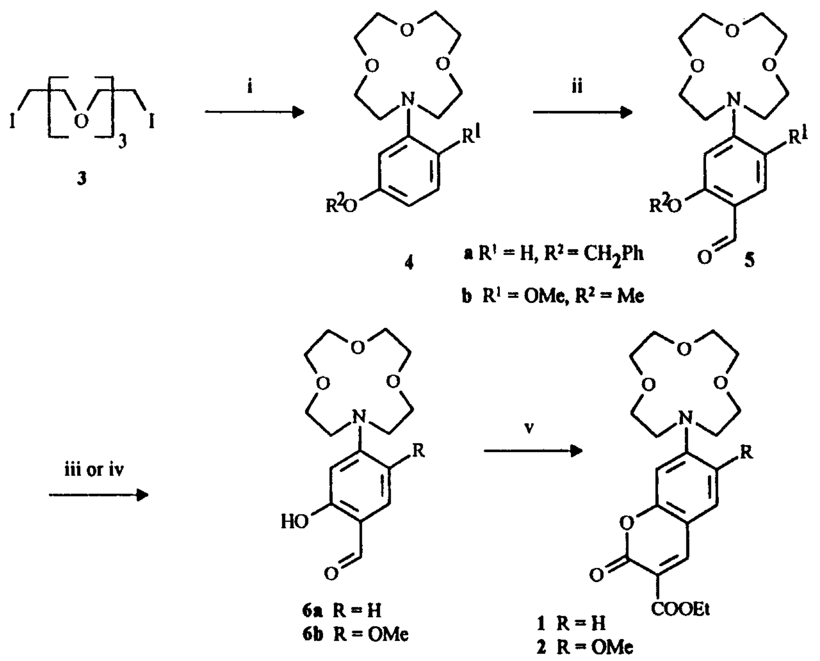

Scheme 1. *Reagents and conditions:*

i) $ArNH_2$, MeCN, Na_2CO_3, 82°C, 100h.
ii) DMF, $POCl_3$, Pyridine, 0°C to 25°C, 2h.
iii) H_2, 10% Pd/C, AcOH, 1 atm., 25°C.
iv) $AlCl_3$, CH_2Cl_2, 25°C, 24h.
v) $CH_2(COOEt)_2$, Piperidine, MeOH, AcOH, 50°C, 2h.

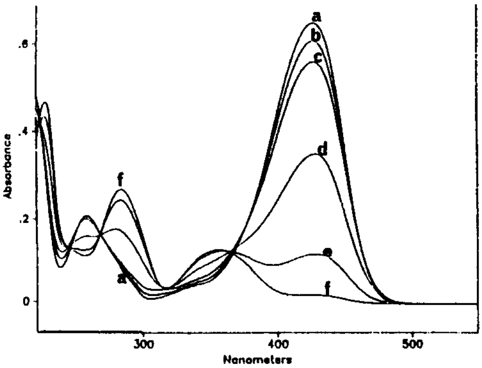

Figure 1. Effect of the addition of $LiBF_4$ on the absorption spectrum of 2 (2 x 10^{-5} M).

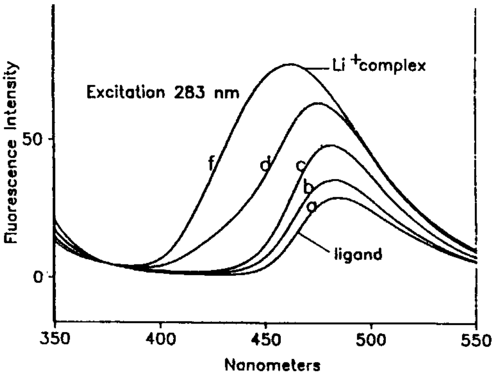

Figure 2. Effect of the addition of $LiBF_4$ on the fluorescence spectrum of 2 (2 x 10^{-5} M).

a) 0; b) 1.0; c) 20; d) 30; e) 45; f) 100 molar equivalents of $LiBF_4$.

Table 1. Properties of Fluoroionophores, 1 and 2, and their Lithium complexes in MeCN

	Absorption		Emission		
Fluorophore	λ_{abs}^{max}, nm	ϵ x 10^3 L $mol^{-1}cm^{-1}$	λ_{em}^{max}, nm	Φ_F	K_{assoc}, L mol^{-1}
1	412	59.0	466	0.12	-
	240	17.5			
1:Li^+ complex	324	4.6	-	-	5.55 x 10^2
	283	8.5			
2	427	29.0	485	0.02	-
	256	9.2			
2:Li^+ complex	350	6.6	462	0.04	1.41 x 10^3
	283	14.9			

In MeCN solution, fluorophore 1 showed absorption maxima at 412 nm and 240 nm. Excitation of 1 at 412 nm gave rise to a fluorescence emission band with a maximum at 466 nm (quantum yield[8], ϕ = 0.12). When $LiBF_4$ was added to a solution of 1 in MeCN the absorbance of the bands at 412 nm and 240 nm decreased and new absorptions were noted at 324 and 283 nm due to the lithium complex[9] (Table 1). When solutions were excited at 412 nm (the absorption maximum of uncomplexed 1), the emission intensity at 466 nm decreased with increasing Li^+ concentration. Solutions containing a large excess of Li^+ were then excited at 327 nm (near the absorption maximum of the 1:Li^+ complex), but no fluorescence could be detected from the 1:Li^+ complex. We attribute this quenching effect to Li^+ complexation within the azacrown cavity causing deconjugation of the N lone pair from the π system of the coumarin with a consequent increase in the freedom of rotation about the N-aryl bond.

The absorption and emission bands of the methoxy-substituted fluorophore 2 appeared at longer wavelengths than those of 1 and the fluorescence quantum yield was lower (Table 1). The effect of added Li^+ on the absorption spectrum of 2 was similar to that noted for 1 (Fig. 1). The intensity of the fluorescence band of uncomplexed 2 at 485 nm (excitation wavelength 427 nm) also decreased with increasing concentration of Li^+ in solution. In marked contrast to 1, fluorophore 2 formed a fluorescent Li^+ complex. Thus, excitation of MeCN solutions of 2 at 283 nm (one of the absorption maxima of the 2:Li^+ complex) gave rise to the fluorescence spectra shown in Fig. 2 which were recorded at varying Li^+ concentrations. At low Li^+ concentrations the fluorescence spectrum corresponds to that of uncomplexed 2 (which absorbs weakly at 283 nm). As the Li^+ concentration is increased the fluorescence maximum shifts to shorter wavelengths with an increase in intensity and finally reaches saturation. We attribute the fluorescence band at 462 nm to the 2:Li^+ complex. The fluorescence quantum yield of this complex, ϕ = 0.04, is greater than that of uncomplexed 2. This fact, coupled with the observation that fluoroionophore 1 devoid of the methoxy group does not form a fluorescent Li^+ complex, indicates that the methoxy side-arm of 2 increases the stability of the Li complex by coordinating to the ring-bound Li^+

ion, and reduces the tendency towards nonradiative deactivation of the excited state[10] by restricting rotation about the N-aryl bond. Note the larger K_{assoc} for **2**:Li^+ compared to **1**:Li^+.

Addition of sodium perchlorate to solutions of **1** or **2** in MeCN did not give rise to new absorption bands attributable to the sodium complexes even when greater than two hundred molar equivalents of this salt had been added. On addition of more salt, we were able to estimate an upper limit of K_{assoc} for **1**:Li^+ at about 1×10^2 $Lmole^{-1}$.

Coumarin fluoroionophores with the macrocycle positioned at the donor end of the molecule have been reported previously[11] but fluorophore **2** is the first example of such a system that responds to Li^+ by undergoing large shifts in absorption and emission wavelengths. We are investigating the properties of the carboxylic acids derived from **1** and **2** as well as related water soluble macrocycles in attempts to develop fluorescent Li^+ ion indicators.

Acknowledgement

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References and Notes

1. For a recent example see Mason, M.; Sutherland I.O., *J. Chem. Soc. Chem. Commun.* **1994**, 1131. For reviews see Lohr, H.G.; Vogtle, F. *Acc. Chem. Res.* **1985**, *18*, 65; Takagi, M.; Ueno, K. *Topic Curr. Chem.* **1984**, *121*, 39.
2. Griffiths, J. *The Colour and Constitution of Organic Molecules, Academic Press: London* **1976**, pp. 172.
3. Fery-Forgues, S.; Le Bris, M.; Guette, J.P.; Valeur, B. *J. Chem. Soc. Chem. Commun.* **1988**, 384; *J. Phys. Chem.* **1988**, *92*, 6233.
4. Minta, A.; Tsien, R.Y., *J. Biol. Chem.* **1989**, *264*(32), 19449; Smith, G.A.; Metcalfe, J.C.; Clarke, S.D. *J. Chem. Soc. Perkin 2* **1993**, 1195.
5. Bourson, J.; Pouget, J.; Valeur, B. *J. Phys. Chem.* **1993**, *97*, 4552.
6. Calverly, M.J.; Dale, J. *Acta Chem. Scand. B* **1982**, *36*, 241.
7. All new compounds were characterized by elemental analysis and/or mass spectrometry. IR and ^1H NMR spectra were in complete accord with the assigned structures, *e.g.*, compound **1** ^1H NMR ($CDCl_3$) δ 1.39 (t, 3H), 3.61 (m, 12H), 3.90 (t, 4H), 4.37 (q, 2H), 6.56 (s, 1H) 6.78 (d, 1H), 7.36 (d, 1H) 8.43 (s, 1H). Compound **2** ^1H NMR ($CDCl_3$) δ 1.40 (t, 3H), 3.70-3.85 (m, 19H), 4.40 (q, 2H), 6.82 (s, 1H), 6.84 (s, 1H), 8.44 (s, 1H).
8. Relative to quinine sulfate.
9. Addition of $LiClO_4$ caused the same spectral changes.
10. While this work was in progress, Sammes and co-workers reported that sodium and potassium ions cause an enhancement of the fluorescence of a diaza-18-crown-6 analog of **2**. See Crossley, R.; Goolamali, Z.; Gosper, J.J.; Sammes, P.G.; *J. Chem. Soc. Perkin 2* **1994**, 513.
11. Masilamani, D.; Lucas, M.E.; Hammond, G.S. U.S. Patent Appl. 80721, *Chem. Abstr.* **1990**, *112*, P51780t; Alonso, M.T.; Brunet, E.; Hernandez, C.; Rodriguez-Ubis, J.C. *Tetrahedron Lett.* **1993**, *34*, 7465.

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