Chemosensors with crown ether-based receptors

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**Dedicated to Prof. Irina P. Beletskaya on the occasion of her significant birthday
in recognition of her outstanding contributions to organometallic
and physical organic chemistry**

Abstract
The review highlights the rational design of crown ether-based optical chemosensors that are categorized according to the origin of the signaling unit as chromogenic, fluorogenic, photoswitchable, ambidentate and ditopic. The principal mechanisms that govern the properties of crown ether-based chemosensors of different types are considered and examples of the detection of alkali, alkali-earth, *d*-metal, lanthanide cations, anions and molecules are given.

Keywords: Chemosensors, crown ethers, fluorescence, internal charge transfer, photoinduced electron transfer

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1. Introduction

Selective and sensitive chemosensors are molecules specifically designed for the qualitative and quantitative monitoring of analytes. These chemosensors are widely used in biological and analytical chemistry, in medicine and environmental sciences. Collection, concentration, or preparation of samples using complicated and expensive devices are no longer required for the analysis of cations, anions and even molecules due to facile analyte detection. The binding of an analyte causes substantial changes in physical properties of a system such as absorption and/or fluorescence spectra.

The most common types of chemosensors consist of two components: a receptor and a signaling unit tethered via a spacer.[1–7] In this paper are considered chemosensors with crown-, azacrown- and thiacrown- ether-based receptors as the most popular type of sensor systems. Derivatives of crown ethers such as cryptands, podands, calixarenes, calixcrowns etc. are outside the scope of this review. The variety of simple "crowns" is rather limited and the design of crown ether-based chemosensors (CEBC) is generally directed to the modification of the signaling unit. According to the nature of the latter the most important types of CEBC may be categorized as chromogenic, fluorogenic, photoswitchable, ambidentate and ditopic.

2. Chromogenic CEBC

Chromogenic CEBC are usually of donor-acceptor (D–A) type with a crown ether moiety playing the role of either the donor or the acceptor component. Complexation results in the cation-induced shift of the longest wavelength absorption bands of CEBC (Figure 1). When these hypsochromic or bathochromic shifts are significant and appear in the visible spectral region the CEBC are qualified as colorimetric "naked-eye" sensors. The goal of this review is to convey an idea of mechanisms governing the properties of CEBC and to show their ability of detecting alkali metal, alkaline earth metal, d-metal, lanthanide cations, anions, and molecules.
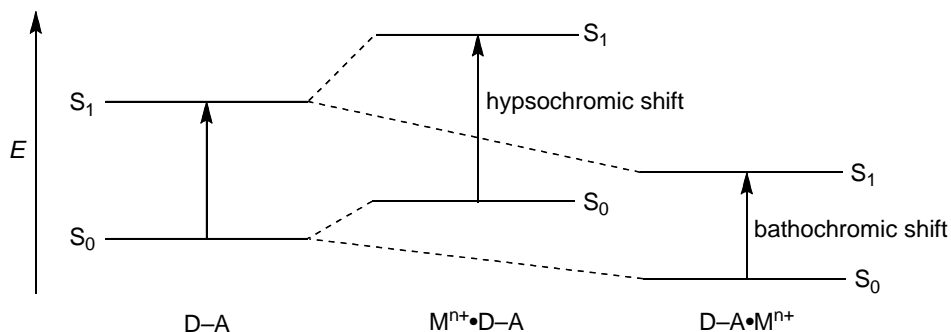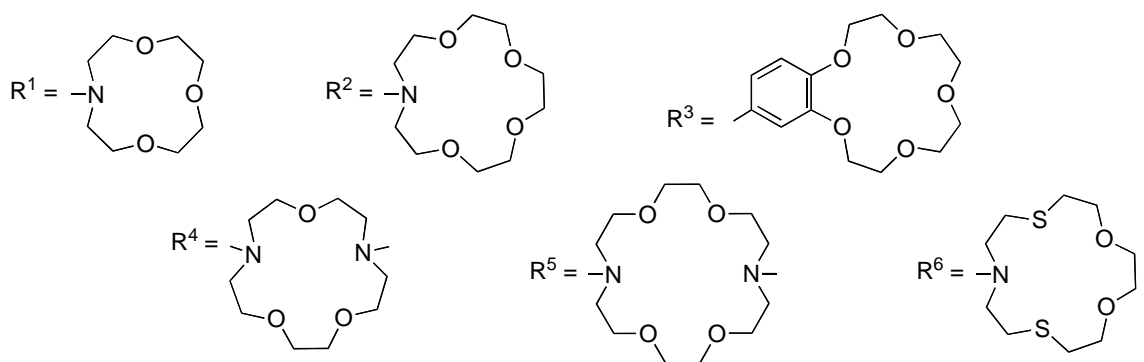

Figure 1. Effect exerted by complexation of CEBC (by its D or A moiety) with a cation (M^{n+}) on the absorption spectra. S_0 and S_1 are energy levels of the ground and lowest singlet excited states.

These compounds, the corresponding analytes, and the detectable parameters are summarized in Tables. The information on the synthesis of CEBC and details of analytical procedures can be found in the referenced original papers. Examples of chromogenic CEBC with the data of changes in absorption spectra are collected in Table 1.
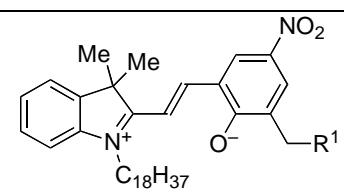
Table 1. Examples of typical chromogenic CEBC
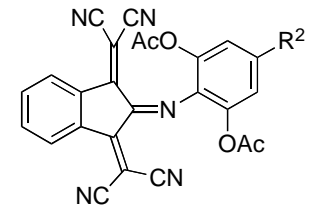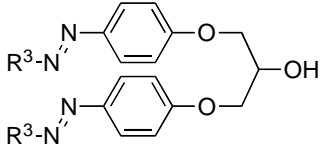
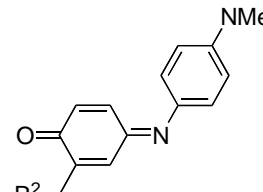|	Compound	Analyte	$\Delta\lambda$ [nm] or change of color	Ref.
1		Li^+	-26^a	8
2		Na^+	-28^a	9
3		K^+	-5.5^a	10
4		Li^+	$+40^b$	11
		Na^+	$+22^b$	11
		K^+	$+18^b$	11

Table 1. Continued

	Compound	Analyte	$\Delta\lambda$ [nm] or change of color	Ref.
5		Mg^{2+}	+48 [b]	12
6		Li^+	colorless → bluish-violet [c]	13
7		Na^+	red → yellow [c]	14
8		K^+	red → yellow [c]	14
9		Ca^{2+}	–89 [c]	15
10		La^{3+}	colorless → red [c]	16
11		AcO^-	yellow → colorless [c]	17
12		(S)-1-NapCH(Me)NH$_3^+$ ClO$_4^{-}$ [d]	–6.5 [a]	18

[a] Hypsochromic shift. [b] Bathochromic shift. [c] Colorimetric "naked-eye". [d] Nap = naphtyl.

The main difference between an analytical reagent and a chromogenic CEBC is the high sensitivity of the latter allowing the detection of metal ions in the concentration range of 10^{-5} to 10^{-6} M. Lanthanide metal cations, anions and even molecules can also be the specific target for the chromogenic CEBC. In the presence of La^{3+} ions in solution, colorless bis(spiropyran) **10** undergoes isomerization into its merocyanine form to produce the absorbance in the 500 nm region. An acetonitrile solution of **11** turns yellow in the presence of Pb^{2+} ions, a highly selective bleaching of **11**·Pb^{2+} is induced by acetate anions. Hypsochromic shift of the long-wavelength absorption band of the chiral CEBC **12** accompanies the chiral recognition of the (*S*)-form of 1-NapCH(Me)NH_3^+ ClO_4^-.

3. Fluorogenic CEBC

Fluorogenic CEBC represent a rapidly developing area of chemosensor chemistry because of the high sensitivity of luminescence measurements. These CEBC can be used as mobile sensors in microscopy. For CEBC immobilized on a tip of an optical fibre, the measurements in real time is possible. Two principal mechanisms governing the action of fluorogenic CEBC are photoinduced electron transfer (PET) and internal charge transfer (ICT).

The two types of fluorogenic PET CEBC with the signaling fluorophore (F) and crown ether receptor (R) units linked by a spacer (S), are chelation induced quenching of fluorescence (CHEQ) and chelation induced fluorescence (CHEF) (Figures 2a and 2b, respectively).
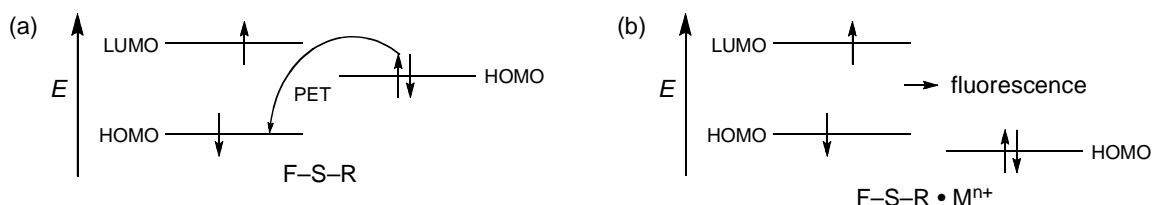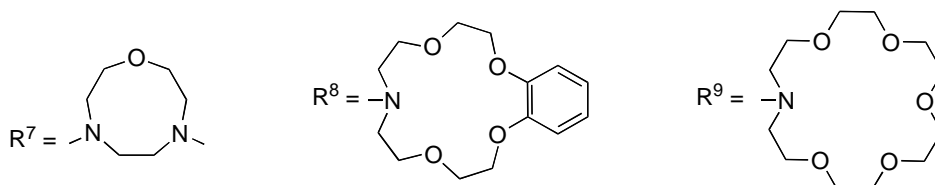

Figure 2. Effect of a cation on the fluorescence spectra (a) "off" state, (b) "on" state. HOMO – highest occupied molecular orbital, LUMO – lowest unoccupied molecular orbital.

Upon excitation of the F-unit in CHEF PET systems an electron from the HOMO is promoted to the LUMO inducing the PET from the HOMO of R to that of F thus causing the fluorescence quenching. Binding of a cation lowers the energy level of the HOMO of R below that of the HOMO of F, and the excited state energy of F is realized as a visible emission. This mechanism provides the "off-on" switching of fluorescence. The opposite mechanism leads to "on-off" switching of fluorescent properties in CHEQ PET systems.

Fluorogenic ICT CEBC are based on mechanisms similar to those of chromogenic D–A CEBC (Figure 1), i.e. hypsochromic and bathochromic shifts of the emission bands must

correspond to the analogous shifts in the absorption spectra. No spacer units S are needed and a crown ether R is directly linked to the F unit. Typical representatives of PET and ICT CEBC are listed in Tables 2 and 3.

Table 2. Typical examples of fluorogenic PET CEBC

	Compound	Analyte	FE[a]	Ref.
13	Me [1-NapCHCCH$_2$]$_2$R^7 O	Li$^+$	5	19
14	9-Ant OMe R^2	Na$^+$	8	20
15	(9-Ant–CH$_2$)$_2$R$^{5\ b}$	K$^+$	24	21
16	SO$_2$R^5 ... N (piperidine) NMe$_2$	Mg^{2+}	4	22
17	9-Ant–CH$_2$–R^5–Ph ^{b}	Ca^{2+}	170	23
18	9-Ant–CH$_2$–R$^{8\ b}$	Zn^{2+}	10	24
19	NO$_2$ R^5 OH	Hg^{2+}	12	25
20	R^9 ... N-H ... O ... coumarin O	Fe^{3+}	15	26
21	MeO ... coumarin ... R^9	saxitoxine	1.5	27
22	9-Ant–CH$_2$–R$^{10\ b}$	Lys^c	2.5	28

^{a} FE: Fluorescence enhancement. ^{b} Ant = anthryl. ^{c} Lys = lysine.

Table 3. Typical examples of the fluorogenic ICT CEBC

	Compound	Analyte	$\Delta\lambda_{fl}$ [nm][a]	λ_{fl} [nm][b]	Ref.
23		Li$^+$	−10	550	29
24		Na$^+$	+81	456	30
25		K$^+$	+12	492	30
26		Cs$^+$	+44	482	30
27		Mg^{2+}	+15	498	31
		Ca^{2+}	+13	496	31
28		Ba^{2+}	−44	536	32
29		Hg^{2+}	no	610	33
30		Cd^{2+}	no	488	34
31		Pb^{2+}	+15	491	35

[a] Blue (–)/red (+) shift of the initial fluorescence. [b] Fluorescence maxima after cation binding.

    PET and ICT CEBC involve different mechanisms. Complexation of PET sensors with cations produces no changes in the position of the fluorescence bands resulting only in the enhancement of the fluorescence intensity (FE). For ICT sensors, changes in fluorescence intensity do not play an important role because binding of metal cations significantly shifts the emission spectrum compared to that of a free sensor. In the case of CHEQ ICT CEBC significant fluorescence quenching may be observed.

4. Photoswitchable CEBC

Photoswitchable CEBC differ from the above described compounds by their ability to switch "on" or "off" chromogenic or fluorescent CEBC properties upon irradiation with UV or visible light.[6,7] The main types of these systems are found among the well known photochromic compounds: spirobenzopyrans, spirooxazines, styryl dyes, chromenes, fulgides, and acylotropic ketoenamines. Only few typical examples of photoswitchable CEBC are considered (Figure 3).
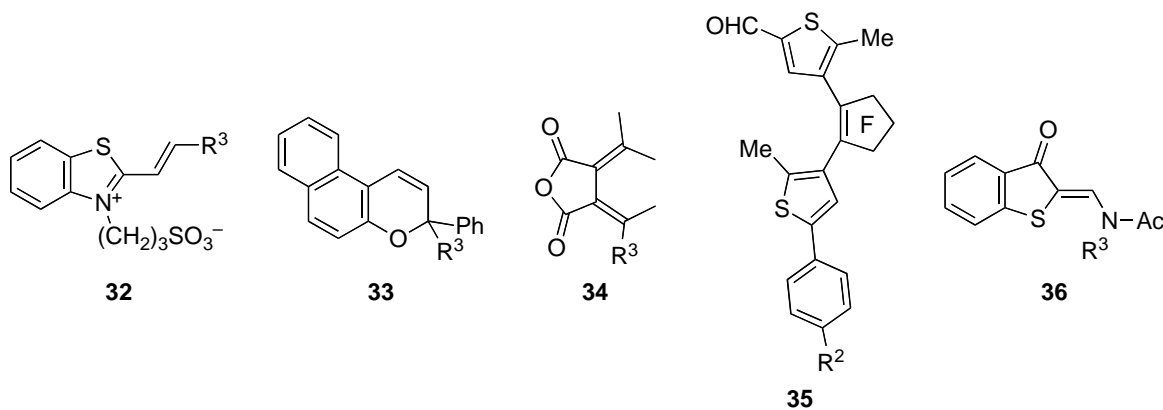

Figure 3

    The binding of La^{3+} to bis(spiropyran) **10** (Table 1) can be switched by K^+ upon photo-irradiation.[16] The *cis*-isomer of benzothiazole derivative **32** (Figure 3) is obtained by UV-irradiation of a solution of the *trans*-isomer and forms stable complexes with Mg^{2+}.[36] The binding of Pb^{2+} with chromene CEBC **33** occurs in the dark, and UV irradiation releases this cation.[37] Fulgide **34** and its photoisomeric colored form behave as chromogenic CEBC displaying blue shift of the longest wavelength absorption band upon complexation with alkali and alkaline earth metal cations.[38] The dithienylethene CEBC **35** bind Na^+, Ca^{2+} and Ag^+ and release them upon photocyclization.[39] Compound **36** acts as a selective chromogenic CEBC for Li^+ ion after N-O acyl rearrangement and switching of the sensor properties by UV-irradiation.[40]

5. Ambidentate CEBC

Ambidentate CEBC containing two binding sites for cations with at least one of which being a crown ether group can also serve as chromogenic or fluorogenic sensors. They are represented by metal chelate compounds containing crown ether cation receptors and CEBC, which can form mono- and binuclear cation complexes.

6. Chelate Ambidentate CEBC

Chelate ambidentate CEBC (Figure 4) behave as typical chemosensors. Chromogenic chelate **37** undergoes a hypsochromic shift upon addition of Li^+ to an acetonitrile solution.[41] A drastic FE (1035 fold) was found upon binding of Mg^{2+} to chelate **38**.[42] Ambidentate CEBC capable of binding two or more cations display additional chemosensor features: CEBC **39** exhibits only slight ICT fluorescence after binding of H^+, but addition of K^+ to **39**·H^+ causes a green fluorescence due to PET quenching.[43] The addition of Na^+ to the ambidentate colorimetric CEBC **40** is accompanied by a pink coloration of an acetonitrile solution with a hypsochromic shift ($\Delta\lambda$ = –30 nm) of the 605 nm band. An Eu^{3+} cation generates a green coloration with a large red shift ($\Delta\lambda$ = +140 nm) of the longest wavelength band absorption.[44]
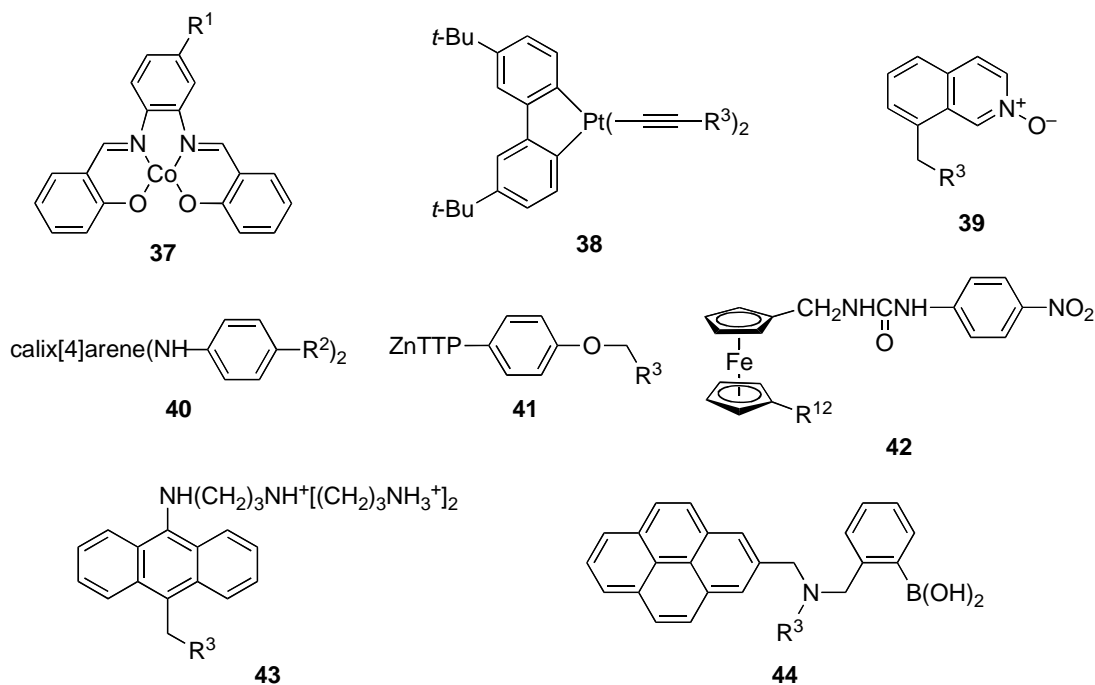

Figure 4

7. Ditopic CEBC

Ditopic CEBC (Figure 4) containing cation and anion binding sites represent a new rapidly growing area of supramolecular chemistry. Although the term "ditopic" is frequently used as an equivalent of "ambidentate", that term will be applied here only to CEBC capable of binding cations and anions. Ditopic colorimetric "naked-eye" CEBC **41** change color from red to green only in the presence of NaCN, whereas sodium salts with other anions like F^-, Cl^-, Br^-, I^-, SCN^- and $H_2PO_4^-$ do not cause this effect.[45] Another "naked-eye" CEBC **42** was specifically designed for the detection of KF. A colorless acetonitrile solution of **42** turns yellow in the presence of F^- but the addition of K^+ restores the initial color.[46] Ditopic fluorogenic CEBC **43** quenches PET and causes FE upon simultaneous binding of Na^+ and PO_4^{3-}.[47] KF can also be recognized by fluorogenic ditopic CEBC **44** due to the efficient PET quenching in an acetonitrile solution.[48]

8. Conclusions

The theory and design of classical chromogenic and fluorescent CEBC represent a rapidly growing area of organic and supramolecular chemistry. The chromogenic CEBC are generally most applicable for sensing alkali and alkaline earth metal cations especially in the "naked-eye" mode.[49] Fluorescent CEBC are also suitable for detecting these ions but some of them can be advantageously used for the selective determination of *d*-metal cations.[50] To a certain extent, PET CEBC are more attractive than ICT CEBC because of the "off-on" switching of fluorescence, which in some cases can be utilized in the "naked-eye" mode. The chromogenic CEBC with crown ether receptors considered in this review are more suitable for detecting anions and molecules than fluorogenic CEBC, which usually require more specific and complex receptors. Both chromogenic and fluorogenic CEBC are less suitable for lanthanide cations. With photoswitchable CEBC, the sensor functions can be operated in the "on-off" and "off-on" modes.[51] The design of CEBC for anions and molecules is generally more complicated. For this purpose the use of cyclic complexing agents other than crown ethers seems to be preferred. The ambidentate CEBC as multifunctional chemosensors for simultaneous detection of two or more cations can be used for express analysis of ion mixtures. The ditopic CEBC for simultaneous detection of cations and anions can revolutionize the chemosensor field of knowledge due to the perspective of creating selective chemosensor for an individual molecule.

It may be concluded that the crown-, azacrown- and thiacrown-ether-based chemosensors represent a powerful tool for monitoring various essential analytes in analytical, biological chemistry, in medicine and in environmental studies.

Acknowledgements

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