Chromo- and Fluoroionophores. A New Class of Dye Reagents

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Color reactions are popular criteria for the identification and quantitative determination of substances. For alkaline-earth metal ions, dye reagents and color indicators are available that allow titrimetric determination of the ionic content with chelating agents of the EDTA type.[1] For alkali metal ions however, only a few color reagents were known before 1977,[2] and these do not allow the photometric ion determination of practical samples. New possibilities were opened by the discovery[3] and development of the crown ether chemistry.[4] The selectivity of non-, mono-, and bicyclic oligoethers to alkali- and alkaline-earth metal ions has forced their use for analytical purposes. Beside their application in separation processes[5] and ionselective electrodes,[6] optical detection methods are practicable. In the latter case, two procedures are distinguishable: (a) ion-pair extractions with colored, lipophilic anions,[7] (b) complex formation with dye ligands (chromoionophores[8]), showing ion-specific color changes.

The Concept of the Molecular Chromophore–Ionophore Combination

In the alkali- and alkaline-earth metal salt complexes of crown compounds, the positive cation charge influences the donor heteroatoms (O, N, S) and their electronic surroundings by ion–dipole forces. If one of the heteroatoms is a constituent of a mesomeric system, the electronic disturbance propagates through the whole (n + π) system. Due to different influences on the ground and photoexcited states by "crowned" cations, changes occur in the absorption spectra.

In 1967 Pedersen used salt-dependent UV measurements for the characterization of complexation processes with crown ethers containing aromatic structure units.[3] However, the determined development of molecular-combined *neutral* crown dyes with high "color sensitivity" to complexed cations, began a decade later.[9] By suited linkages of monoaza-, benzo-, and other crowns with chromophores, we achieved considerable shifts of absorption bands by the use of salts.

For the design of chromoionophores, the following aspects are of particular interest: (1) Which kind of chromophores respond highly sensitive to local electronic disturbances by cations? (2) What kind of connections between ionophores and chromophores allow the strongest electronic interactions with complexed

cations? (3) How far can color effects be realized by steric effects on cation complexation? (4) How do complexed cations act on the fluorescence spectra of fluoroionophores? (5) How and to what extent can chiral chromoionophores differentiate visually between enantiomers? (6) How can chromoionophores be best utilized for analytical and diagnostic purposes, and which further applications are offered?

Simultaneous with our development of neutral chromoionophores, Takagi et al. independently synthesized colored crown ether *anions*,[10] having the same construction principle. Mono- and di*protonic* chromophores were set into a crown skeleton in such a way that the complexation of positively charged metal ions was accompanied by the dissociation of protons of the chromophore.

The purpose of these *"acidic" chromoionophores* is primarily the improvement of the phase transfer of cations in extraction experiments. Their color effects in such experiments can be referred primarily to the spectral differences of the protonated and deprotonated species. For example, 1 exhibits on deprotonation a color change from yellow (λ_{max} = 390 nm) to violet (518 nm). However, the differences between the absorption spectra of the complexes are fairly poor: The absorption maximum of the potassium complex of 1 in 1,2-

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(1) For example, see: (a) Anderegg, G.; Flaschka, H. A.; Sallmann, R.; Schwarzenbach, G. *Helv. Chim. Acta* **1954**, *37*, 113. (b) Bermejo-Martinez, F. In "Chelates in Analytical Chemistry"; Flaschka, H. A., Barnard, A. J., Eds.; Marcel Dekker: New York, 1976. (c) Vögtle, F.; Ohm, C. *Chem. Ber.* **1984**, *117*, 948 and references cited therein.

(2) (a) Lange, B.; Vejdelek, C. J. "Photometrische Analyse"; Verlag Chemie, Weinheim/Bergstr., Germany, 1980. (b) Budesinsky, B.; Menclova, B. *Chem. Anal.* **1967**, *56*, 30.

(3) (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495. (b) Pedersen, C. J. *Ibid.* **1967**, *89*, 7017.

(4) For recent reviews on crown compounds, see: (a) "Macrocyclic Polyether Syntheses"; Gokel, G. W., Korzeniowski, S. H., Eds.; Springer Verlag: Berlin, 1982. (b) Vögtle, F.; Weber, E. In "The Chemistry of Functional Groups"; Patai, S., Ed.; Wiley and Sons: Chichester, 1980; Supple. E., Part 1. (c) "Progress in Macrocyclic Chemistry"; Izatt, F. M.; Christensen, J. J., Eds.; Wiley: New York, 1979; Vol. 1. (d) *Ibid.*, 1981, Vol. 2.

(5) For example, see: (a) Blasius, E.; Janzen, K. P. *Top. Curr. Chem.* **1981**, *98*, 163. (b) Mitchell, J. W.; Shanks, D. L. *Anal. Chem.* **1975**, *47*, 462. (c) Jepson, B. E.; Dewitt, R. *J. Inorg. Nucl. Chem.* **1976**, *38*, 1175.

(6) (a) Shanzer, A.; Libman, J.; Frolow, F. *Acc. Chem. Res.* **1983**, *16*, 60. (b) Morf, W. E.; Ammann, D.; Bissig, R.; Pretsch, E.; Simon, W. In "Progress in Macrocyclic Chemistry"; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1979; Vol. 1. (c) Schindler, J. G. *J. Clin. Chem. Clin. Biochem.* **1979**, *17*, 573.

(7) (a) Takeda, Y. *Top. Curr. Chem.* **1984**, *121*, 1. (b) Kolthoff, I. M. *Can. J. Chem.* **1981**, *59*, 1548. (c) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 4684.

(8) We generally signify such molecules as chromoionophores, which contain a chromophore as well as an ionophore moiety. An intramolecular "electronic coupling" between chromo- and ionophore is not a precondition.

(9) Dix, J. P.; Vögtle, F. *Angew. Chem.* **1978**, *90*, 893; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 857.
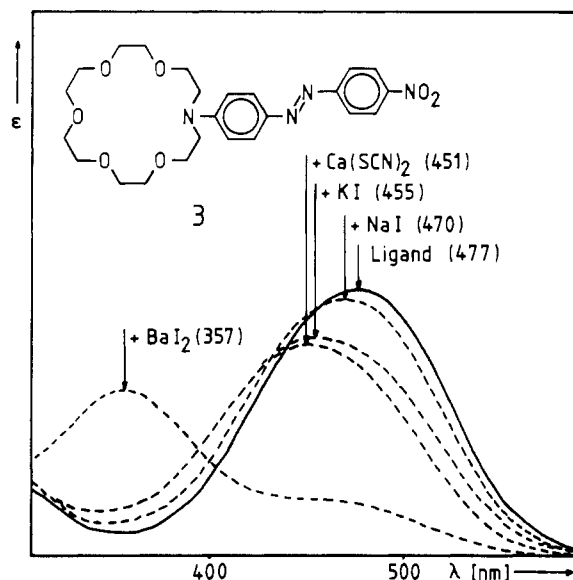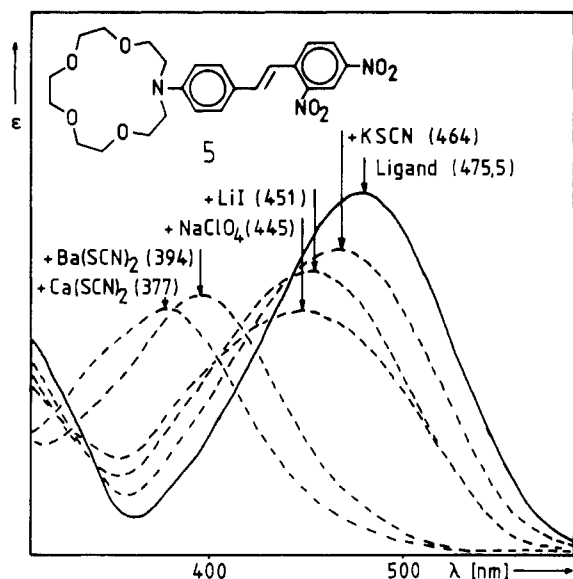
(10) (a) Takagi, M.; Nakamura, H.; Ueno, K. *Anal. Lett.* **1977**, *10*, 1115. (b) Lamb, J. D. Izatt, R. M.; Christensen, J. J.; Eatough, D. L. in "Coordination Chemistry of Macrocyclic Compounds"; Melson, A. A., Ed.; Plenum Press: New York, 1979. (c) Bubnis. B. P.; Pacey, G. E. *Tetrahedron Lett.* **1984**, *25*, 1107.

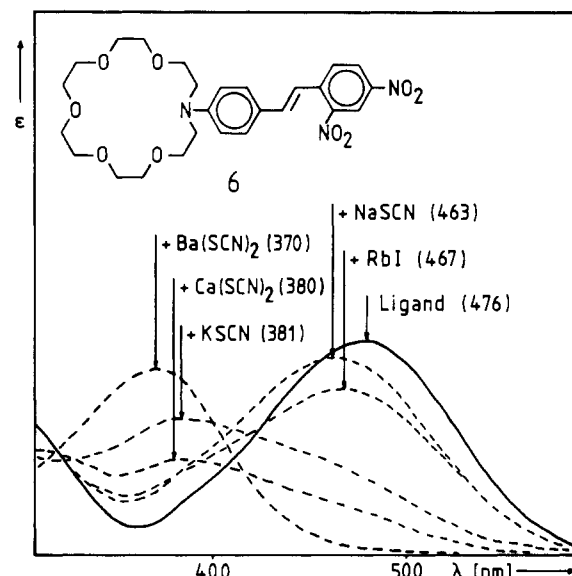**Figure 1.** Scheme of the molecular construction of a chromoionophore.

Figure 2. Absorption spectra of the chromoionophore 3: free ligand and in the presence of salts; solvent, acetonitrile (λ_{max} in nanometer).[13,14]
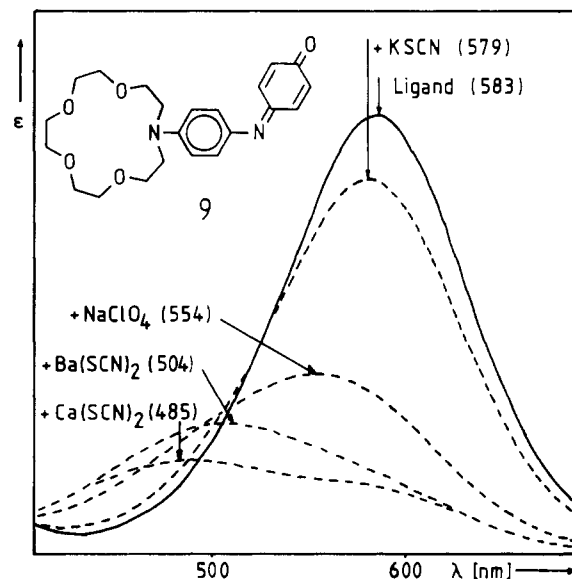

Figure 3. Absorption spectra of the chromoionophore 5: free ligand and in the presence of salts; solvent, acetonitrile (λ_{max} in nanometer).[13,14]

Figure 4. Absorption spectra of the chromoionophore 6: free ligand and in the presence of salts; solvent, acetonitrile (λ_{max} in nanometers).[13,14]

Figure 5. Absorption spectra of the chromoionophore 9: free ligand and in the presence of salts; solvent, acetonitrile (λ_{max} in nanometers).[13,14]

Donor–Acceptor-Type[12] Chromoionophores with Cation-Induced Hypsochromic Band Shifts

A simple but effective combination of dyes and crown ethers exists in the formal replacement of amino substituents of chromophores by azacrowns. In the resulting chromoionophores the amine nitrogens possess simultaneously an electron-donor function to complexed cations as well as to the chromophore. The majority of the chromoionophores described until now meet this construction scheme.[13–15]

The absorption bands of the chromoionophores 2–9 in the visible region are all hypsochromically shifted by

dichloromethane lies at 575 nm and of the sodium complex at 571 nm.[11] Hence, there is hardly a differentiation as a consequence of cation influence on the absorption behavior of the *anionic* chromophore. Therefore the obtained selectivities have to be referred to the position of the extraction equilibria—similar to the extractions with lipophilic color anions.[7]

(11) Takagi, M.; Ueno, K. *Top. Curr Chem.* **1984**, *121*, 39.

(12) For the classification of chromophores applied primarily in this review, see: Griffiths, J. "Colour and Constitution of Organic Molecules"; Academic Press: London, 1976.
(13) Dix, J. P.; Vögtle, F. *Chem. Ber.* **1980**, *113*, 457.
(14) Dix, J. P.; Vögtle, F. *Chem. Ber.* **1981**, *114*, 638.
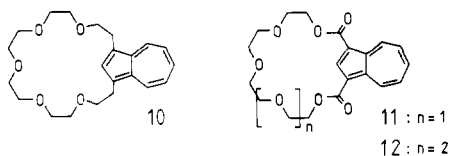(15) Vögtle, F. *Pure Appl. Chem.* **1980**, *52*, 2405.

alkali- and alkaline earth metal ions.[13-15] Mostly, the
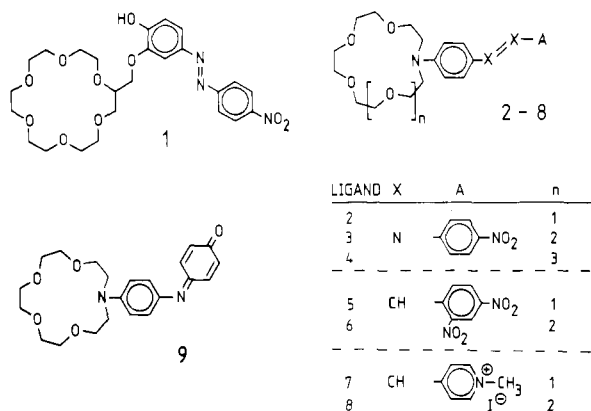
color shifts induced by doubly charged ions are significantly larger than those of monovalent cations of comparable size (see Figures 2–5). The influence of the ligand ring size on the selectivity is obvious by the rule that always the strongest λ_{max} shift is effected by the cation (of same charge) which fits best into the ligand cavity. Thus, we observed the largest band shifts of the ligands 2 and 5 with sodium ions in the alkali metal ion series and of the larger crowns 3 and 6 with potassium salts. The related "uncrowned" chromophores mostly show only negligible or no changes in their absorption spectra on addition of salts.

The alterations of the electron spectra of the donor–acceptor dyes 2–9 by complexed cations are accompanied by clear color changes. Thus, barium salts effect a yellow coloring of the red-orange solution of the azodye 3. The orange-red color of the stilbene dye 6 shifts to yellow on complexation of K^+ and Ca^{2+} ions; with Ba^{2+} ions the CH_3CN solution appears nearly colorless. The characteristic blue of the quinone imine dye 9 (phenol blue analogue) turns to yellowish-orange when Ca^{2+} salts are added, whereas red-violet colorings occur with Li^+, K^+, and Ba^{2+}.

The fact that aromatic π-systems can be influenced by direct interactions with alkali- and alkaline-earth metal ions in suited crown ethers has been surmised for some time by different investigators.[16] Misumi and co-workers corroborated this hypothesis by ^{1}H NMR investigations of cyclophanes.[17] In the course of our work we found an analogous electronic disturbance of the ^{1}H NMR and, furthermore, of the UV absorption for the azulene ligands 10–12 with complexed cations.[18]

The visible absorption band of 10 (λ_{max} = 618 nm) is shifted hypsochromically with salts (Ca^{2+}, λ_{max} = 610 nm; Ba^{2+}, λ_{max} = 612 nm) under considerable extinction growth. Because in this system the chromophore itself does not contain any heteroatoms, the salt-dependent

effects have to be referred to a direct interaction of complexed cations with the π-system (presumably via the negative polarized five-membered ring).

Thermodynamic investigations indicate that the observed cation selectivities of the color effects do not correlate with the stability constants of the complexes in each case. The complex formation constants of the ligands 3, 5, 6, and 8 with several alkali- and alkaline-earth metal salts were compared with the corresponding λ_{max} shifts of the complexes.[19] Whereas the largest band shifts are produced mostly by the cation, which optimally fills out the ligand cavity, the next smaller cation (of the same charge) exhibits a higher complex formation constant. Thus, for the stilbene dye 6 in the alkali metal series, the largest λ_{max} shift is observed with K^+ (cf. Figure 3; "color selectivity"), whereas Na^+ shows the highest stability constant (K^+, 7×10^2; Na^+, 3×10^3 $L\cdot mol^{-1}$; "thermodynamic selectivity"). The latter result can be related easily to the positive polarization of the amine nitrogens in the donor–acceptor dyes, which tends to repulse adjacent cations.

The observable changes of the absorption spectra can be described satisfactorily by the electrostatic interactions between the complexed cations and the chromophore dipoles: The solvation of alkali- and alkaline-earth metal ions occurs "charge controlled"; i.e., the stabilization of the cations in the polarophilic crown ether cavities is primarily steered by charge dipole interactions.[20] Conversely, the electronic states of the chromophores are influenced by these ion–dipole forces, depending on the size and direction of the dipole moment (μg and μe). If μg and μe have different values, the ground and photoexcited states are stabilized and destabilized, respectively, to a different extent.[21] In consideration, the more the dipole moment alters during the excitation, the more the absorption band shifts.

In donor–acceptor chromophores, the electronic excitation is mostly accompanied by a charge density shift in the direction of acceptor substitutents of the chromophore; i.e., increases of the dipole moments take place.[22] Because it can be supposed that the amine nitrogen atoms of the chromoionophores 2–9 are positively polarized, the excited states are more strongly destabilized by cations than the ground states, wherefore hypsochromic shifts result.

The color effects of the azulene derivatives 10–12 can also be interpreted qualitatively by dipole considerations: Azulene has a dipole moment of μ_g = 2.65 × 10^{-30} C·m in the ground state.[23] It is suggested by theoretical considerations that the five-membered ring is negatively polarized. During the electronic excitation a reversal of the dipole direction occurs, producing a positive partial charge of the five-membered ring.[23] A positive

(16) (a) Frensch, K.; Vögtle, F. *Tetrahedron Lett.* 1977, 2573. (b) Reinhoudt, D. N.; De Jong, F. In "Progress in Macrocyclic Chemistry"; Izatt, R. M., Christensen, J. J., Eds.; 1979; Vol. 1, p 157 ff.

(17) Kawashima, N.; Kawashima, T.; Otsubo, T.; Misumi, S. *Tetrahedron Lett.* 1978, 2025.

(18) Löhr, H.-G.; Vögtle, F.; Schuh, W.; Puff, H. *Chem. Ber.* 1984, *117*, 2839.

(19) Tümmler, B.; Fliess, A.; Wolfes, H.; Maass, G.; Dix, J. P.; Vögtle, F., manuscript in preparation.

(20) For example, see: (a) Pedersen, C. J.; Frensdorff, H. K. *Angew. Chem.* 1972, *84*, 16; *Angew. Chem., Int. Ed. Engl.* 1972, *11*, 16. (b) Weber, E.; Vögtle, F. *Chem. Ber.* 1976, *109*, 1803.

(21) This consideration corresponds with the well-investigated models of solvatochromism and electrochromism. Cf. Liptay, W. *Angew. Chem.* 1969, *81*, 195; *Angew. Chem., Int. Ed. Engl.* 1969, 8, 177.

(22) (a) Reichardt, C. "Solvent Effects in Organic Chemistry"; Verlag Chemie: Weinheim/Bergstr., Germany, 1979; pp 189–223. (b) Labhart, H. In "Optische Anregung organischer Systeme"; Verlag Chemie: Weinheim/Bergstr., Germany, 1966; pp 160–176. (c) Liptay, W. *Ibid.*, pp 263–339.

(23) Baumann, W. *Chem. Phys.* 1977, *20*, 17.
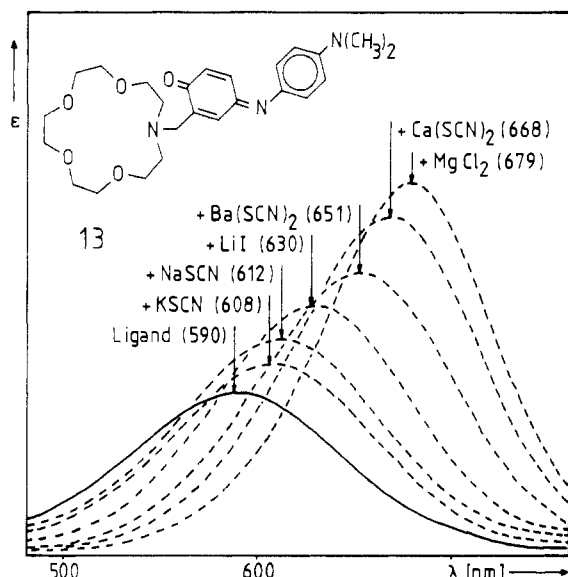
Figure 6. Electron spectra of the ligand **13** in acetonitrile and under addition of salts (λ_{max} in nanometers).[14,24]

charge (M^+) in close contact to the five-membered ring of the azulene therefore stabilizes the ground state energetically and destabilizes the photoexcited states [μ_e (S_1) = -1.88 × 10⁻³⁰ C·m, μ_e (S_2) = -1.16 × 10⁻³⁰ C·m]. This consideration corresponds to the observed hypsochromic shifts of the ligand **10** on addition of salts.[10]

## Donor–Acceptor-Type Chromoionophores with Cation-Induced Bathochromic Band Shifts

In accordance with the ion–dipole model described before, we obtained bathochromic band shifts when the ionophore part was placed in the molecule in such a way that complexed cations were coordinated with the electron acceptor of the chromophore.

Thus, the quinone imine ligands **13** and **14** show significant bathochromic shifts with enhanced extinctions. Concerning the λ_{max} shifts, the smaller ions Li⁺ and Mg²⁺ are favored in comparison with large ions of the same charge (Figure 6). Apparently, a charge density controlled selectivity due to the "cavity flexibility" is present for the compounds **13** and **14**.[14]
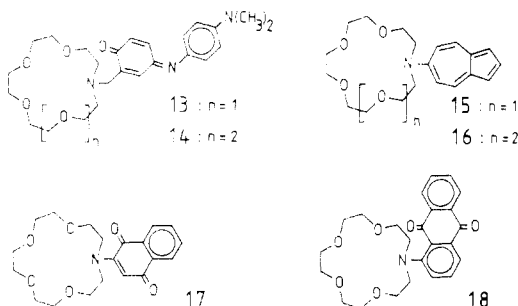
The 6-aminoazulene derivatives **15** and **16** like the azacoronand-substituted donor–acceptor dyes **2–9** provide ionophores which are electronically coupled with the chromophore via the amine nitrogens. Nevertheless, we found for the ligands **15** and **16** (in contrast to **2–9**) bathochromic shifts of the visible absorption bands on addition of salts (Figure 7).[24] The high sensitivity and color selectivity of the chromophore **16** to Ba²⁺, shown in Figure 7, is expressed visually by a color change from

(24) Löhr, H.-G.; Vögtle, F. *Chem. Ber.*, in press.
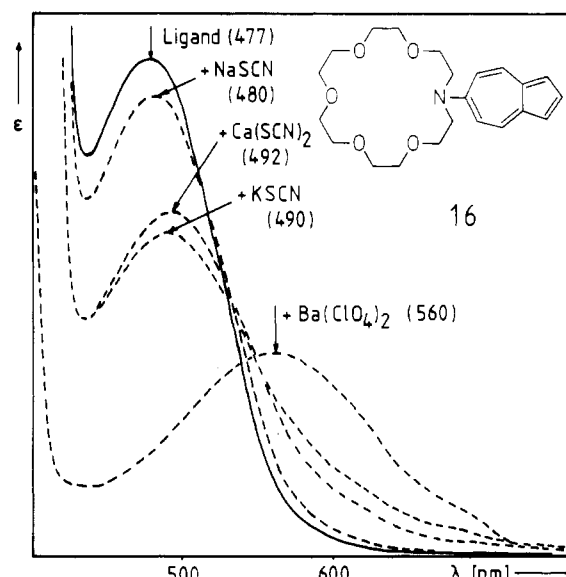
Figure 7. Electron spectra of ligand **16** in acetonitrile and under addition of salts (λ_{max} in nanometers).[14,24]

yellowish-orange to blueish-violet. Relatively small alterations of color from orange up to red are gained with other salts (K⁺, NH₄⁺, Ca²⁺).

For an elucidation of these red-shifts, ion–dipole considerations can serve again. 6-(Dimethylamino)-azulene shows negative solvatochromism;[24] i.e., it can be supposed that the dipole moment is reduced or reversed in its direction on the electronic excitation (cf. ref 21). Because the amine nitrogen will surely be polarized positively in the ground state, a shift of charge density from the five-membered ring of the azulene in direction of the N-substituted seven-membered ring is implied during the excitation process. Therefore, the amino group has to be considered itself as a part of the electron acceptor of the chromophore.[25] Accordingly, cations complexed by the ligands **15** and **16** will destabilize the ground state and stabilize (or less destabilize) the excited state, causing bathochromic band shifts.

In the chromoionophores **17** and **18**, complexed cations can interact with the electron donor as well as the electron-acceptor constituents of the chromophores. Whereas the long-wave absorption band of the amino-anthraquinone ligand **18** at 493 nm, ascribed to an intramolecular charge transfer transition,[26] is shifted hypsochromically by salts, the shoulder at 317 nm belonging to a quinoid transition moves bathochromic. Similar findings exist for the aminoanthraquinone ligand **17** under the influence of cations.[27]

If the aminoanthraquinone derivative **17** is reduced with alkali metals in tetrahydrofuran, radical ion pairs are formed. Their ENDOR spectra[28] show a dependence of the coupling constant from the charge and radius of the metal cations, which is typical for strong ion-pair interactions.[29]

(25) Witzinger, R. *Chimia* **1961**, *15*, 89. See also ref 12.
(26) Singh, I.; Ogata, R. T.; Moore, R. E.; Chang, C. W. J.; Scheuer, P. J. *Tetrahedron* **1968**, *24*, 6053. Cf. ref 12.
(27) Dix, J. P. Thesis, Universität Bonn, Bonn, Germany, 1980.
(28) Lubnitz, M.; Plato, M.; Möbius, K.; Biehl, R. *J. Phys. Chem.* **1979**, *83*, 3402.
(29) Bock, H.; Hierholzer, B.; Vögtle, F.; Hollmann, G. *Angew. Chem.* **1984**, *96*, 74; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 57.

## Cyanine-Type Chromoionophores

In the absorption spectra of cyanine ligands like **19** there is no observable change which would indicate the uptake of alkali- or alkaline-earth metal ions.[9,27,30] The reason might be the highly symmetric charge distribution in the dye molecules, admitting no or respectively only small changes of the dipole moments on excitation.[31]
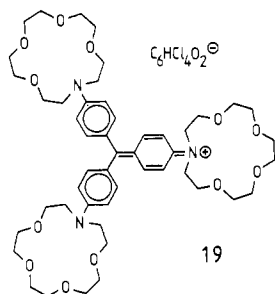
Chromoionophores with Charge-Controlled Cation Effects

The molecular linkage of the ionophore part at the (δ–)-polarized end of the chromophore (chromoionophores **20–23**) guarantees higher complex formation constants. However, the salt-dependent UV–vis spectra reveal a new problem: The interactions of cations with anionic chromophores are considerably stronger than the ion-dipole forces with the coronand. Thus, a thereupon resulting charge density control, which favors doubly charged ions and Li^+, can counteract the cation selectivity especially of larger crowns.

Accordingly, the azamerocyanines **20** and **21** exhibit the largest hypsochromic band shifts with Mg^{2+} and Ca^{2+}.[32] It seems that the coronand skeletons respective to their size disturb or support the specific interactions of the chromophores with cations.
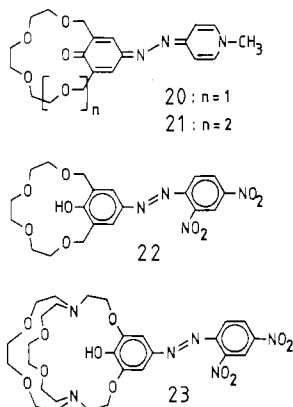
Misumi and co-workers reported a significant selectivity of the (2,4-dinitrophenyl)azophenol **22** in a trichloromethane/pyridine solution. On addition of lithium salts, the yellowish solution (λ_{max} = 400 nm) turns to purple-red (LiCl: λ_{max} = 563 nm), whereas other alkali metal salts are inactive under these conditions.[33]

(30) Struck, R.; Vögtle, F., unpublished results.

(31) For reviews on cyanine dyes, see: (a) Feichtmayr, F.; Schlag, J. In "Optische Anregung organischer Systeme", Verlag Chemie, Weinheim/Bergstr., Germany, 1966; pp 356–374. (b) Cf. ref 12 and 22. (c) Fabian, J.; Hartmann, H. "Light Absorption of Organic Colorants"; Springer Verlag: Berlin, 1980.

(32) Hollmann, G.; Vögtle, F. *Chem. Ber.* **1984**, *117*, 1355.

(33) (a) Kaneda, T.; Sugihara, K.; Kamiya, H.; Misumi, S. *Tetrahedron Lett.* **1981**, *22*, 4407. (b) Nakashima, K.; Nakatsuji, S.; Akiyama, S.; Kaneda, T.; Misumi, S. *Chem. Lett.* **1982**, 1781.
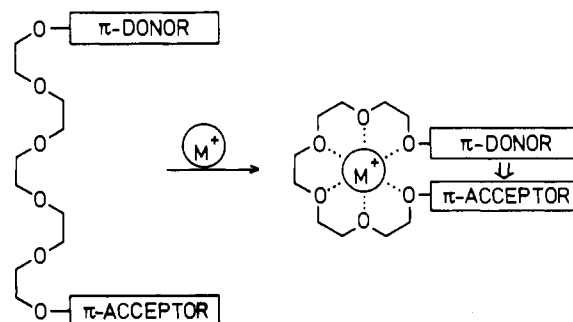
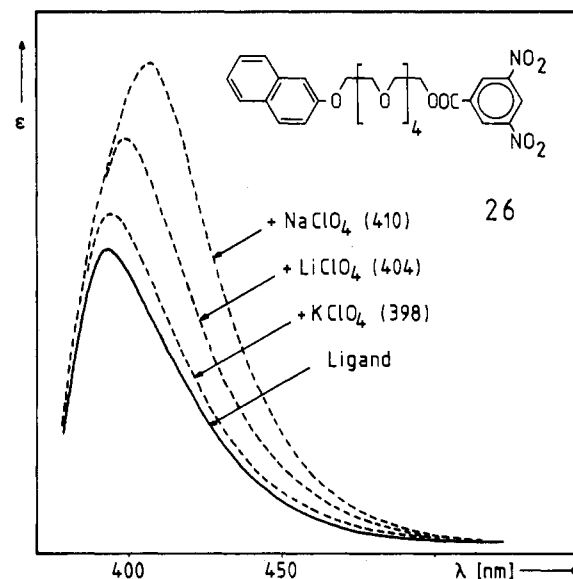**Figure 8.** Principle of the cation-steered charge transfer absorption.[35]

Figure 9. The influence of alkali metal salts on the charge transfer absorption of ligand **26** (measured as difference absorption: ligand minus 3,5-dinitrobenzenoic acid methyl ester[36]).

The chromoionophore **23** with a bicyclic ligand part, an output of industrial investigations,[34] offers a remarkable selectivity for K^+ ions in a water/dioxane/morpholine mixture, which is only disturbed by Rb^+. The occurring color change from pink to blue or violet allows the qualitative and quantitative determination of K^+ ions in the ppm region in homogeneous solutions as well as in test stripes.[34]
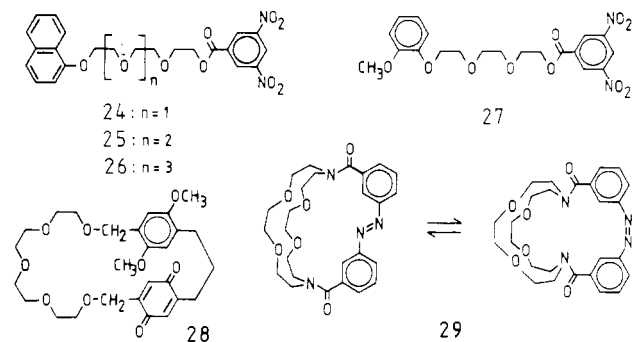
Chromoionophores with Structure-Controlled Effects

Among the chromoionophores **1–23**, conformational changes during cation complexation do not play a decisive role for observable color effects. In contrast, the ligands **24–28** show intramolecular electron donor-acceptor interactions, which are essentially steered by steric-complexation effects (Figure 8).[35]

Long-chained electron donor–acceptor (EDA) podands like **26**[36] exhibit considerable extinction increases and bathochromic shifts (Figure 9) on addition of salts, partially accompanied by visually well-perceptible color deepening (pale yellow → yellow). Shorter chained ligands (**24, 27**) show a decrease of extinction and hypsochromic shifts combined with distinct brightening

(34) Merck Patent GmbH (Inv. Klink, R.; Bodart, D.; Lehn, J. M.; Helfert, B.; Bitsch, R.) Eur. Pat. Apl. 83100281.1 (14.01.83).

(35) Vögtle, F.; Hollmann, G.; Löhr, H.-G. 8. Int. Farbensymposium, Baden-Baden, Sept 1982.

(36) Löhr, H.-G.; Vögtle, F. *Chem. Ber.*, in press.

24 : n = 1
25 : n = 2
26 : n = 3

27

28

29

Figure 10. Model of the chiral recognition of substrates with C_1 symmetry (Newman projection H_3N^+–CSML with S = small, M = medium, L = large) by receptors with (a) C_2, (b) D_2, and (c) D_3 symmetry. (●) Groups above the macro ring plane (e.g., $CONH_2$). (O) Groups below the macro ring plane.

of the solutions with Li^+ and Na^+. An electronic influence on the "donor and acceptor force" of the EDA systems by complexed cations is of less importance for the change of the absorption intensity than steric effects.[36]

As Staab's group showed, this principle is analogously applicable for monocyclic ligands of the cyclophane type. Thus, the ligand **28** with a "built-in quinhydrone charge transfer indicator" (λ_{max} = 462 nm, ϵ = 324) notifies with NaSCN in $CHCl_3$ a nearly trebled extinction (ϵ = 874) and a red-shift of the visible absorption band of 16 nm.[37] The fixation of the π-donor and π-acceptor molecular parts in the ligands **24–28** by the cation-induced conformational arrangement of the polyether chain is reversible and can therefore be considered and used as a "switching mechanism".

The reverse aspect, the allosteric influence of the ligand cavity by structurally variable chromophoric framework units, is the topic of a series of investigations with azodye crown ethers ("photoresponsive crowns").[38] The azo link, e.g., in the chromoionophore **29**, can be converted from the more stable E configuration to the Z form by photoisomerization, modifying the cavity proportions and therewith the complex formation and extraction constants; i.e., the azodye ligands can mediate the conversion of light energy to chemical function.[39]

Chiral Chromoionophores

The behavior of crown ethers to form complexes with organic ammonium compounds, amino acids, and organic neutral molecules[40] has led to the use of chiral crown ethers as model compounds for substrate-receptor studies.[41] Their ability to discern between differently configurated guest molecules (chiral recognition) was the base for our efforts to synthesize chromoionophores with asymmetric units. They are constructed with the aim of indicating the chiral recognition visually or by UV–vis spectroscopy and therewith to permit conclusions of the configuration of the guest molecules or their enantiomeric purity. For that purpose, dif-

ferently intensive interactions (ion–dipole, dipole–dipole, hydrogen bridges) have to work between the chromophore and the binding site of the enantiomers in their diastereomeric complexes.

The chromoionophore **30** is the first chiral dye crown ether synthesized.[32] Due to the azamerocyanine units, which show strong solvatochromism, the optically active ligand is a potential receptor for the differentiation between the enantiomers of optically active substrates (e.g., amines, alcohols, carbohydrates, etc.). However,

30
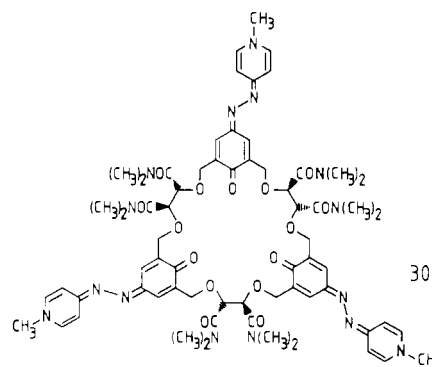
the discrimination of an enantiomer with **30** could not be ascertained in the UV–vis spectra until now.[42] Presumably, this has to be referred primarily to a lack of steric interactions between the guest molecules and the periphery of the macro ring. Molecular model considerations as illustrated by the stylized receptor-substrate models in Figure 10 suggest that especially the D_3 symmetry of the ligand **30** is responsible for the insufficient chiral recognition.

In the stylized ligands of the symmetry groups C_2 and D_2, the different distances of the guest substituents M and S to the lateral groups of the macro ring are immediately obvious. An analogous host–guest interaction with the D_3 symmetric ligand does not lead to a sterically conditioned differentiation of the R and S substrate: In the arrangement shown in Figure 10c, the substituents M and S can be exchanged without alteration of the distances to equal groups of the D_3 host.[43] Only by a declination of the substrate angles from the ideal tetrahedral angle or by a sloping positioned guest molecule, i.e., the nonparallelism of the C–N bond and the C_3 axis of the macro ring, distance and energy differences appear in the stereoisomeric complexes.
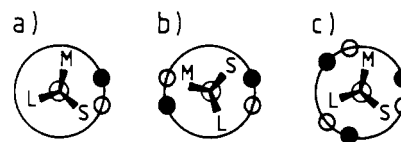
(37) Bauer, H.; Briaire, J.; Staab, H. A. *Angew. Chem.* **1983**, *95*, 330; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 334.

(38) For a recent review on crown ethers with responsive functions, see: Shinkai, S.; Manabe, O. *Top. Curr. Chem.* **1984**, *121*, 67.

(39) (a) Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, K.; Manabe, O. *J. Am. Chem. Soc.* **1981**, *103*, 111. (b) Cf. Shinkai, S.; Minami, T.; Kusano, Y.; Manabe, O. *Ibid.* **1982**, *104*, 1967.

(40) For a recent review, see: Vögtle, F.; Müller, W. M.; Watson, W. H. *Top. Curr. Chem.* **1984**, *125*, 131. Cf. also El-Basyouni, A.; Brügge, H. J.; von Deuten, K.; Dickel, M.; Knöchel, A.; Koch, K. U.; Kopf, J.; Melzer, D.; Rudolph, G. *J. Am. Chem. Soc.* **1983**, *105*, 6568.

(41) For reviews on chiral crown ethers, see: (a) Jolley, S. T.; Bradshaw, J. S.; Izatt, R. M. *Heterocycl. Chem.* **1982**, *19*, 3. (b) Weber, E.; Vögtle, F. *Kontakte* **1981**, *1*, 24. (c) Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85. (d) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8.
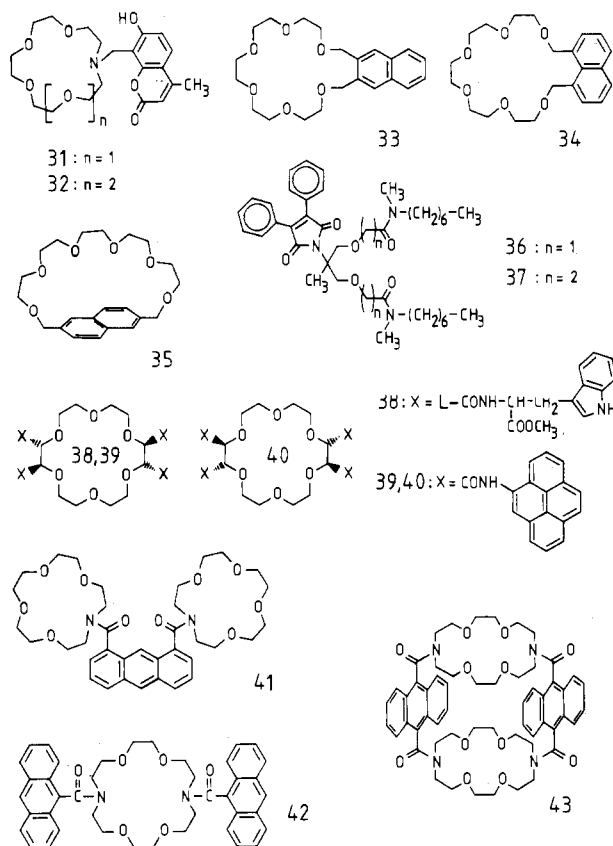
(42) A distinction between the enantiomers of organic ammonium compounds in homogeneous solution is not possible, because a protonation of the dye occurs with RNH_3^+. Hollmann, G. Thesis, Universität Bonn, Bonn, Germany, 1983.

(43) The two model stereoisomers (Figure 10c) remarkably neither indicate different distances between equally built structure units nor are they mirror images of one another: i.e., the two represented *model* associates are *isometric diastereomers*. Analogous considerations can be made for stereoisomers, which are built by the combination of structures of the symmetry group C_{3n} or D_{3n} (n = 1, 2, 3, ...) with C_1 symmetric structures.

The view is analogously valid for any conformation of the macro ring with D_3 symmetry; on each side of the ligand three equal "niches" are steadily provided at the periphery. It seems therefore that molecular receptors with C_2 and D_2 symmetry offer better (pre)conditions for a chiral recognition than ligands with D_3 symmetry. This may also be the reason why a successful differentiation of enantiomers by D_3 configured crown ethers has not been reported until now.[44]

Fluoroionophores

Because of its high sensitivity and the high selectivity, fluorimetry is of increasing importance for chemical trace analyses. Due to the formation of metal-chelate compounds, inorganic analyses can be carried out by fluorimetric measurements. For alkaline-earth metal salts, numerous fluorophores with structural elements of the EDTA type are available.[45] Alkali metal ions can be determined in extraction processes by ionophores and fluorescent counterions (e.g., eosine).[46] The phenolic chromoionophores with umbelliferone units show Li^+ (31) and K^+ (32) affinity in extraction experiments.[47]

31: n = 1
32: n = 2

33

34

36 : n = 1
37 : n = 2

35

38,39

40

38: X = L-CONH-CH-CH₂

39,40: X = CONH

41

42

43

Sousa and Larson designed the naphthalene crowns 33–35 as model systems for the study of the geometric requirements of perturber–chromophore interactions.[48]

An important feature of these molecules is the predetermined orientation of the chromophore and a complexed perturber. The influence of alkali metal ions on the naphthalene derivatives is reflected by the emission properties. Whereas a decrease of the fluorescence quantum yields occurs for the ligands 33 and 35 with alkali metal salts in alcohol glass at 77 K (ϕ_f, free > NaCl > KCl > RbCl > CsCl), a distinct increase is observed for 34 (ϕ_f, RbCl > KCl > CsCl > NaCl > free). The phosphorescence quantum yields are influenced in the reverse sense, i.e., increase for 33 and 35, decrease for 34. The heavy atom perturbation by Cs^+ causes increased rate constants for all three crowns in processes involving singlet–triplet interchanges.[48]

Noncyclic fluoroionophores (36 and 37) with diphenylmaleinimide units have been examined by Simon et al. in view of the ionselectivity and transport behavior in membranes and were compared with similar ionophores without chromophore subunits.[49] The ligand 36 was proved to be a carrier for Li^+ in PVC membrane electrodes, whereas in the one-phase system (ethanol) a high selectivity for Ca^{2+} is revealed by fluorescence quench titrations.

Distinctions between the enantiomers of the dipeptides glycine-phenylalanine (Gly-Phe) and glycine-tryptophan (Gly-Trp) are assigned by the emission spectra of the chiral coronands 38–40 and the therein complexed guests.[50] From quenching data, Tundo and Fendler obtained the stability constants of the diastereomeric complexes and calculated a "chiral efficiency" of ca. 4–7%.

The anthracenoyl crowns 41–43 from our laboratory have been used as fluorescent probes for the solid-phase transition of phosphatidylcholines.[51] The least lipophilic compound 41 is excluded from the hydrocarbon phase, whereas the most lipophilic compound 42 is located at the bilayer surface. The anthracenophane cryptand 43 preferentially partitions into solid-phase lecithins with the highest affinity for the phases L_ϵ and L_β. Fluorescence quenching titrations (with Cu^{2+}, SCN^-, N,N-dimethylaniline) suggest that the average position of 43 discontinuously shifts from the glycerol backbone to the choline headgroup during the gel to liquid crystalline transition. Due to its large change of fluorescence intensity, the fluorophore 43 is a sensitive probe for the detection of pretransition of symmetrically substituted and of the subtransition of asymmetrically substituted phosphatidylcholines.[51]

Conclusions and Future Aspects

Although crown ether and dye chemistry are well investigated, the development of chromoionophores was at the beginning connected with problems and unexpected results. Only the synthesis of representative charged and neutral chromoionophores and their thorough spectroscopic investigations gave an insight into cation–chromophore interactions. The ion–dipole model can now serve for the design of new effective dye crown ethers: Accordingly, high dipole-moment changes

(44) For chiral crowns with D_3 symmetry, see ref 41 and (a) Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Dotsevi, Y.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* 1977, 42, 4173. (b) Curtis, W. D.; Laidler, D. A.; Stoddart, J. F.; Jones, G. H. *J. Chem. Soc., Perkin Trans. 1* 1977, 1756. (c) Lehn, J. M.; Vierling, P.; Hayward, R. C. *J. Chem. Soc., Chem. Commun.* 1979, 296.
(45) For example, see: (a) Hoelzl Wallach, D. F.; Steck, T. L. *Anal. Chem.* 1963, 35, 1035 and references cited therein. (b) Rink, T. J. *Pure Appl. Chem.* 1983, 55, 1977. (c) Tsien, R. Y. *Biochemistry* 1980, 19, 2396.
(46) Sanz-Medel, A.; Gomis, D. B. *Talanta* 1981, 28, 430.
(47) Nishida, H.; Katayama, Y.; Katsuki, H.; Nakamura, H.; Takagi, M.; Ueno, K. *Chem. Lett.* 1982, 1853.

(48) (a) Sousa, L. R.; Larson, J. M. *J. Am. Chem. Soc.* 1977, 99, 307. (b) Larson, J. M.; Sousa, L. R. *Ibid.* 1978, 100, 1943.
(49) Villiger, A.; Morf, W. E.; Simon, W. *Helv. Chim. Acta* 1983, 66, 1078.
(50) Tundo, P.; Fendler, J. H. *J. Am. Chem. Soc.* 1979, 101, 1760.
(51) Herrmann, U.; Tümmler, B.; Maass, G.; Koo Tze Mew, P.; Vögtle, F. *Biochemistry* 1984, 23, 4059. Tümmler, B.; Herrmann, U.; Maass, G.; Eibl, H. *Biochemistry* 1984, 23, 4068.

during the electronic excitation of the chromophore seem to be a necessary precondition for a sensitive cation indication, as well as the construction of bicyclic ionophore parts for the enhancement of the cation selectivity. The linkage of the ionophore at the (δ–)-polarized chromophore side—without doubt advantageous for the complex formation constants—might be suited primarily for cations with high charge density.

Cation-induced changes of the absorption spectra allow the experimental verification of the dipole direction in chromophores, contributing to the theory and classification of dyes. The principle of the cation-steered charge-transfer absorption ("molecular dye switches") can serve as a visual and photoresponsive indication for the study of allosteric effects.

The determined influence of the fluorescence, the cation-steered chemiluminescence,[52] as well as the optical enantiomer discrimination with chiral receptor dyes should be realized in the near future.

(52) Duchêne, K.-H.; Vögtle, F., unpublished.