Chromoionophores Based on Crown Ethers and Related Structures for Alkali Metal Ion Sensing in Aqueous Media

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Abstract. Recent progress in chromoionophores based on (1) spherand and hemispherand, (2) cryptand, and (3) dibenzo-16-crown-5 and calix[4]crown which selectively respond to alkali metal ions in aqueous media is reviewed in relation to their molecular structure and photometric function. The design concept of the chromoionophores for colorimetry in aqueous media is discussed in the light of their acid dissociation and metal complex formation equilibria.

Key words: Chromoionophore, spherand, hemispherand, cryptand, crown ether, calix[4]crown, colorimetry, aqueous media.

1. Introduction

Crown ether compounds are useful synthetic ionophores for the recognition of alkali metal and alkaline earth metal cations in aqueous solutions [1–3]. The introduction of proton-ionizable chromophore groups into a crown ether represents a further elaboration in which extraction of the metal cation from aqueous solution into an organic phase produces a distinct color change in the organic medium. Such crown ether chromoionophores have been utilized in the extraction photometric determination of alkali metal and alkaline earth metal cations in aqueous solutions [4–6]. However the extraction photometry by the crown ether chromoionophore

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(1)   **(2)**
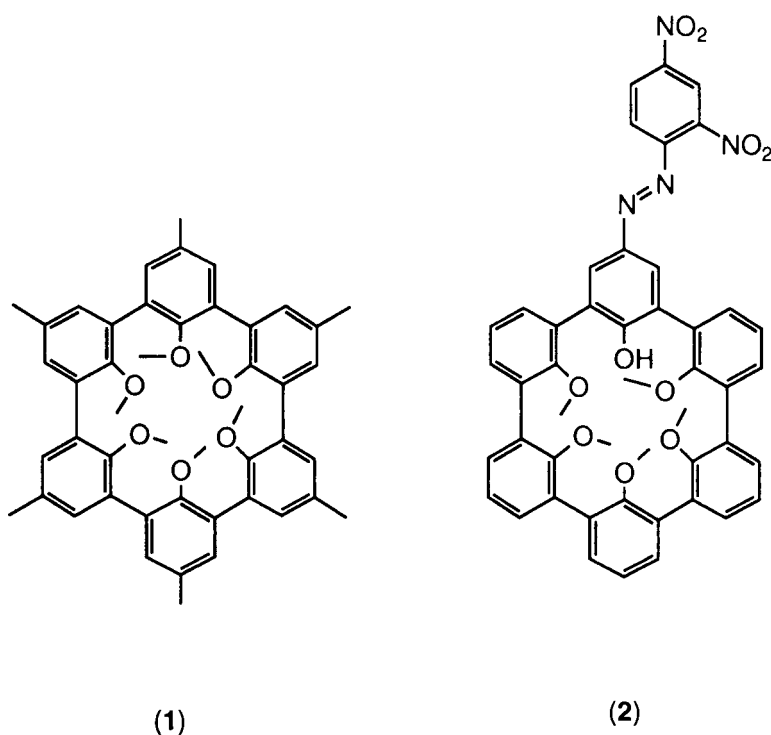
Formulas 1–2.

requires toxic and volatile organic solvents and an inconvenient phase separation process in the analysis. If alkali metal cation photometry could be performed in homogeneous aqueous media, a wide variety of applications would be feasible.

This paper describes a new approach for alkali metal ion sensing in aqueous media and recent progress in the design of chromoionophores based on crown ethers and related structures for this purpose.

2. Spherand and Hemispherand Based Chromoionophores

Spherand (**1**) developed by Cram *et al.* [7] is known to exhibit a strong metal binding ability toward alkali metal cations in aqueous solution owing to the high complementarity and preorganization of the cavity for metal complexation [8, 9]. When the medium is changed from organic to aqueous solution, the stability constants for metal ion-macrocyclic ligand interactions decrease by three to four log units due to a strong hydration of metal ions in water [10]. However, the spherand can complex strongly enough to coordinate with metal ions even in aqueous media. Thus an introduction of chromophore groups into the spherand type ionophores is expected to provide promising chromoionophores which can function in aqueous media [4].
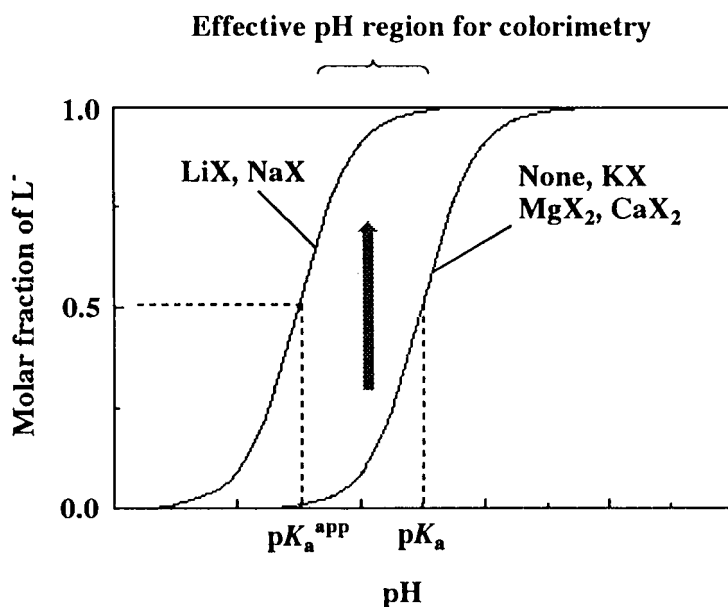
Effective pH region for colorimetry

Figure 1. Coloration mechanism of a chromoionophore (HL) in an aqueous medium.

The spherand based chromoionophore (**2**) in which 4-(2,4-dinitrophenylazo) phenol is introduced as a chromophoric moiety was first developed by Cram et al. [11]. Interestingly the pK_a value in 80% 1,4-dioxane $-$ 20% water (v/v) changes dramatically from 13.0 for uncomplexed spherand (**2**) to 5.9 for the Li^+ complex and 6.3 for the Na^+ complex. The presence of K^+, Mg^{2+}, and Ca^{2+} in the solution does not affect the pK_a value. The deprotonation of the phenolic hydroxy group is enhanced by the strong binding of (**2**) with Li^+ or Na^+ in aqueous dioxane solution. The spectrum of spherand (**2**) (HL form) is yellow ($\lambda_{max} = 396$ nm, $\epsilon = 17500$ M^{-1} cm^{-1}), whereas the spheraplex $(2)^- \cdot Li^+$ ($\lambda_{max} = 586$ nm, $\epsilon = 35500$ M^{-1} cm^{-1}) and $(2)^- \cdot Na^+$ ($\lambda_{max} = 596$ nm, $\epsilon = 17500$ M^{-1} cm^{-1}) are blue or violet. Thus in the pH regions of the apparent pK_a of the spheraplex $(2)^- \cdot M^+$, a distinct color change is observed upon addition of Li^+ or Na^+ in aqueous dioxane solution. To our best knowledge, this is a first example of the chromoionophore which exhibits a chromogenic response for alkali metal ions in aqueous media.

The coloration mechanism is shown in Figure 1 [4, 12]. The molar fraction of deprotonated chromoionophore (L^-) increases with the increase of solution pH. This generally causes an increase in absorption intensity at longer wavelength (590 nm for (**2**)). Since the apparent pK_a (pK_a^{app}) value shifts to lower pH in the presence of Li^+ or Na^+ for (**2**), the increase in absorption intensity due to metal binding can be detected most effectively in the pH region between pK_a and pK_a^{app} (Figure 1). Unfortunately the complexation kinetics of (**2**) is very slow. It takes several hours to reach the complexation equilibrium.
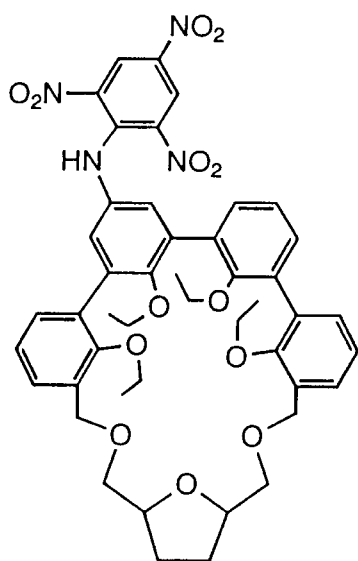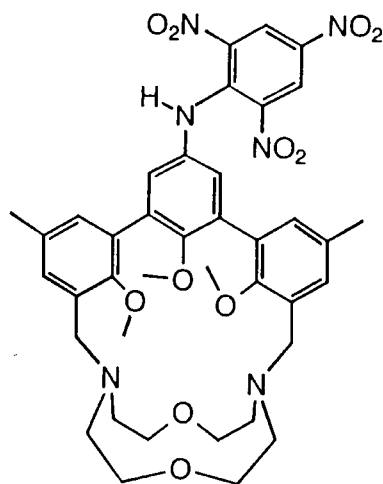
Formulas 3–4.

To provide relatively flexible host molecules with an enhanced complexation rate, crown ether and cryptand structures are combined with a spherand moiety. Helgeson et al. have designed chromogenic hemispherand (**3**) and cryptahemi-spherand (**4**) bearing picrylamino chromophores [13]. In these chromoionophores, the picrylamino group is introduced in a position remote from the binding site so as not to affect the metal-binding selectivity of these highly preorganized hosts.

In Table I are summarized the spectral characteristics and pK_a values for (**3**) and (**4**). For (**3**), the pK_a value of the KL form is apparently lower than that of HL and NaL forms in 80% 1,4-dioxane − 20% water (v/v). The λ_{max} shows a bathochromic shift of ca. 70 nm on going from HL form to KL complex with enhanced absorptivity. Thus compound (**3**) responds to the addition of KCl in the 10^{-4}–10^{-5} M range in the presence of Na^+ at pH 10.0.

Although cryptahemispherand (**4**) has not been isolated in the HL form, the cryptahemispheraplex (**4**)·LiX is easily handled and stored as solids. This crypta-hemispheraplex also exhibits a substantial spectral response in essentially aqueous solution. As shown in Table I, the pK_a of (**4**)·LiBr and (**4**)·KBr are both 7.85 in 1% diethyleneglycol diethyl ether (DEGDE) − 99% water (v/v), whereas the pK_a of (**4**)·NaBr is 6.95. At pH 8.0, (**4**)·Li^+ gives λ_{max} at 395 nm ($\epsilon = 11800$ M^{-1} cm^{-1}), (**4**)·K^+ provides λ_{max} at 398 nm ($\epsilon = 11930$ M^{-1} cm^{-1}), whereas for (**4**)·Na^+, λ_{max} appears at 445 nm ($\epsilon = 14600$ M^{-1} cm^{-1}). The chromoionophore (**4**)·Li^+ has been

Table I. Spectral characteristics and acidity constants of chromoionophores (**3**) and (**4**).

Compound	Species	λ_{max}, nm	ϵ, M^{-1} cm^{-1}	pK_a
(**3**)[a]	HL[b]	388	10300	11.10
(**3**)[a]	NaL[c]	454	15400	10.76
(**3**)[a]	KL[c]	449	16350	9.35
(**4**)·LiBr[d]	LiL[e]	395	11800	7.85
(**4**)·NaBr[d]	NaL[f]	445	14600	6.95
(**4**)·KBr[d]	KL[f]	398	11930	7.85

[a] In a mixture of 80% 1,4-dioxane − 20% water (v/v); chromoionophore concn., 7.6×10^{-5} M.

[b] In the presence of 0.020 M HCl.

[c] In the presence of 0.020 $M(CH_3)_4NOH$ and 0.010 M in NaCl or KCl.

[d] In a mixture of 1% DEGDE − 99% water (v/v); chromoionophore, 1.0×10^{-4} M.

[e] In the presence of 0.30 M imidazolium acetate (IMA, pH 8.0).

[f] In the presence of 0.30 M IMA and 0.010 M in NaCl or KCl.

shown to exhibit a high sensitivity with detection limits of 2×10^{-5} M for Na^+, and selectivity estimated to be greater than 100 for Na^+/K^+ [13].

3. Cryptand Based Chromoionophores

Bartsch and Kumar et al. reported cryptand based chromoionophores (**5a–d**) and investigated in detail their chromogenic responses toward Na^+ and K^+ in 50% 1,4-dioxane − 50% water (v/v) [14]. Table II summarizes the spectral characteristics of (**5a–d**) at optimum pH for metal ion response. It is evident that the cavity size of cryptand affects the chromogenic responses. Thus chromoionophores (**5a**) and (**5c**) show only slight differences in absorption maximum (λ_{max}) and molar absorptivity (ϵ) between their NaL and KL forms, where ML is defined by the compound in the presence of a large excess of M^+ ions. A 61 nm bathochromic shift in λ_{max} and an increase in ϵ value for the KL form are observed for (**5b**) on going from the NaL to the KL form. Although (**5d**) has a larger cavity size as compared with (**5a**) and (**5c**), the NaL form exhibits a larger λ_{max} than the KL form by 26 nm and almost twice the absorptivity. These results reveals that compounds (**5b**) and (**5c**) are the potential indicators for the photometric determination of K^+ and Na^+, respectively.

The chromoionophore (**6**) carrying inward-facing phenolic groups has been prepared by Zazulak et al. for Li^+ ion sensing [15]. At pH 12.0 in 10% diethyleneglycol monoethyl ether (DEGMEE) − 90% water (v/v), the λ_{max} shifts from 379 nm ($\epsilon = 13.3 \times 10^3$ M^{-1} cm^{-1}) for NaL and KL to 512 nm (8.8×10^3 M^{-1} cm^{-1}) for LiL. The cryptand (**6**) has been shown to possess exceptionally high selectivity

(5a) m=1, n=0
(5b) m=1, n=1
(5c) m=2, n=1
(5d) m=2, n=2

(6)
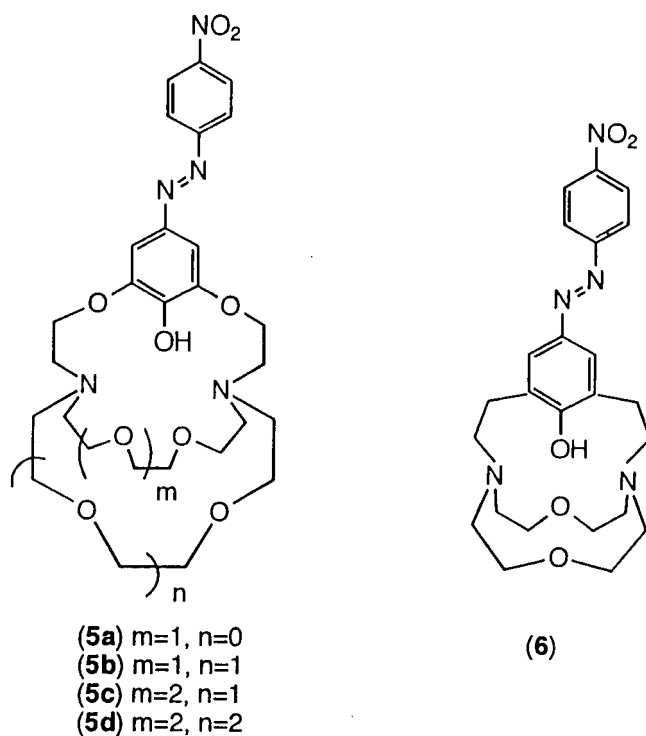
Formulas 5–6.

Table II. Spectral characteristics and acidity constants of chromoionophores (5a)–(5d) in a mixture of 50% 1,4-dioxane − 50% water (v/v).

Compound	pH^a	λ_{max} (nm) ϵ (M^{-1} cm^{-1})			pK_a
		HL	NaL^b	KL^b	
(5a)	10.0	349 (4200)	513 (10000)	499 (10000)	ND^c
		493 (21000)			
(5b)	11.0	383 (12140)	502 (18800)	563 (27800)	ND
		483 (22070)			
(5c)	11.0	391 (15100)	529 (22400)	529 (22300)	ND
		485 (12700)			
(5d)	10.0	397 (16500)	561 (34900)	535 (19800)	9.2
		482 (16700)			

a Optimum pH for metal ion response; 0.10 M N-cyclohexyl-2-aminoethanesulfonic acid buffer (pH 10.0), 0.10 M N-cyclohexyl-3-aminopropanesulfonic acid buffer (pH 11.0).
b NaL and KL are the compounds in the presence of a large excess of Na$^+$ and K$^+$, respectively.
c Not determined.

(7)   (8)
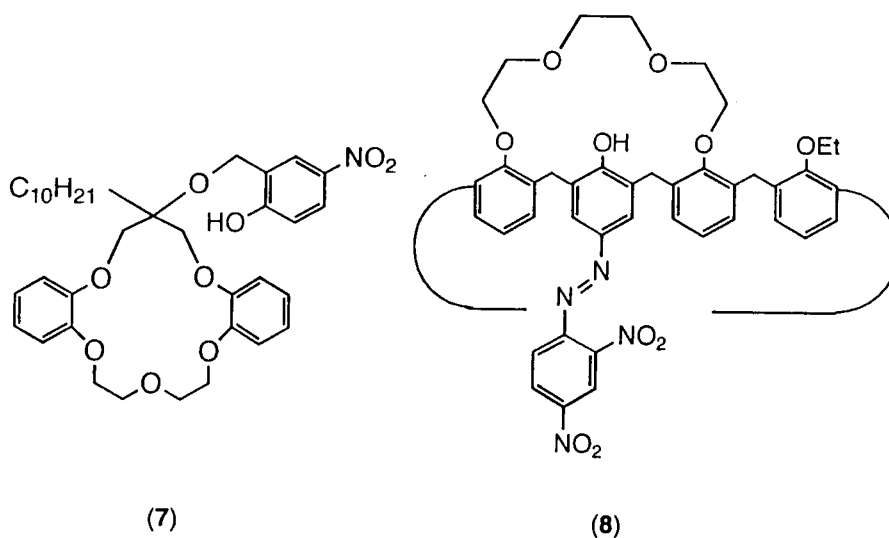
Formulas 7–8.

for Li^+ over Na^+ (4000 for Li^+/Na^+) and has successfully been applied to the photometric determination of Li^+ concentration in blood serum [16].

4. Crown Ether and Calix[4]crown Based Chromoionophores

The attachment of a decyl group to the same polyether ring carbon that bears the chromophore side arm in dibenzo-16-crown-5 (DB16C5) (7) is proposed to orient the phenolic group of the chromophore over the crown ether cavity [17]. This preorganization enhances selective interaction of the DB16C5 binding site toward Na^+ over other alkali metal cations in solution. Spectral characteristics of chromoionophore (7) are examined in 50% 1,4-dioxane − 50% water (v/v) in the presence of 0.10 M tetramethylammonium chloride (TMACl) or alkali metal chlorides [18, 19]. Similarly to the spherand and cryptand based chromoionophores, the apparent pK_a value (pK_a^{app}) shifts significantly to lower pH in the presence of Na^+. The observed spectral characteristics of (7) are summarized in Table III. The response of (7) to Na^+ at pH 7.5 in 50% 1,4-dioxane-50% water (v/v) is perfectly linear and 10^{-3} M order of Na^+ can be detected.

Since calix[4]crown based chromoionophore (8) possesses a highly preorganized binding site, much stronger interaction with metal cation in aqueous media is expected [20, 21]. Spectral characteristics of (8) are examined in 70% 1,4-dioxane − 30% water (v/v) in the presence of 0.10 M TMACl or alkali metal chlorides. Interestingly this chromoionophore shows a unique colorimetric response in acidic aqueous solution [22]. The UV-Vis spectra at pH 3.5 are shown in Figure 2. It is seen that a selective coloration appears only in the presence of Na^+. The maximum wavelength changes from 422 nm (HL form) to 457 nm (MHL form).

Table III. Spectral characteristics, acidity constants, and stability constants of chromoionophore (**7**) in a mixture of 50% 1,4-dioxane-50% water (v/v).

Salt[a]	λ_{max} (nm) ϵ (M^{-1} cm^{-1})		pK_a[b]	ΔpK_a	K_{ML} (M^{-1})
	HL	L$^-$			
TMACl	323 (9500)	416 (20600)	8.68	–	–
LiCl	323 (9700)	415 (20600)	8.68	0.00	$<0.10 \times 10^2$
NaCl	323 (9500)	412 (22300)	7.37	1.31	2.00×10^2
KCl	323 (9700)	411 (20700)	8.36	0.32	0.21×10^2

[a] Salt concn.: 0.10 M.
[b] $pK_a = -\log K_a$.

Table IV. Spectral characteristics, acidity constants, and stability constants of chromoionophore (**8**) in a mixture of 70% 1,4-dioxane − 30% water (v/v).

Salt[a]	λ_{max} (nm) ϵ (M^{-1} cm^{-1})		pK_a[b]	ΔpK_a	K_{MHL} (M^{-1})	K_{ML} (M^{-1})
	HL	L$^-$				
TMACl	421 (20600)	626 (66600)	10.97	–	–	
LiCl	422 (20400)	607 (62700)	7.31	3.66≪1	4.57×10^4	
NaCl	462 (36000)[c]	612 (63300)	6.10	4.87	22.0	2.37×10^6
KCl	422 (20200)	612 (63300)	9.77	1.20	≪1	1.48×10^2

[a] Salt concn.: 0.10 M.
[b] $pK_a = -\log K_a$.
[c] ϵ_{MHL}.

Chapoteau et al. reported that 4-(4′-nitrophenylazo)-2,6-dimethoxyphenol forms only the quinone phenylhydrazone structure in 50% 1,4-dioxane − 50% water (v/v) to exhibit the maximum absorption at 480 nm, whereas 4-(4′-nitrophenylazo)-2,6-bis(methoxymethyl)-phenol shows only the phenylazophenol form possessing the maximum absorption at 380 nm [23]. Thus the hydrazone form exhibits the higher maximum absorption than that of azophenol structure in the HL species. This result indicates that the bathochromic shift observed in Figure 2 is ascribed to a tautomerism from the phenylazophenol structure (**8a**) to the quinone phenylhydrazone form (**8b**) (Figure 3).

Above pH 6.0, calix[4]crown (**8**) selectively responds to Na$^+$ ion and shows a new absorption spectrum at 612 nm (ML form). The spectral characteristics of (**8**) are summarized in Table IV. The observed selectivities are 16000 for Na$^+$/K$^+$ and 56 for Na$^+$/Li$^+$, respectively.
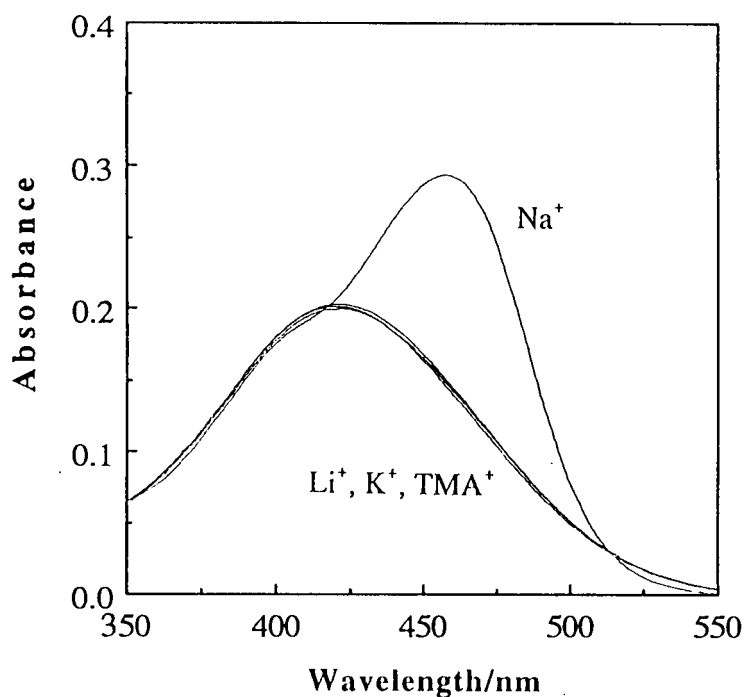
Figure 2. UV-Vis spectra of (**8**) in 70% 1,4-dioxane − 30% water (v/v) at pH 3.5 in the presence of 0.10 M LiCl, NaCl, KCl, and TMACl.
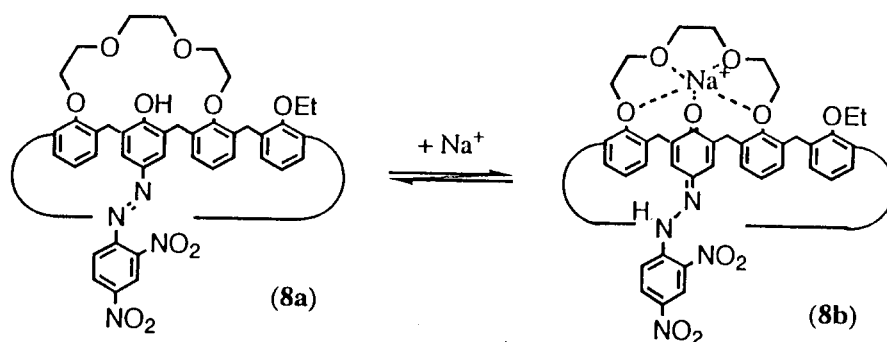

Figure 3. Tautomerism from the phenylazophenol structure (**8a**) to the quinone phenylhydrazone form (**8b**).

5. Colorimetric Behavior in Aqueous Micellar Solution

The micellar solution is expected to provide a hydrophobic circumstance which solubilizes the lipophilic crown ether chromoionophores in aqueous solution and enhances the ionophore metal interaction (Figure 4) [24]. The spectral characteristics of chromoionophore (**7**) in 10.0 mM micellar solution of (a) CTAB
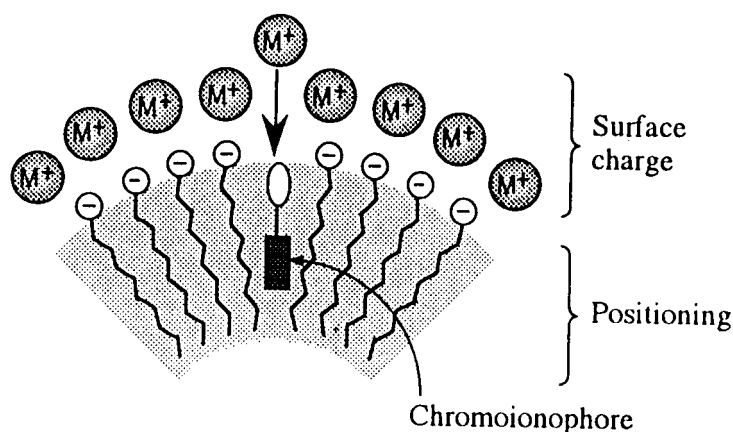
Figure 4. Concept of metal ion sensing in aqueous micellar solution.

(cetyltrimethylammonium bromide), (b) Triton X-100 (nonionic surfactant), and (c) TMADS (tetramethylammonium dodecylsulfate) have been examined [25]. Increasing the pH promotes proton dissociation of the phenolic chromophore and absorptions based on the dissociated species (L^-) appear at 405–408 nm. The apparent pK_a values calculated from these data are summarized in Table V. In both CTAB and Triton X-100, no significant differences in the pK_a values are noted. The low pK_a values observed for CTAB reveal that the cationic charge of the micellar surface accelerates proton dissociation of the phenolic chromophore. For Triton X-100, the pK_a values are apparently higher than that of *p*-nitrophenol in aqueous solution ($pK_a = 7.1$). Presumably this is attributed to a hydrogen bonding between the chromophore proton and the polyoxyethylene unit in Triton X-100. In contrast, a selective coloration of chromoionophore (**7**) is observed in TMADS solution. Thus the absorbance at 406 nm increases only in the presence of Na^+ ion. The anionic charge of the micellar surface inhibits a loose ion-pair formation of the metal-chromoionophore complex due to an electric repulsion of the surface charge with the phenolate anion of the chromophore. Thus complex formation would be restricted to cations which can form a tight ion-pair in the binding site. This may be the reason that the selective color change is obtained for Na^+ in the anionic micellar solution of (**7**).

6. Design Concept of Chromoionophore for Colorimetry in Aqueous Media

In Figure 5 are shown the acid dissociation and the complex formation equilibria for the monobasic acid chromoionophore (HL). The equilibrium constants are,

$$K_a = \frac{[H^+][L^-]}{[HL]} \tag{1}$$

Table V. Apparent acidity constant of chromoionophore (**7**)[a]

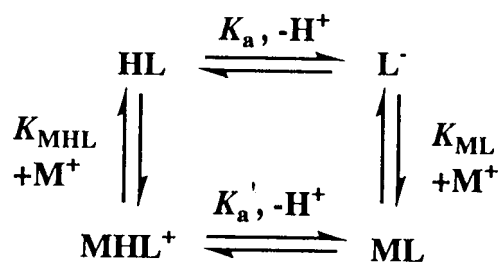| Surfactant	pK_a^{app}			
	Li^+	Na^+	K^+	TMA^+
CTAB	6.62	6.69	6.69	6.65
Triton X-100	8.73	8.57	8.75	8.85
TMADS	–	8.72	–	–

[a] Surfactant concn.: 10.0 mM; salt concn.: 0.10 M.

Figure 5. Proton dissociation and metal complex formation equilibria.

$$K_a' = \frac{[H^+][ML]}{[MHL^+]} \tag{2}$$

$$K_{ML} = \frac{[ML]}{[M^+][L^-]} \tag{3}$$

$$K_{MHL} = \frac{[MHL^+]}{[M^+][HL]} \tag{4}$$

The apparent molar absorptivity ($\bar{\epsilon}$) of the chromoionophore is expressed as,

$$\bar{\epsilon} = \frac{\epsilon_{HL}' + \dfrac{K_a(1 + K_{ML}[M^+])}{[H^+](1 + K_{MHL}[M^+])}\epsilon_L'}{1 + \dfrac{K_a(1 + K_{ML}[M^+])}{[H^+](1 + K_{MHL}[M^+])}} \tag{5}$$

$$\epsilon_{HL}' = \frac{\epsilon_{HL} + \epsilon_{MHL}K_{MHL}[M^+]}{1 + K_{MHL}[M^+]} \tag{6}$$

$$\epsilon_L' = \frac{\epsilon_L + \epsilon_{ML}K_{ML}[M^+]}{1 + K_{ML}[M^+]} \tag{7}$$

where ϵ_{HL}, ϵ_L, and ϵ_{ML} are the molar absorptivities of HL, MHL$^+$, L$^-$, and ML species, respectively. When the system does not contain the metal complex, the apparent molar absorptivity is more simply expressed as,

$$\bar{\epsilon} = \frac{\epsilon_{HL} + \frac{K_a}{[H^+]}\epsilon_L}{1 + \frac{K_a}{[H^+]}} \tag{8}$$

From Equations (5) and (8), the apparent acid dissociation constant (K_a^{app}) is defined as,

$$K_a^{app} = K_a \frac{1 + K_{ML}[M^+]}{1 + K_{MHL}[M^+]} \tag{9}$$

$$\Delta pK_a = \log \frac{1 + K_{ML}[M^+]}{1 + K_{MHL}[M^+]} \tag{10}$$

When $K_{ML}[M^+]$ and $K_{MHL}[M^+]$ are large enough to satisfy the relation of $1 \ll K_{ML}[M^+]$, $K_{MHL}[M^+]$, Equation (10) is rewritten as,

$$\Delta pK_a = \log \frac{K_{ML}}{K_{MHL}} \tag{11}$$

In Equation (11), the ΔpK_a is independent to the metal ion concentration in the solution. Thus the largest ΔpK_a is dominated by the ratio of K_{ML} and K_{MHL}. It is evident that a large K_{MHL} reduces the chromogenic response of the chromoionophore in aqueous media. To suppress the MHL complex formation, the proton-ionizable group of the chromophore should be positioned within a binding site of the ionophore so as to promote the proton dissociation by metal ion binding. The chromoionophores possessing the inward-facing phenolic chromophores such as (**2**), (**5**), (**6**) and (**8**) and the preorganized chromoionophore (**7**) are in line with this concept.

Chromoionophore (**9**) developed by Takagi et al. which possesses the picrylamino group remote from the metal binding site exhibits a relatively high K_{MHL} value in 10% 1,4-dioxane $-$ 90% water (v/v) (K_{MHL} = 41.7 M^{-1} and K_{ML} = 83.2 M^{-1} for K$^+$) [26]. Thus the K_{ML}/K_{MHL} and ΔpK_a values for (**7**) are calculated to be 2.0 and 0.3, respectively, and no effective chromogenic response is observed. It is evident for this type of chromoionophore that the introduction of a positive charge in the crown ether ring (alkali metal complex formation) exerts only a small electron withdrawing effect on the acidity of the picrylamino nitrogen.

It has also been reported that cryptand based chromoionophores (**10a**) and (**10b**) show no colorimetric response to alkali metal ions in 50% 1,4-dioxane $-$ 50% water (v/v) [27]. Only the hemispherand based chromoionophores (**3**) and (**4**) which have strong binding with alkali metal cations are shown to be effective for colorimetry in aqueous media.
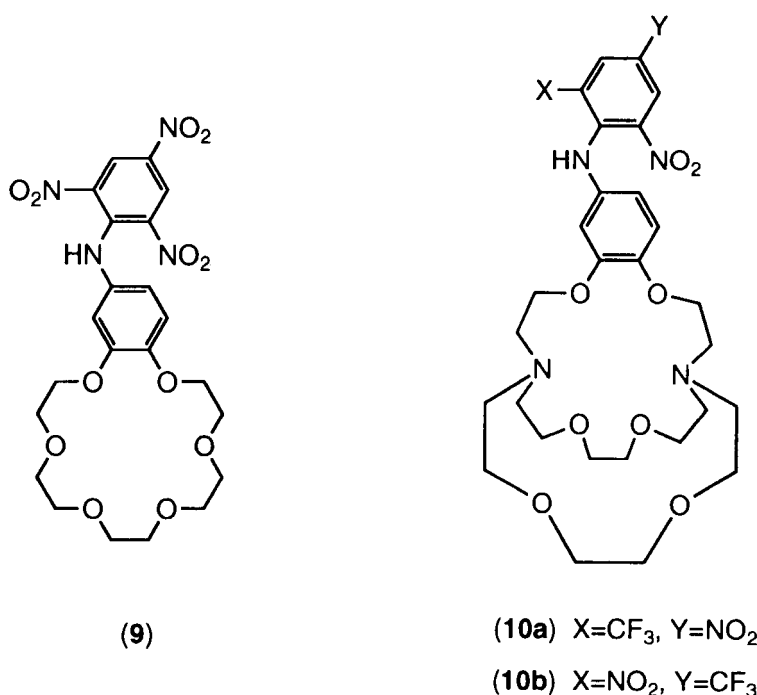
Formulas 9–10.

    The calix[4]crown chromoionophore (**8**) exhibits a selective color change for Na^+ by forming the MHL complex in acidic aqueous media. This coloration is based on the tautomerism from the phenylazophenol structure to the quinone phenylhydrazone form, which is different from the coloration mechanism discussed above. In general, the MHL complex formation is enhanced in a high ionic strength and a high dielectric constant of solution. Thus this system would have potential for use in aqueous salt solution as well as in aqueous micellar solution.

7. Conclusions

This paper describes the recent progress of synthetic chromoionophores for alkali metal ion sensing in aqueous media. Three-dimensionally preorganized crown ether binding sites show strong binding ability toward alkali metal cations. Introduction of the proton-ionizable chromophores into these skeletons at the proper site provides a new class of chromoionophores which can selectively respond to alkali metal cations in essentially aqueous solution. For this type of colorimetry, we can eliminate the toxic and volatile organic solvents as well as the inconvenient phase separation step required in extraction photometry. It is hoped that these new classes of synthetic chromoionophores will be utilized not only in simple ion sensing but

also in microscopic evaluation of naturally occurring chemical processes such as those in biological systems.

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