Russian Chemical Reviews **83** (3) 196 – 224 (2014) © 2014 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2014v083n03ABEH004414

Optical methods for the detection of heavy metal ions

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The review covers an important area of the modern chemistry, namely, the detection of heavy metal ions using optical molecular detectors. The role of this method in metal ion detection and the physicochemical grounds of operation of chemosensors are discussed, and examples of detection of most abundant heavy metal ions and synthetic approaches to molecular detectors are presented. The immobilization of molecular detectors on solid substrates for the design of analytical sensor devices is described.
The bibliography includes 178 references.

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I. Introduction

The development and advancement of sensitive and reliable methods for determination of the contents of elements and compounds is a topical task of modern chemistry. There exists an enormous diversity of natural and synthetic compounds that are to be analyzed under various conditions and for various purposes. In a human body, it is necessary to recognize and determine genes and gene expression products (proteins and RNA), various metal ions and biologically important anions. The preservation of the human environment should be constantly monitored; for this purpose, it is necessary to perform rapid and reliable analyses of a multitude of compounds, including recently synthesized ones. No less important is a similar monitoring in agriculture, food production and industrial production, in particular, monitoring of the processes resulting in environmental pollution. Detection occupies a special place in the provision of safety of the contemporary society.

Traditional approaches to the qualitative and quantitative analysis of various subjects include the use of instrumental analytical methods such as atomic absorption spectroscopy, atomic emission spectroscopy, NMR spectroscopy, mass spectrometry, X-ray fluorescence spectroscopy and electrochemical methods. These methods ensure the high sensitivity but often require a thorough multistage sample preparation procedure and sophisticated expensive equipment and, hence, a one problems occur when rapid and/or field analysis is required. Therefore, it is necessary to develop methods that make use of inexpensive portable devices for detection and, first of all, this requires the design of effective sensors.

This review is devoted to determination of heavy metal cations by means of molecular detectors, which operate on the basis of changes in the optical properties of the detector – analyte ion system. We demonstrate the role of this method in the chemical sensorics and consider the physicochemical principles of operation of optical molecular detectors and their use in analytical sensor devices. The successful development of this promising approach to the determination of heavy metal ions depends to a large extent on the efforts of organic chemists, who can offer and

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Current research interests: metal complex catalysis, amination, macrocycles, chemosensors.

Received 20 June 2013
Uspekhi Khimii **83** (3) 196 – 224 (2014); translated by Z P Svitanko

implement the synthesis of organic compounds with specified properties. However, most of organic chemists are not adequately familiar with the operation principles of molecular detectors, and we hope that this review will draw their attention to this practically significant area. Owing to the large amount of factual data published in this area in recent years, we will give only some examples explaining the principles of operation and application of molecular detectors. More examples can be found in recent reviews and monographs.[1–13]

II. Chemical sensorics and optical molecular detectors

A sensor can be defined as a primary transducer which receives a particular information and converts it to a signal compatible with our perception and knowledge. According to the IUPAC definition, a chemical sensor is a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal.[14,15] Both a specially designed molecule and a tiny analytical instrument that transmits, on a real time basis, the information about the presence of particular compounds in a complex mixture can be regarded as sensors. Therefore, it is convenient to use the notion 'molecular sensor' (chemosensor) when speaking about detection by organic molecules. Sensors can provide information on not only the chemical composition but also on the change in its physical properties. For example, luminescence sensors based on molecular rotors provide information about viscosity changes related to polymerization, particle aggregation and conformational changes in the protein molecules.[16]

In order to obtain information on detection, interaction of at least two participants is needed. One of them is the subject to be detected, which is called the analyte. The second participant of the interaction is the sensor, which performs two basic functions. The first one is the selective interaction with the analyte, which ensures its recognition in the system being examined in the presence of other subjects having similar structure and properties. The sensor subunit responsible for this function is called the receptor. The other function of the sensor is to transmit the recognition information by means of a particular signal that can be analyzed and measured. The sensor subunit that forms this signal is the signalling subunit, the signal itself is called the analytical signal or response, while the conversion of information about analyte realized by the sensor is called the transduction. The methods used for transmitting information about the interaction with the subject to be detected are based on a variety of physical principles. Electrochemical and optical sensors are most popular.[17] Sensors that use optical methods for transmitting the information — chromogenic (change in the electronic absorption spectra) and luminescence (change in the luminescence spectra) — are convenient due to the fact that they provide rapid, direct and easily recordable response to the interaction with the analyte. Furthermore, noteworthy is the versatility of this approach as an optical label can be used in solution, immobilized on a solid surface or even on a biomolecule, and also used *in vivo*.[18]

The research in this area swiftly develops along many avenues. Currently, particular attention is drawn by the development of luminescence methods.[19] This method of signal recording is very sensitive and has high resolving power on both wavelength and time scales, and experiments are inexpensive and unsophisticated. Many studies are being in progress aimed at the search for new fluorescent groups, elucidation of the fluorescence generation and quenching mechanisms. These works construct the foundation for the design of new detectors, and many new procedures will undoubtedly appear in this field in the near future, for example, the use of fluorescence of conjugated polymers[20] or luminescence of lanthanides.[21]

Multisignal detectors that implement several ways of transduction seem promising.[22,23] Most popular is the combination of signalling subunits possessing electrochemical and optical properties in one sensor.

The use of supramolecular chemistry in detection brings interesting results. For example, it was found that self-assembled organometallic crown ether analogues can be used as receptors.[24] The employment of micelles as nanosized containers for the self-assembly of the sensor components serves to substantially increase the local concentrations of the receptor and transducer.[25,26]

A very important aspect is the detection medium. In the case of analysis of the environment, these are water and air in which numerous pollutants are to be monitored.[27] In view of the need to solve a multitude of biological and medical tasks, detection in biological media receives permanent attention.[28] In this case, the requirements to the selectivity and biopenetrability of the sensor and to the sensor ability to function both in the cells and in the intercellular space are very high.

When solving practical tasks, one should have in mind that it is impossible to attain the absolute sensor selectivity (strictly individual response to the presence of the analyte). For practical purposes, not the absolute selectivity is of prime importance but the selectivity as applied to a particular task, *e.g.*, potable water analysis or diagnosis of diseases. The purposes of quantitative analysis are interpreted in a similar way. A linear dependence of the detector response on the analyte concentration is necessary, as a rule, only in a particular concentration range defined by the particular task. Since the design of a sensor is a time-consuming and laborious process, the use of the combinatorial approach to the construction of libraries of sensors for the search for the best system substantially accelerates the work. These libraries are based, most often, on variations in the receptor subunit of the detector.[29,30]

The problem of detection in a complex system can also be solved using a kit of sensors, for example, integrated on a support. Since a set of responses of each sensor exists for any analyte, then for a mixture of analytes a multicomponent analysis is possible. Templates that contain sensors of the same type mimic human senses such as olfaction and taste, being often called 'electronic nose' or 'electronic tongue'.[31,32]

The operation principles of optical molecular detectors will be demonstrated in relation to the detection of metal ions because metal cations are of special interest among various molecular detection objects. Many of them are involved in biological processes in living organisms, and their contents may serve to diagnose diseases. Many metal ions, being biologically significant micronutrients, still may be detrimental to health when present in high concentrations. Toxic metals are hazardous pollutants of the environment, and their contents in food and potable water are

subject to strict control. The topical task of detection of heavy metal ions having large coordination numbers is fairly complicated, because similar coordination properties bring about the problem of selectivity. Optical molecular detectors are especially important in this field as they are able to ensure selective, fast and cheap analysis both in the environment monitoring and in dealing with biological media.

III. Physicochemical grounds of functioning of optical chemosensors and chemodosimeters

Molecular detectors can be classified into chemosensors and chemodosimeters.[11] Chemosensors are molecules of the abiotic nature able to selectively and reversibly react with the analyte to produce a measurable signal with a real-time response (usually in less than several seconds). The general principle of operation of chemosensors is based on the phenomenon of coordination. The most widely used type of chemosensors comprises the receptor and signalling units connected by a covalent bond or through a spacer, which produces an optical response upon the analyte coordination. For repeated use of the sensor, it is necessary that its binding to the analyte be reversible. In most cases, coordination is not accompanied by a rearrangement of the system of covalent bonds; however, there are also chemical sensors in which coordination is accompanied by reversible structural changes, *i.e.*, when the analyte is removed, the sensor molecule is recovered in the initial form.

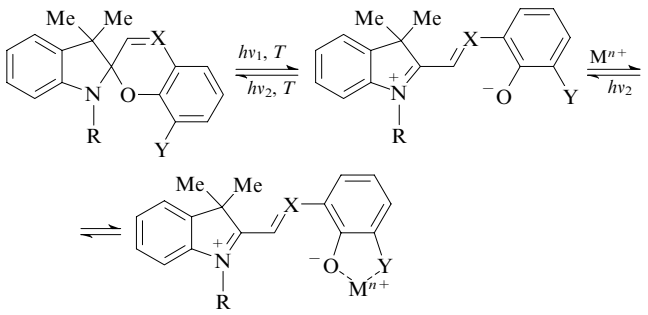
Another principle of operation of chemosensors is based on the substitution concept. An optical detector of this type also consists of the receptor and signalling subunits, which are not, however, bound by covalent bonds. After analyte coordination to the receptor, the signalling unit is liberated, and this is accompanied by the change in the optical properties of the system.

Chemodosimeters also comprise the same subunits. An analyte is covalently bonded to one or several atoms of the chemodosimeter, thus inducing cleavage of covalent bonds in the system, which gives rise to new chemical compounds, and this distinguishes chemodosimeters from chemosensors. In this case, the optical response can be caused by either the molecule containing no analyte or the structural moiety containing the analyte. Thus, when designing selective chemodosimeters, it is necessary to find a specific reactivity, while the design of chemosensors requires selective coordination.

When dealing with detection of ions, the receptor unit of chemosensors responsible for the analyte binding is customarily called the ionophore, while the signalling unit is called either the chromophore in the case of the chromogenic detector (change in the electronic absorption spectra) or the fluorophore in the case of the fluorescence detector (change in the fluorescence spectra).

A special group are photoswitchable optical chemosensors capable of reversible on–off switching of the chemosensor properties on exposure to electromagnetic radiation in the UV or visible range. Basically, these systems do not differ from usual optical chemosensors and they also comprise an ionophore and a signalling unit. Their specific feature is that reversible phototransformation of one part of the chemosensor (most often, the signalling unit) results in two different states of the detector. One state is able to produce a detectable response to the presence of the analyte, while the other does not produce such response. As a result, the sensing properties of the molecule are controlled by exposure to light. The most popular phototransformations used to manufacture such chemosensors are electrocyclic and cycloaddition reactions.[3] For example, photochromic spirocyclic compounds — spiropyrans and spirooxazines — are converted under the action of short-wavelength radiation to the merocyanine form (Scheme 1), which is able to coordinate metal ions to give complexes having specific characteristics of the absorption and fluorescence spectra.[33]

Scheme 1



X = CH, N; Y is donor group, ionophore macrocycle, *etc.*

Spiropyrans and spirooxazines are widely studied as photodynamic sensors for transition metals of the 4th Period and lanthanides due to a pronounced increase in the fluorescence intensity of merocyanine complexes.[34]

1. Ionophores for metal cations

The design of receptor groups for metal cations often utilizes the coordination of metal cations to various heteroatoms (nitrogen, oxygen, sulfur). These heteroatoms may occur as parts of either simple amines, alcohols, thiols, ethers and thioethers or more intricate functional groups (carbonyl, carboxyl, ester, amide, thiocarbonyl, imine, diethoxyphosphoryl and so on) and aromatic heterocycles (pyridine, pyrimidine, quinoline, triazole, isoxazole, *etc.*). The so-called 'hard' alkali and alkaline earth metals and lanthanides are preferably coordinated to hard O-donor ligands and are less prone to coordination to softer N-donor ligands. First-row transition metals up to cobalt also prefer O-donors, whereas transition metals of the subsequent rows are better coordinated to N-donors. There is a general regularity according to which the cation 'softness' (and, hence, proneness to coordination to soft donors) increases from left to right in the Period and from top to bottom in the Group provided that the metal oxidation state is not high. Indeed, mercury and silver are preferably coordinated to sulfur, and platinum group metals and gold prefer sulfur and phosphorus donor atoms. The presence of only one coordinating group in the ionophore cannot ensure the efficiency and selectivity needed for the detection. Therefore, in the design of chemosensors, receptors with different complexity of the structure are used and are adjusted to the metal coordination sphere. Complexes of metal cations with polydentate ligands have enhanced stability due to the chelate and/or macrocyclic effect.

An ionophore can have a linear or cyclic structure; first, we will consider acyclic ionophores. The chelate effect ensures the efficiency of complexation by linear polyamines containing ethylene- and trimethylenediamine units, poly-

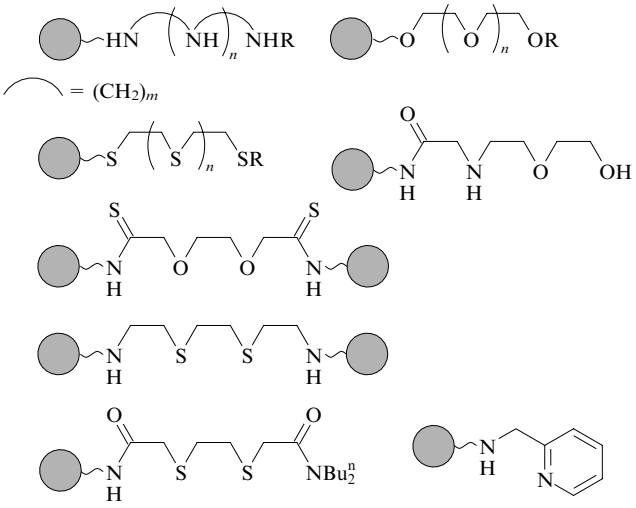


Figure 1. Structures of typical chelating ligands (chelators). Here and below, the grey circles designate non-ionophore moieties of chemosensors comprising signalling groups and linkers.

ethylene glycols, polythioethers and compounds with different heteroatoms; in addition, functional groups or heterocycles can be added to the same linear sequence incorporating heteroatoms.[2, 33] The mentioned structural moieties are shown in Fig. 1.

Among acyclic ionophores, branched structures are frequently encountered (Fig. 2). Most often, a nitrogen atom serves as the branching point as it is trivalent and

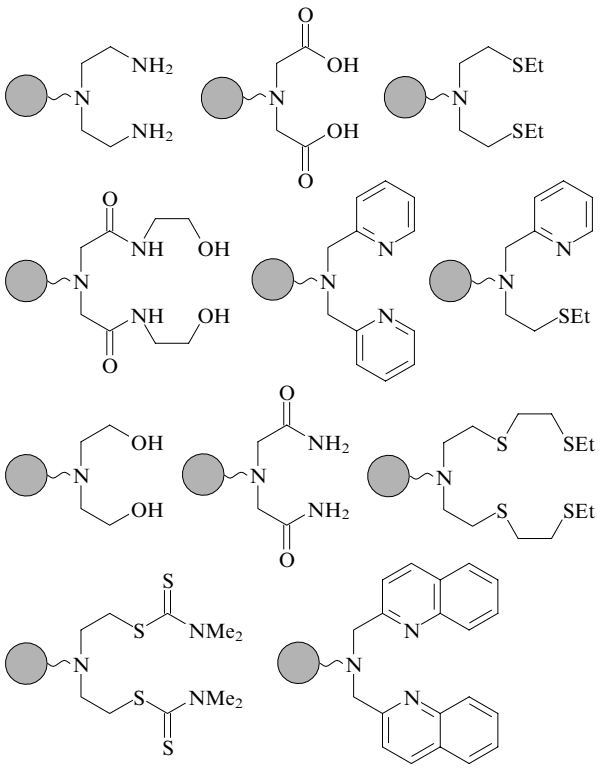


Figure 2. Examples of ionophores with a branched structure.

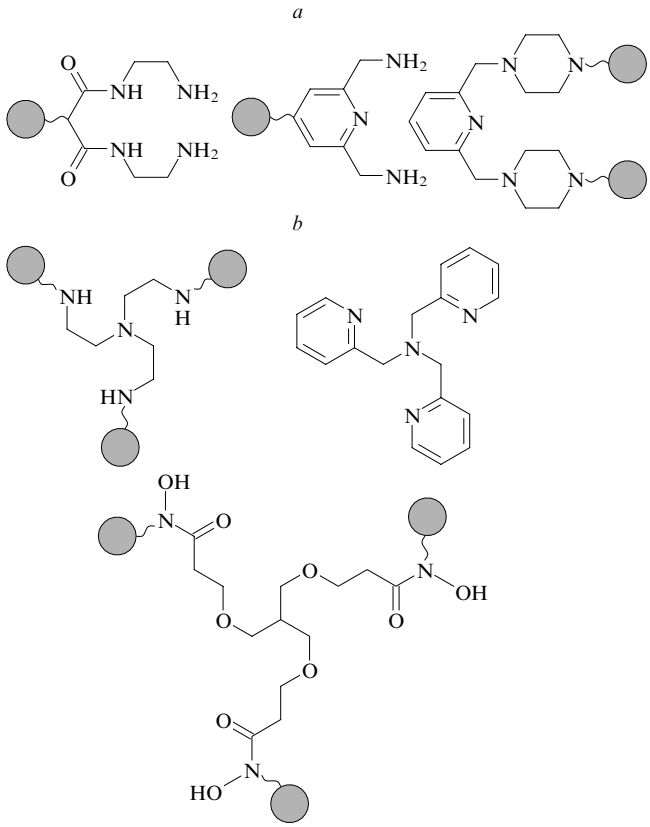


Figure 3. Examples of ionophores based on dioxotetraamine and bis(aminomethyl)pyridine moieties (*a*) and on tripodal ligands (*b*).

can be functionalized by various chemical transformations.[2, 4]

There are also other examples of chemosensors with branched ionophores, for example, those containing a dioxotetraamine moiety or bis(aminomethyl)-substituted pyridines (Fig. 3 *a*).[2, 4] Quite interesting are ionophores based on tripodal ligands (see Fig. 3 *b*).[2]

Ionophores with cyclic structure are often macroheterocycles. Vigorous studies of these complexing agents started after the pioneering works of C J Pedersen, D Cram and J M Lehn, who won the Nobel Prize of 1987 in chemistry 'for their development and application of molecules with highly selective structure-specific interaction'. The simplest cyclic ionophores are crown ethers, aza- and thia-crown ethers and polyazamacrocycles (Fig. 4 *a*).[4, 6, 33]

Examples of more complex cyclic ionophores are lariat ethers, cryptands, calixarenes (Fig. 4 *b*).[7, 33] In addition, in order to increase the complexing selectivity and the stability of complexes, the above cyclic ionophores are modified by introduction of additional functional groups both directly into the ring and as side chains (Fig. 4 *c*).[2, 4]

Certainly, the above examples of cyclic and acyclic ionophores do not exhaust all organic moieties suitable for construction of the receptor unit of molecular detectors. Combinations of several of the mentioned groups within one ionophore, the use of two (or more) ionophores, inclusion of the signalling unit into the cyclic receptor, participation of the signalling unit in the cation coordination and so on are also possible. Macrocyclic ionophores such as calixarenes and polyazamacrocycles are often used

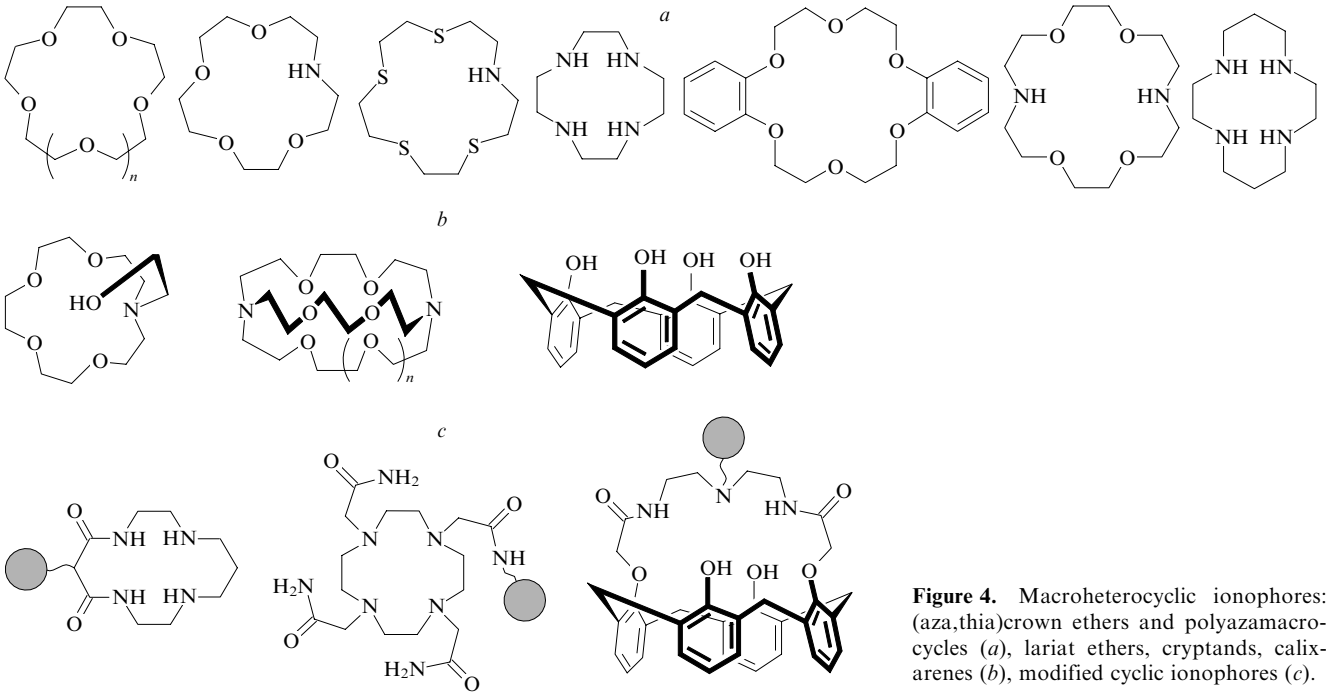


Figure 4. Macroheterocyclic ionophores: (aza,thia)crown ethers and polyazamacrocycles (*a*), lariat ethers, cryptands, calixarenes (*b*), modified cyclic ionophores (*c*).

as the frame (platform) for the development of chemosensors, because they can be easily modified by other ionophore and signalling groups.

Below we demonstrate the diversity of applied ionophores for particular cases of heavy metal ion determination.

2. Signalling mechanisms of optical molecular detectors

The optical response to the presence of an analyte is provided by the signalling group of the molecular detector. Below we consider in more detail the mechanisms of optical signal generation in the detection of metal cations.

In the case of spectrophotometric detection, the complex formation of the analyte changes the absorption spectrum of the system. It is most convenient to use absorption and emission bands with the longest possible wavelength, because a great number of compounds absorb in the UV region, which can interfere with selective detection; in addition, visual detection is possible in the visible range. Therefore, organic compounds that incorporate both electron-donating and electron-withdrawing substituents connected by a common system of conjugated bonds are convenient as chromophores. In this case, intramolecular charge transfer (ICT) from the donor to acceptor moiety is possible in the excited state.[35] The changes in the absorption spectrum of the chromophore upon binding of the analyte are due to different effects of complex formation on the energy levels of the ground and excited states. When a cation is coordinated to the donor (D) part of the chromophore molecule, the electronically excited state S_1 is destabilized to a larger extent than the ground state S_0; therefore, the gap between the molecular energy levels increases and the absorption band shifts hypsochromically. If the metal cation is coordinated to the acceptor (A) part of the chromophore, the excited state is substantially stabilized and the absorption band shifts bathochromically (Fig. 5).

To make this effect of complexation on the electronic absorption spectrum sufficiently large and suitable for

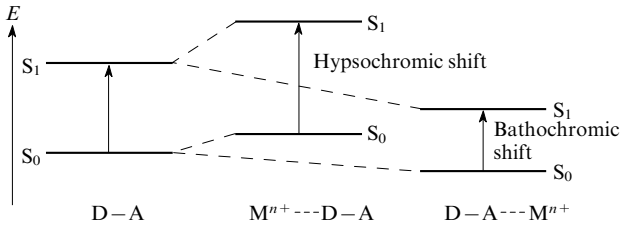


Figure 5. Effect of complexation of metal cation M^{n+} with the chromophore D–A on the absorption spectrum.

recording, the chromophore should participate in the coordination of the metal cation, *i.e.*, it should be a part of the ionophore moiety. In principle, any organic dye can serve as the chromophore in the spectrophotometric detection in the visible region. Figure 6 shows chromophores that are used for derivatives of azobenzene, ferrocene, anthraquinone, fluorescein and rhodamine and squaraine dyes.[6, 33, 36, 37]

More diverse and complex mechanisms produce the signal response of the fluorophore. Here we consider only the mechanisms that are most important and used most often to determine metal cations. This issue is considered in more detail in monographs.[18, 35, 38] Upon absorption of a photon, an electron migrates from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the molecule. If the electron can go back to the HOMO with photon emission, then the molecule is fluorescent. The excited electron has a high energy, which enables processes that are usually impossible in the ground state. These processes may represent electron, charge, proton or energy transfer, which affects the emission of photons by the excited molecule. Binding of the analyte may affect these processes, which is manifested as a change in the fluorescence spectrum. Several mechanisms of

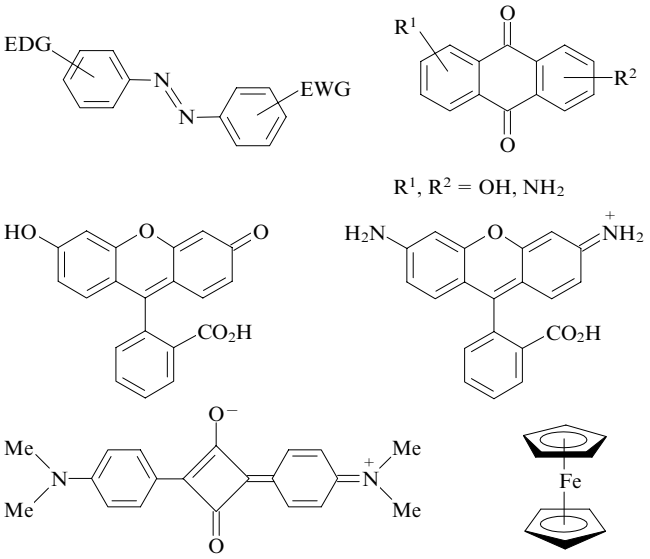


Figure 6. Most popular chromophores.
EDG and EWG are the electron-donating and electron-withdrawing groups, respectively.

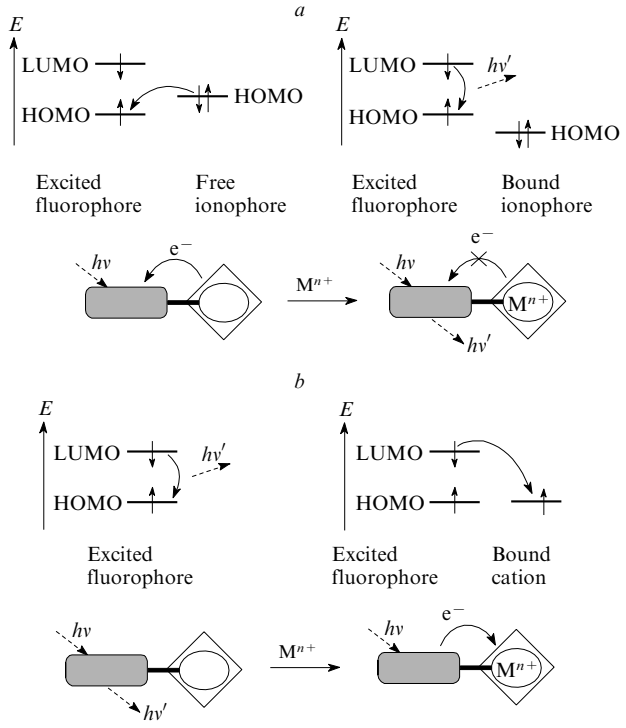


Figure 7. Schematic diagrams of the PET process in a chemosensor (see text).

transmission of information about the complex formation are possible in this case.

Photoinduced electron transfer (PET) means transfer of an electron from the excited site to another site or *vice versa*. For this transfer to take place, these two sites should be closely located in space and their redox potentials should be suitable.[18] For example, the PET process can occur between the excited fluorophore and the ionophore containing a redox-active site (for example, a lone pair of a heteroatom) and connected to the fluorophore either directly or through a short spacer (Fig. 7 *a*).

In the excited state, one electron of the fluorophore is located in the LUMO, and this enables an electron transition from the ionophore HOMO (occupied by the lone pair) to the fluorophore HOMO, resulting in quenching of the fluorophore fluorescence. After coordination of the ionophore to the metal cation, the HOMO level (cation-bonded electron pair) becomes lower than the HOMO of the fluorophore, the PET process cannot take place, and fluorescence enhancement may be observed (see Fig. 7 *a*).[12] In the case of transition metal cations, another PET process is possible in which the electron transfer is directed from the LUMO of the fluorophore to the bonded metal cation (see Fig. 7 *b*), which induces fluorescence quenching.[8]

This mechanism is used most often to detect metal cations because it does not imply any special requirements to the fluorophore structure; this may be any aromatic group with suitable HOMO and LUMO levels. A secondary *N*-benzylamino group or tertiary *N*,*N*-dialkylamino group located closely to the fluorophore and being a part of the ionophore serves most often as the redox-active site of the ionophore. However, PET chemosensors are not logometric (ratiometric), because a change in the fluorescence intensity is not accompanied by shifts of the absorption and fluorescence bands, and this appreciably restricts their applicability to quantitative determination of metal ions. In addition, fluorescence of some simple fluorophores such as naphthalene, anthracene and pyrene derivatives, which have often been used in PET chemosensors, is sensitive to the presence of oxygen, which substantially decreases their attractiveness for detection especially in biological media.

Yet another abundant signalling mechanism is the photoinduced charge transfer (PCT) also called intramolecular charge transfer (ICT). In principle, PCT is also an electron transfer; however, it is implemented within one and the same electronic system or between systems with a high degree of electron conjugation.[37] Usually, fluorophores of PCT chemosensors contain electron-donating and electron-withdrawing groups (often these are the dialkylamino and carbonyl groups, respectively) and the mechanism of response generation upon complexation is based on the same principles as in the case of chromogenic chemosensors (see Fig. 6). The interaction of a cation with the electron-donating group leads to the destabilization of the excited state of the fluorophore and to the shift of the absorption and emission bands to shorter wavelengths. Note that usually the fluorescence response to cation binding by the electron-donating group is rather low. This is due to the fact that in the excited state, dissociation of the cation is facilitated by unfavourable electrostatic interaction. In turn, when the cation interacts with the electron-withdrawing group, the Coulomb forces are favourable for the complex formation and stabilization of the excited state of the system. This induces a bathochromic shift of the absorption and fluorescence spectra. Apart from the shift of the emission band, the change in the fluorescence intensity is possible in both cases.[12]

The compounds often used as fluorophores operating by the PCT mechanism include derivatives and analogues of such compounds as dansylamide, aminonaphthalimide,

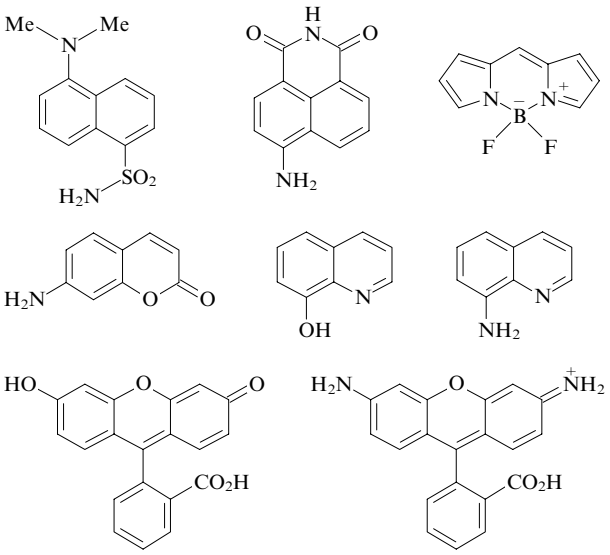


Figure 8. Fluorophores operating by the PCT mechanism.

BODIPY (boron-dipyrromethene), 7-aminocoumarin, 8-hydroxy- and 8-aminoquinolines, fluorescein, rhodamine (see, for example, the review[39] devoted to chemosensors based on naphthalimide derivatives) (Fig. 8).

Some fluorophores, for example, naphthalene, anthracene and pyrene can form excimers (excited dimers) when an excited molecule approaches a non-excited one. In this case, two fluorescence bands are observed: one corresponds to monomer emission and the other (a broader band at longer wavelength) corresponds to excimer emission. If the chemosensor contains two fluorophores, the distance between them being affected by complexation with the cation, this cation can be recognized by measuring the fluorescence intensity ratio of the monomer and the excimer. Cation bonding may either promote or hamper the excimer formation. In both cases, the possible ratiometric detection is quite interesting from the standpoint of a practical application in quantitative analysis.[12]

The fluorescence resonance energy transfer (RET or FRET) from the excited donor fluorophore to the acceptor can also be used in detection. Both fluorophore and chromophore can serve as the acceptor; in this case, the emission spectrum of the donor should overlap with the absorption spectrum of the acceptor. The efficiency of this energy transfer depends on the distance between the donor and the acceptor and the extent of overlap of the spectra;[18] the complexation with the cation can influence both factors. The energy transfer can occur by two mechanisms. The first one is related to absorption and emission of radiation by the donor and the acceptor separated by more than 0.5 nm and is known as the Förster mechanism. In the second case, energy transfer occurs upon overlap of the donor and acceptor electron shells; it is called the Dexter mechanism. The efficiency of energy transfer in the latter case decreases following increase in the distance between the donor and the acceptor much faster than in the former case; therefore, it is more rarely encountered. The energy transfer has started to be used in detection only recently and has received much attention in the past years.

If the energy acceptor is a chromophore exhibiting no fluorescence, the change in the efficiency of energy transfer upon coordination of the cation can induce a change in the emission intensity of the donor fluorophore. When the energy transfer occurs from one fluorophore to the other, the so-called wavelength conversion takes place: the energy acceptor shows longer-wavelength fluorescence. The cascade energy transfer is even more curious: a sequence of energy transfers take place, resulting in a considerable shift of the emission spectrum and in the amplification effect where a large number of donors transfer the energy to a small number of acceptors, thus increasing the fluorescence intensity of the latter.[18]

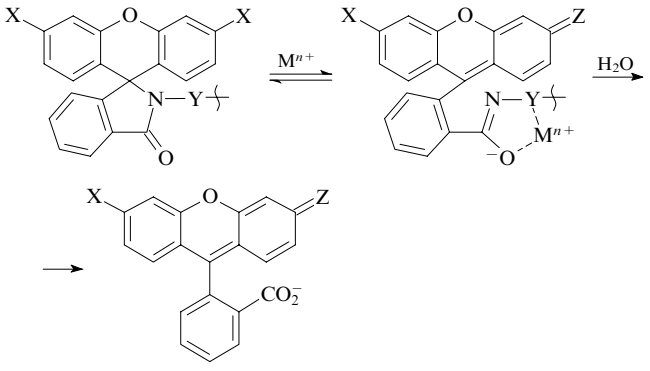
The above-listed signalling mechanisms result in the fluorescence spectrum of the molecular detector being changed upon analyte binding. Fluorophores that allow for detection of cation binding based on a change in the lifetime of the excited state are less widely used due to a more complicated procedure of recording the signal response.[18, 38]

3. Reactions used in chemodosimeters

As noted above, the operation of chemodosimeters is based on irreversible chemical reactions, and they are often used for optical detection of heavy metal cations. In many cases, these cations cause fluorescence quenching upon complex formation with chemosensors. This is inconvenient for quantitative analysis and detection of trace amounts of toxic metals. When chemodosimeters are used, binding of the analyte gives rise to a fluorescent compound, which usually does not contain a metal cation. This is convenient in the case of low analyte concentrations or for analysis of biological media. The reaction of a chemodosimeter with an analyte may induce a change in the electronic absorption spectra and in the colour, which allows visual detection. We will consider several key reactions used in the design of chemodosimeters for metal cations.[11]

Ring opening in spirocyclic systems based on fluorescein and rhodamine derivatives upon stoichiometric transformations involving metal cations leads to conversion of colourless non-fluorescent compounds into coloured compounds with intense fluorescence (Scheme 2).

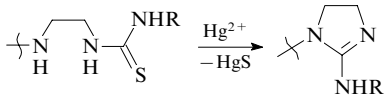
Scheme 2



X = OH, Z = O; X = NR_2, Z = $\overset{+}{N}R_2$; Y is a donor group, ionophore macrocycle, *etc.*

Intramolecular cyclic guanylation of thiourea derivatives can be used to manufacture chemodosimeters for mercury cations (Scheme 3).

Scheme 3



The transformation of thiourea into the less electron-donating imidazoline moiety induces a hypsochromic shift of the absorption and fluorescence maxima.

The transformation of thiocarbonyl compounds into carbonyl compounds can also be useful for detection of mercury. The thiocarbonyl group can be involved in fluorescence quenching; therefore, its replacement by a carbonyl group as a result of a hydrolytic reaction involving Hg^{2+} leads to a increase in the fluorescence intensity, which is in some cases accompanied by a shift of the emission band.

IV. Detection of metal ions

This Section presents particular examples of chemosensors and chemodosimeters. In view of the enormous amount of relevant literature, out of the sensors synthesized to date, we have chosen only those examples that best illustrate the diversity of construction modes and physicochemical principles of operation.

1. Detection of Zn^{2+} cations

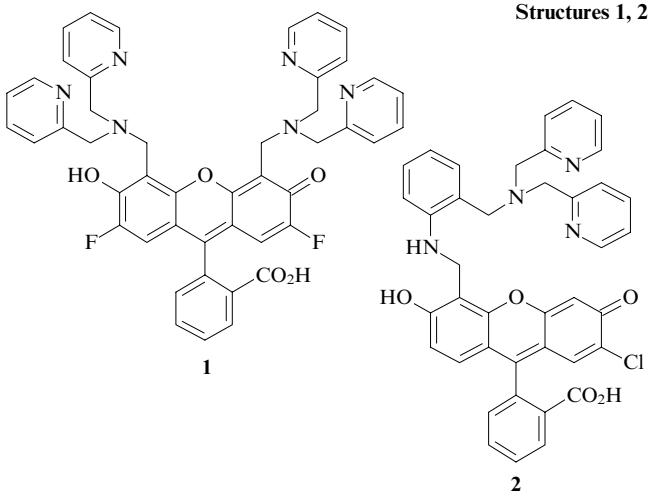
Zinc, which is an important micronutrient, is present almost in any food and potable water as salts or organic complexes. In a human body, zinc is the second most abundant transition metal, the highest zinc concentration being present in brain.[5] The most important source of zinc in the body is the usual diet. Although the concentration of zinc in the surface and underground waters usually does not exceed 0.01 and 0.05 mg litre^{-1}, respectively, its amount in tap water can be much higher due to zinc dissolved from water-supply pipes. The maximum permissible concentration (MPC) of zinc in potable water currently established by the World Health Organization (WHO) is 3 mg litre^{-1}.[40]

As compared with other transition metals, considerable progress has been made in Zn^{2+} detection, and numerous fluorescent chemosensors for Zn^{2+} detection in living cells have been manufactured.[5] This is related, first of all, to availability of fairly selective receptors to this ion, which can be exemplified by dipicolylamine derivatives, and also to the fact that the Zn^{2+} d-orbitals are occupied, which makes the development of PET sensors much easier.[4]

By combining fluorescein as a signalling group and a dipicolylamine receptor, Lippard and co-workers[41,42] prepared a family of fluorescent chemosensors for Zn^{2+}, for example, compounds **1** and **2**. Both sensors operate by the PET mechanism. After complex formation with zinc ions, they demonstrate a sixfold enhancement of fluorescence with absorption and emission spectra in the region of 500–530 nm typical of fluorescein. In addition, they ensure high selectivity to Zn^{2+} among biologically significant cations, operate at neutral pH and can penetrate into the cells; therefore, they are suitable for visualization of Zn^{2+} content in neurons.

It is of interest to compare coumarin derivatives **3** and **4** in which the receptor dipicolylamino group is located in different positions of the coumarin moiety.[43,44] As expected, compound **3** operates as a plain PET sensor, whereas derivative **4** behaves in a different way: participation of the lactone oxygen atom in complex formation with Zn^{2+} induces a bathochromic shift by 21 nm due to the PCT mechanism, which enables ratiometric detection.

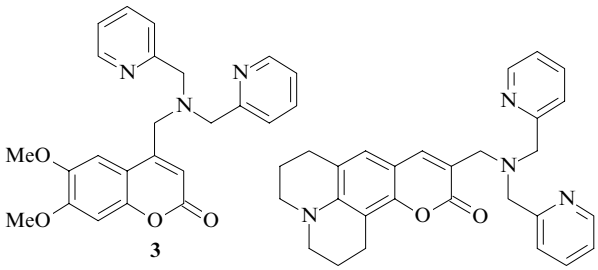
Structures 1, 2



1

2

Structures 3, 4

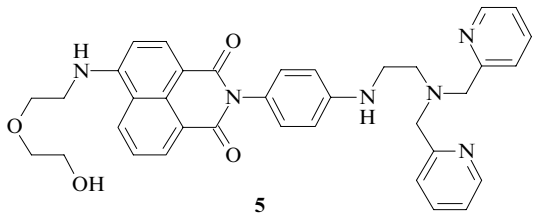


3

4

Compound **5** is yet another example of a PET sensor having a dipicolylamino group as the receptor for Zn^{2+} ions.[45] This compound has high affinity for zinc ions; the fluorophore is represented by the 4-aminonaphthalimide moiety with absorption and emission maxima in the visible region (449 and 538 nm, respectively).

Structure 5

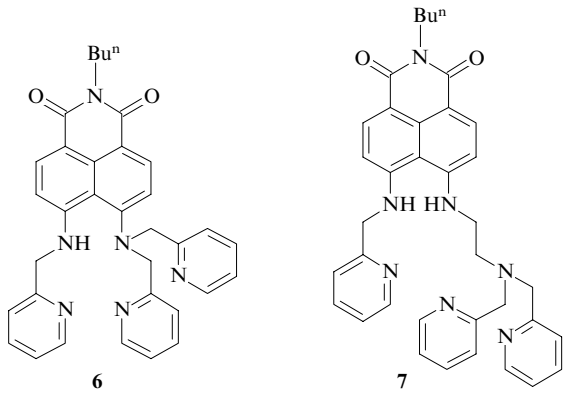


5

4,5-Diaminonaphthalimide derivatives **6** and **7** are also highly selective and sensitive sensors for Zn^{2+}. However, unlike compound **5**, the absorption and fluorescence bands of these chemosensors shift bathochromically in the presence of Zn^{2+} by 56 and 27 nm, respectively, which is related to deprotonation of the aromatic amino group.[46,47]

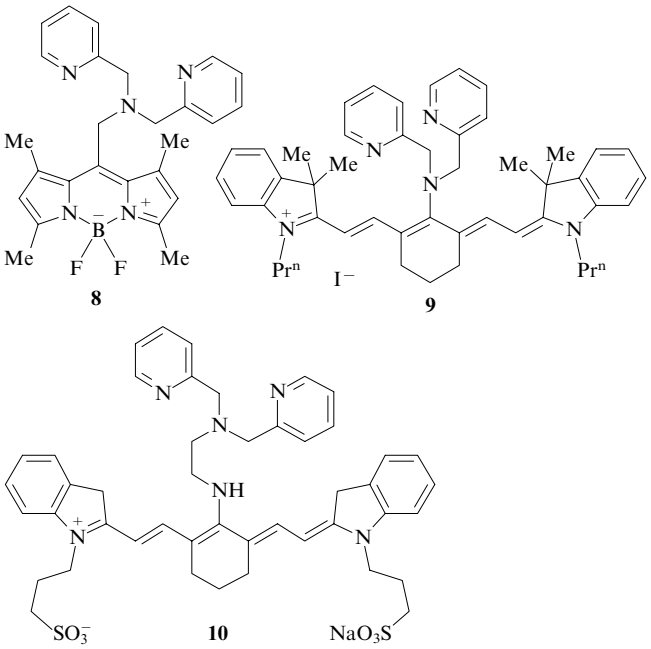
Chemosensor **8** based on the BODIPY structure, providing a sevenfold increase in the fluorescence intensity upon binding of Zn^{2+}, also possesses convenient optical characteristics (absorption maximum at 491 nm and emission maximum at 509 nm) and is able to penetrate into the cells.[48]

Structures 6, 7



6 **7**

Structures 8–10



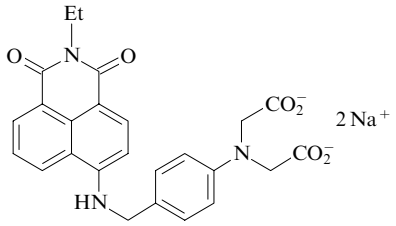
8 **9**

10

Fairly interesting are chemosensors **9** and **10**[49, 50] combining a tricarbocyanine dye and a dipicolylamine receptor. These compounds absorb and emit in the near infrared region of the electromagnetic spectrum and, therefore, they can be very useful for detection *in vivo*. Sensor **9** has an absorption maximum at 730 nm and an emission maximum at 780 nm, and the complex formation with Zn^{2+} induces a 20-fold enhancement of fluorescence. For compound **10**, along with the fivefold increase in the fluorescence intensity, a bathochromic shift of the absorption maximum from 627 to 671 nm is observed, which allows for the ratiometric detection of Zn^{2+} ions.

One more selective receptor for zinc ions is the bis(carboxylatomethyl)amino group (iminodiacetate group, IDA), which is among simple receptor groups. An interesting example of a PET chemosensor with a receptor of this type is compound **11**, which contains a 4-aminonaphthalimide moiety as the fluorophore.[51] It is interesting because it is suitable for Zn^{2+} determination in the pH range of the physiological salt solution and because the complex formation causes a sharp (50-fold) increase in the fluorescence intensity.

Structure 11



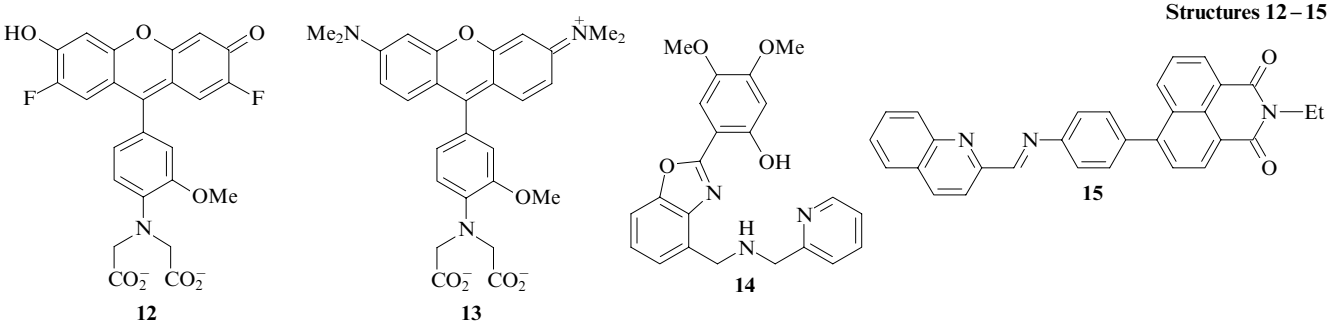
11

A combination of the IDA group with fluorescein and rhodamine derivatives afforded sensors **12** and **13** with high affinity for Zn^{2+}, which are able to determine micro- and millimolar concentrations of zinc ions.[52]

Currently, considerable attention is devoted to the search for other receptor groups capable of selective detection of zinc ions. Indeed, ratiometric sensor **14** containing benzoxazole as the fluorophore and the substituted phenol and picolylamino groups as substituents provides effective binding of and high selectivity to zinc ions.[53] The complex formation with Zn^{2+} induces a bathochromic shift of both the absorption spectrum (from 337 to 376 nm) and the fluorescence spectrum (from 407 to 443 nm).

More intricate molecular detectors containing several signalling groups were obtained. Chemosensors with two fluorescent groups can be used for ratiometric determination. For example, naphthalimide derivative with a quinoline substituent **15** was used to form a fluorescent ratiometric sensor for zinc cations operating in a $MeCN-H_2O$ mixture (4 : 1 by volume).[54] Excitation of the molecule at 360 nm brings about emission of the quinoline moiety at 448 nm, which is accompanied by quenching of the PET-induced fluorescence of the naphthalimide moiety. The addition of zinc ions results in orange fluorescence (550 nm) due to inhibition of the PET mechanism after coordination of the zinc cation to imine nitrogen, and the emission intensity at 448 nm sharply decreases. The change

Structures 12–15

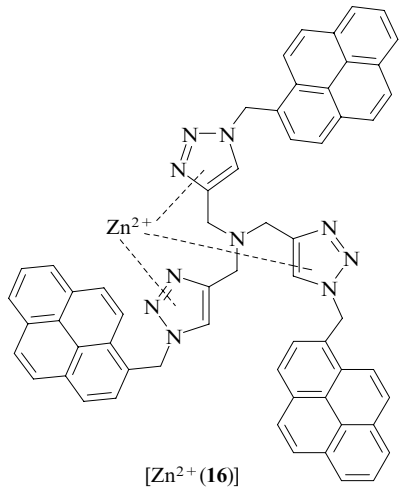


12 **13** **14** **15**

in the fluorescence occurs up to the ligand to metal ratio of 1 : 1.

The detection of zinc ions by highly selective sensor **16** based on the tris-triazole trimethylamine derivative with three pyrene fluorophores is based on the sharp change in the intensity ratio of the monomer (376 nm) and excimer (465 nm) emissions upon binding of metal cations in acetonitrile.[55] In the starting compound, this ratio is 0.21, while upon the addition of 10 equiv. of zinc salt it increases to 16.9. The limit of detection of zinc ions by this chemosensor is 0.2 μmol litre^{-1}.

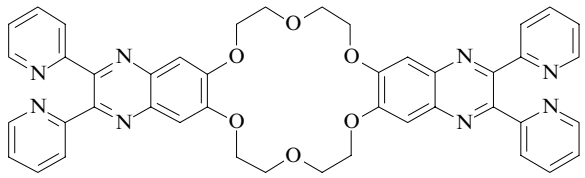
Structure of the complex [Zn^{2+}(16)]†



[Zn^{2+}(**16**)]

Crown ether-based ligand **17**, which contains two independent ionophore moieties, both as parts of the fluorophore, forms a complex with a ligand to metal ratio of 1 : 2 upon coordination to zinc cations in acetonitrile.[56] The initial ligand emits at 396 nm, while emission of the complex is at 460 nm; this chemosensor can be used as ratiometric.

Structure 17

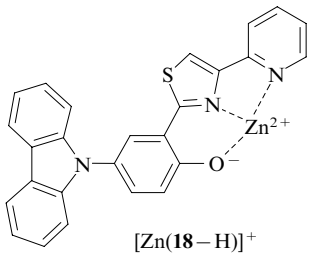


17

† Hereinafter, only fragments of coordination spheres of the complexes responsible for colour change are shown.

Of interest are chemosensors in which binding of the metal cation induces considerable structural changes in the signalling group and is accompanied by pronounced changes in the optical properties. For example, the carbazole chemosensor **18** is coordinated to zinc ions by the O···N···N receptor triad in the EtOH – H_2O system (3 : 1 by volume).[57] It is convenient for detection, as the free ligand exhibits fluorescence bands at 426 and 537 nm corresponding to the ketone and enol forms. Emission at 492 nm linearly increases upon the addition of zinc cations until the ligand to metal ratio is 1 : 1. The intensity of emission at 426 nm decreases. The limit of detection by this highly sensitive ratiometric chemosensor is 2.1 μmol litre^{-1}.

Structure of the complex [Zn(18 – H)]$^+$



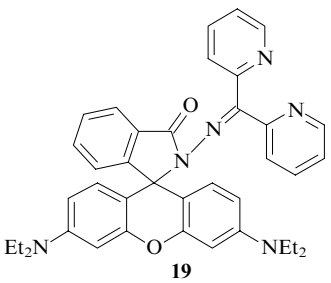
[Zn(**18** – H)]$^+$

Several multisignal chemosensors for determination of Zn^{2+} were described. In an ethanol–water mixture, the colourless spirolactam form of the rhodamine derivative **19** is opened upon the addition of zinc cations. As this takes place, the solution is coloured pink and emission at 581 nm appears.[58] The addition of other cations virtually does not change the fluorescence; however, copper cations also form complexes with this ligand, which is a substantial drawback of this chemodosimeter.

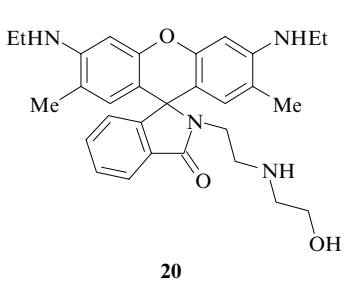
A similar example was reported by Sivaraman *et al.*[59] Detector **20** has a linear receptor and is coordinated to zinc cations in water to form a 1 : 1 complex. The solution colour changes from pink to red and fluorescence arises. It is noteworthy that the same colour change also occurs upon the addition of Fe^{3+} cations; however, the iron(III) complex does not fluoresce, and this serves to discriminate these two ions.

Chemosensor **21** based on cyclen[60] can also be used to determine ions in aqueous solutions but its selectivity is low. After the addition of zinc or cadmium cations, emission is appreciably enhanced, and after the addition of mercury ions, not only enhancement of the emission is observed, but also the emission maximum shifts by 25 nm to shorter wavelengths. The selective detection of zinc is possible

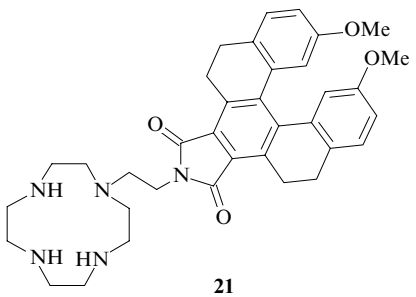
Structures 19 – 21



19



20



21

upon addition of cysteine, which forms complexes with metal ions that interfere with the determination.

2. Detection of Cu^{2+} cations

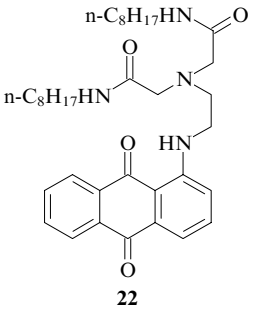
Copper is also an important micronutrient that gets into the human body with food and water. In natural water sources, the content of copper is relatively low; however, its concentration in tap water may considerably increase due to corrosion of pipes, especially in systems with low pH values and in carbonate-enriched waters with alkaline pH. The currently accepted MPC of copper in potable water is rather high being 2 mg litre^{-1}.[41] This allows for the wide use of colorimetric chemosensors for determination of this metal.

The Cu^{2+} ion can induce fluorescence quenching by different mechanisms. This feature enables rather easy design of fluorescent sensors that can be switched off.[4] However, the mechanism of detection in which fluorescence quenching serves as the response is not convenient for determination of metal ions in low concentrations and, in some cases, it may give a false-positive signal. This brings about the task of development of chromogenic optical sensors, which change colour in the presence of copper, or fluorescent sensors, in which the response induces an increase in the fluorescence intensity or to a change in the emission maximum.

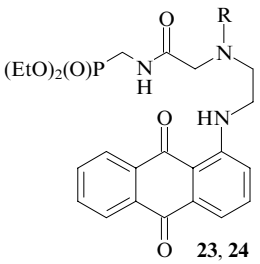
The colorimetric chemosensor **22** gives a selective response to Cu^{2+} ions in a water–methanol mixture (1 : 1).[61] In the presence of Cu^{2+}, the absorption band of ligand **22** at 512 nm undergoes a pronounced bathochromic shift (~100 nm), which induces a red to blue change in the solution colour. This colour change was attributed to deprotonation of the aromatic amino group upon coordination to copper ions. Chemosensor **22** was noted as a highly selective and sensitive colorimetric sensor, which allows even naked eye detection; however, it cannot be used for analysis of aqueous solutions due to low water solubility.

Our research groups synthesized water-soluble 1-aminoanthraquinones **23** and **24** containing a diamine moiety modified by one (**23**) or two (**24**) (diethoxyphosphorylmethyl)amide groups.[62]

Structures 22–24



22



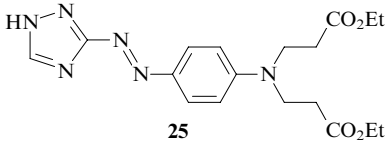
23, 24

R = H (**23**),
$CH_2C(O)NHCH_2P(O)(OEt)_2$ (**24**)

The addition of 1 equiv. of Cu^{2+} to an aqueous solution of ligand **23** or **24** induces a visible colour change from red to blue due to the bathochromic shift of the absorption maximum. Chemosensor **24** has very high selectivity, and ligand **23** can be used for simultaneous determination of copper and nickel ions in aqueous solutions. The limit of naked-eye detection of Cu^{2+} using chemosensor **24** is 0.4 mg litre^{-1}, and by using a standard laboratory spectrophotometer, the limit of detection can be reduced to 0.02 mg litre^{-1}.

Triazole aza derivative **25** is one more example of colorimetric detectors for Cu^{2+} ions.[63] Compound **25** has an ICT absorption band with a maximum at 416 nm. The coordination of copper ions by the acceptor moiety of the chromophore induces a bathochromic shift of the absorption band maximum to 535 nm, resulting in a yellow to violet colour change. The authors noted high selectivity of chemosensor **25** to copper ions in the presence of other transition metal ions in acetonitrile solutions.

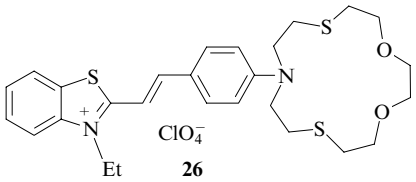
Structure 25



25

Tulyakova *et al.*[64] synthesized sensor **26** for copper(II) ions in which dithiaazacrown ether serves as the ionophore. On coordination to Cu^{2+} ions in acetonitrile, the absorption band of the initial ligand at 521 nm disappears and a new absorption band at 461 nm and two long-wavelength bands at 777 and 862 nm appear.

Structure 26

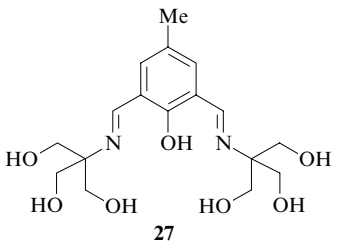


26

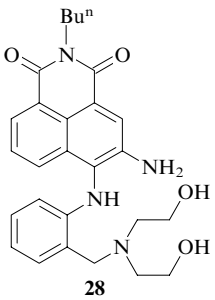
A rather simple colorimetric sensor for determination of copper cations was proposed by Chandrasekhar *et al.*[65] *p*-Cresol derivative **27** containing two imine groups and six hydroxy groups absorbs at 434 nm (at pH 7.5). Upon the addition of 2 equiv. of a copper salt, the yellow colour of the solution disappears as the resulting complex absorbs at 380 and 415 nm. Other cations do not exert this effect. The limit of detection of copper cations by this detector is 20 mg litre^{-1} for naked-eye detection and 4 mg litre^{-1} for spectrophotometric detection.

1,8-Naphthalimide derivatives can be used for both colorimetric and fluorescence determination of copper cations. Huang *et al.*[66] reported a visual detection of Cu^{2+} in aqueous solutions by 3,4-diamino 1,8-naphthalimide derivative **28**. Upon the addition of 1 equiv. of copper salt to a solution of compound **28**, the solution colour changes from orange to violet due to the bathochromic shift of the absorption maximum (from 462 to 540 nm). This pro-

Structures 27, 28



27

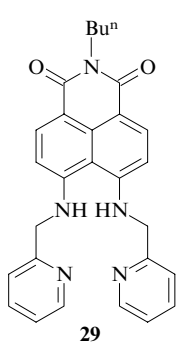


28

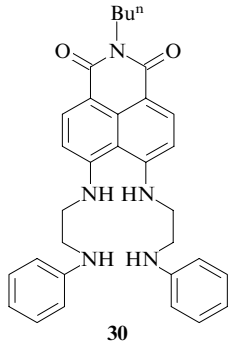
nounced change in the colour is possible because of deprotonation of the substituted amino group upon coordination to copper. The limit of detection of Cu^{2+} ions by chemosensor **28** in aqueous ethanol is 19 mg litre^{-1}.

1,8-Naphthalimide can also be utilized to design fluorescent chemosensors. Indeed, it is of interest to compare two 4,5-diamino derivatives **29** and **30**.[67,68] When **29** is complexed with copper ions, the fluorescence maximum shifts hypsochromically (from 525 to 475 nm) due to weakening of the electron-donating properties of aromatic amino groups upon coordination to Cu^{2+}. Conversely, chemosensor **30** shows a bathochromic shift of the emission band (by 74 nm) due to deprotonation of the aromatic amino groups, while the bathochromic shift of the absorption spectrum is 50 nm, which is sufficient to record the orange to red colour change.

Structures 29, 30



29

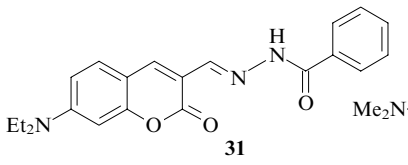


30

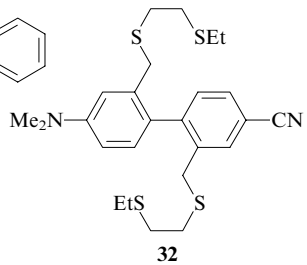
The recently discovered coumarin-based fluorescence sensor **31** serves for copper determination in a DMSO–H_2O mixture (1 : 9 by volume).[69] Free ligand has an intense emission band at 523 nm, which is quenched almost completely upon the addition of copper ions. Other cations do not interfere with the determination of copper.

An interesting example of the fluorescent chemosensor for Cu^{2+} ions is compound **32**, containing a donor–acceptor biphenyl as a fluorophore and thioether receptors.[70] On coordination to Cu^{2+} or Cu^{+}, ligand **32** undergoes substantial conformational changes, which result in a hypsochromic shift (39 nm) of the fluorescence maximum.

Structures 31, 32



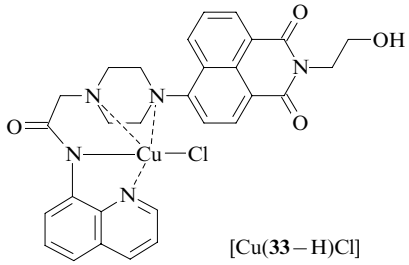
31



32

Compound **33** has two fluorophore moieties and is a highly selective ratiometric sensor for copper(II).[71] In a 35% aqueous ethanol, the ligand is responsible for two emission bands (435 and 526 nm) corresponding to the aminoquinoline and aminonaphthalimide moieties, respectively. The addition of copper cations does not change the emission intensity at 435 nm but decreases the emission intensity at 526 nm. Nevertheless, the authors suppose that the Cu^{2+} coordination involves the aminoquinoline and piperazine moieties.

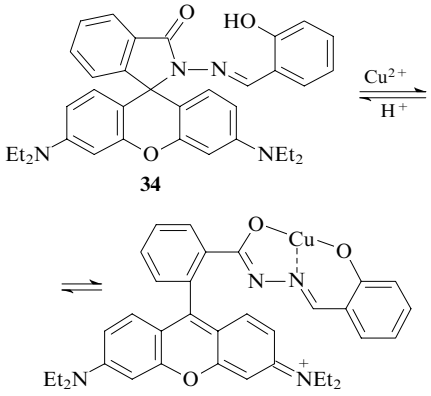
Structure of the complex [Cu(33 – H)Cl]



[Cu(**33** – H)Cl]

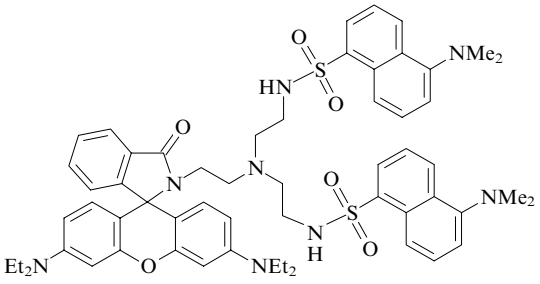
Compound **34** based on rhodamine hydrazone can serve as a multisignal chemosensor for Cu^{2+} in a H_2O–MeCN mixture (1 : 1, pH 7).[72] Using this detector, determination is possible by either spectrophotometry or fluorescence spectroscopy. Compound **34** itself does not absorb in the visible region and does not fluoresce. The addition of Cu^{2+} leads to the opening of the spirolactam ring, the equilibrium being shifted towards the rhodamine open form, and this brings about solution colour and fluorescence. The absorption band maximum of complex **34** with Cu^{2+} ions is at 520 nm and the emission band maximum is at 585 nm. It is noteworthy that the ring opening is reversible (Scheme 4), and chemosensor **34** can be isolated in the cyclic form after acidification of the solution. This ligand serves for determination of micromolar concentrations of copper ions and shows good selectivity in the presence of many biologically significant metal ions.

Scheme 4



The same principle, namely, the opening of the spirolactam ring is made use of an unusual chemosensor **35**[73] in which three fluorophores (rhodamine and two dansyl groups) are connected by the triehyleneamine nucleus. In the free ligand, the spirolactam rhodamine form does not absorb in the visible region, and irradiation at 420 nm gives rise to an emission band with a 507 nm maximum corresponding to fluorescence of the dansyl groups. When Cu^{2+} ions are added to a solution of compound **35** [MeCN–H_2O (9 : 1), pH 7], red colour appears due to the coordination of the copper ion by the tetraaza ligand and the opening of the spirolactam ring. Hence, the absorption spectrum of the rhodamine open form overlaps with the emission spectrum of the dansyl moiety, thus enabling the resonance energy transfer. The fluorescence maximum shifts to 580 nm, which corresponds to the fluorescence of the energy acceptor (rhodamine).

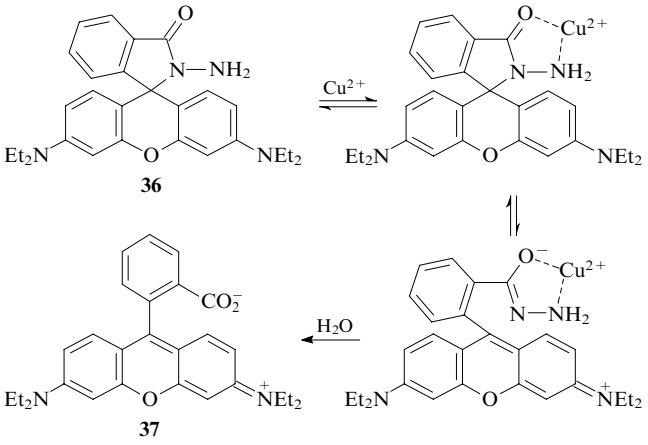
Structure 35



35

Fluorescence quenching due to the direct binding of paramagnetic Cu^{2+} ions can be avoided by using an alternative approach to detection in which copper ions serve as catalysts for hydrolysis of specific bonds, resulting in the formation of fluorescent products. In an early example described by Czarnik's group,[74] the known Cu^{2+}-catalyzed hydrolysis of α-amino acid esters was used for the design of chemodosimeter **36** — rhodamine B hydrazide. Spirolactam **36** does not fluoresce but in the presence of Cu^{2+} ions, it is hydrolyzed to fluorescent acid **37** (Scheme 5). The reaction of compound **36** with Cu^{2+} in an acetonitrile–water mixture (1 : 4 by volume) is sufficiently fast even at low Cu^{2+} concentrations. The increase in the fluorescence intensity obeys a linear dependence on the Cu^{2+} concentration, *i.e.*, this chemodosimeter can be used as ratiometric. It also proved to be highly selective with respect to copper ions in the presence of a broad range of other metal ions.

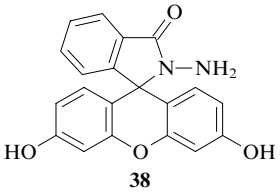
Scheme 5



36 **37**

The same principle was employed to obtain chemodosimeter **38**.[75] The replacement of the rhodamine moiety by a fluorescein moiety made it possible to determine Cu^{2+} in aqueous solutions.

Structure 38



38

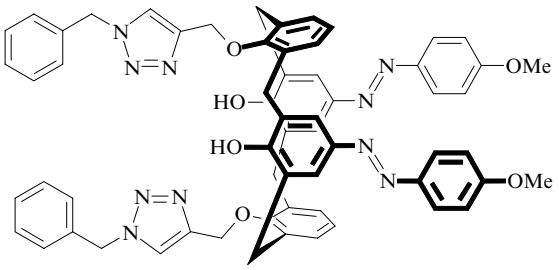
3. Detection of Pb^{2+} cations

The detection of lead is a very important task because lead is among the most toxic elements and can, in particular, be responsible for retarded intellectual development of children.[7] Lead mainly gets into the body with tap water when lead pipes are used in the water supply system; it is also a frequent pollutant of the environment as it is used in car batteries, fuel and dyes. According to WHO recommendations, the MPC of lead in potable water is 0.01 mg litre^{-1}.[40]

Since the lead ion has a large coordination number (up to 10), the formation of lead complexes requires polydentate ligands with a large number of donor groups. The synthesis of such sensors is quite cumbersome, and the structure of these molecular detectors is dictated by not only the coordination behaviour of lead but also by the synthetic possibilities. In addition, the development of highly selective chemosensors is much more difficult because polydentate ligands may prove to be effective chelators for a variety of metal cations.

Among the existing molecular sensors for detection of Pb^{2+}, compounds based on calixarenes are popular. Chang *et al.*[76] synthesized chromogene chemosensor **39** containing two triazole and two azobenzene moieties. Upon complexation with Pb^{2+}, the light-yellow solution of compound **39** becomes red due to the considerable bathochromic shift of the absorption band, thus enabling visual detection. Apart from lead ions, Ca^{2+} ions also induce colouring of solutions of chemosensor **39**.

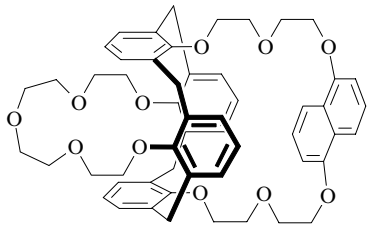
Structure 39



39

Unsymmetrical calix[4]arene-bis(crown ether) **40** has a fluorescent 1,5-dihydroxynaphthalene moiety.[77] The complex formation with Pb^{2+} results in fluorescence quenching.

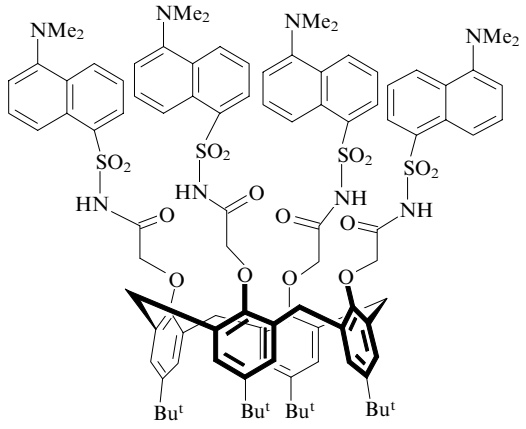
Structure 40



40

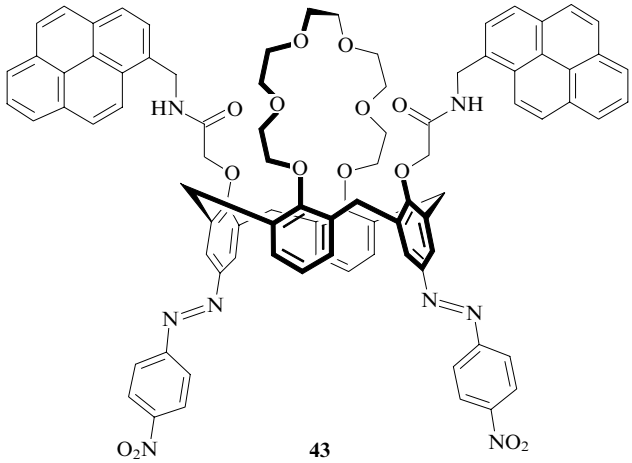
Chemosensor **41** comprising four dansyl groups shows unusually high affinity for Pb^{2+} and high selectivity to Pb^{2+} in the presence of other cations.[78] The addition of lead ions to a water–acetonitrile solution of compound **41** induces a substantial hypsochromic shift of the fluorescence maximum (52 nm) and a 1.7-fold increase in the quantum yield. This can be attributed to deprotonation of the amide groups during complex formation. Later, it has been shown that two complexes with metal to ligand ratios of 1 : 1 and 2 : 3 are formed under these conditions.[79] This restricts the interest in this ligand as a sensor.

Structure 41



41

Structure 43



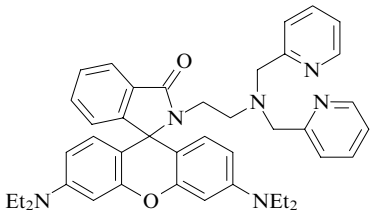
43

The operation of chemosensor **42** is based on a change in the excimer to monomer ratio upon complexation with Pb^{2+} ions.[80] A strong fluorescence band of the excimer is observed without the cation, because the two pyrene moieties are located close to each other. As Pb^{2+} is added, the excimer fluorescence is quenched due to the cation coordination to the carbonyl groups. Note that the addition of K^+ ions to the lead complex of ligand **42** restores the excimer emission, as the complex formation with K^+ results in liberation of Pb^{2+} (Scheme 6). Copper (II) ions are also coordinated to ligand **42**, thus inducing substantial spectral changes.[81] The absorption and emission spectra undergo bathochromic shifts, as Cu^{2+} is coordinated by nitrogen atoms, thus changing fluorescence by the PCT mechanism.

Compound **43** contains two pyrene and two azobenzene moieties. Its fluorescence is low as a result of effective pyrene to azobenzene energy transfer. The coordination of oxygen atoms to Pb^{2+} induces a hypsochromic shift of the long-wavelength absorption band of the diazo groups and decreases the overlap of the pyrene emission and azobenzene absorption spectra.[82] This increases the intensity of pyrene fluorescence.

As above, the principle of operation of chemosensor **44** is the opening of the spirolactam ring.[83] When Pb^{2+} is added to a solution of compound **44**, the solution becomes coloured (absorption band maximum at 553 nm) and the fluorescence intensity increases 100-fold. Similar effects were observed for Zn^{2+} but to a much smaller degree, and chemosensor **44** was evaluated as 200 times more selective for Pb^{2+} determination.

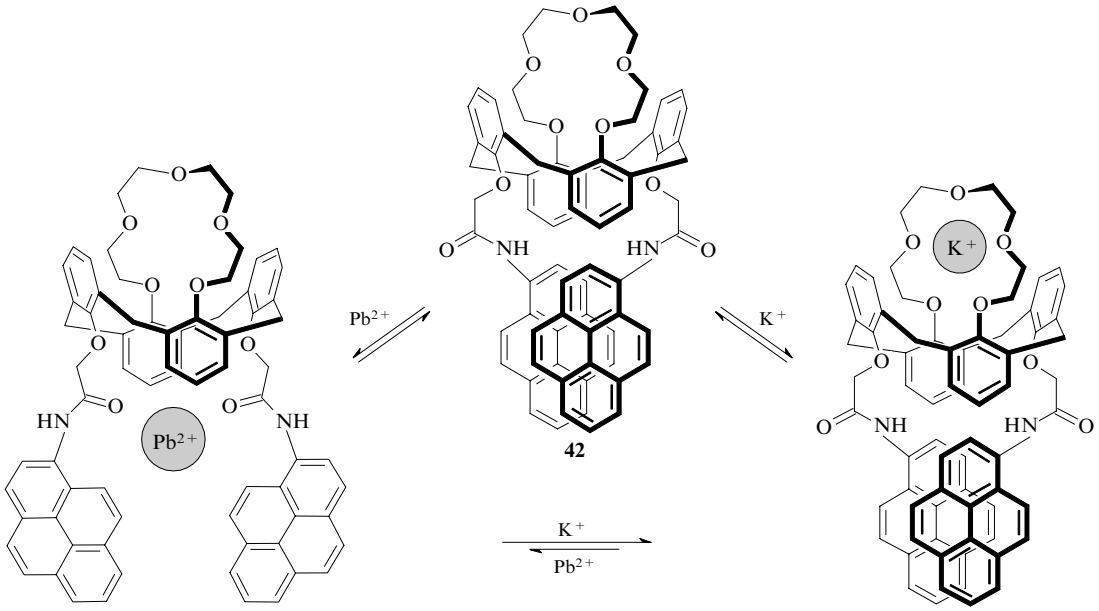
Structure 44



44

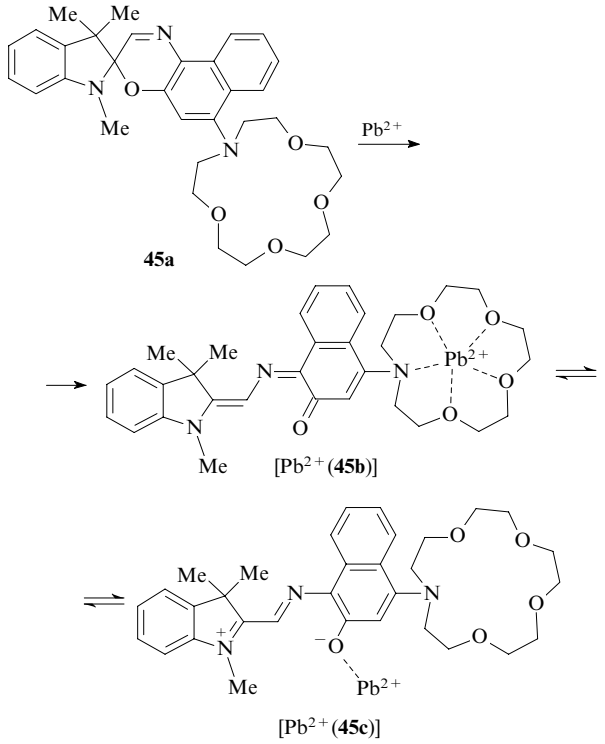
One more alternative for the opening of ring structure was reported. The coordination of compound **45a** to lead ions affords the merocyanine form of ligand **45b** (Scheme 7), which absorbs in a long-wavelength region

Scheme 6



(600 nm).[84] Form **45b** exists in equilibrium with the open betaine form **45c**.

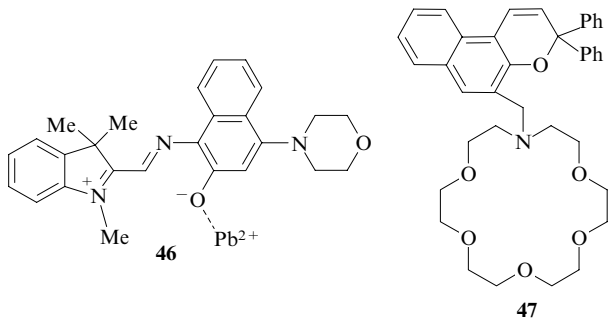
Scheme 7



It is worth noting that after the replacement of the azacrown ether moiety by a morpholine moiety, which obviously cannot coordinate Pb^{2+}, a long-wavelength absorption band (580 nm) is still observed in the presence of lead ions, thus attesting to the formation of the coloured betaine structure **46**.

The same researchers prepared a 1-aza-18-crown-6 ether derivative **47**, the absorption band of which shifts by 90 nm to longer wavelengths upon coordination with lead ions.[85]

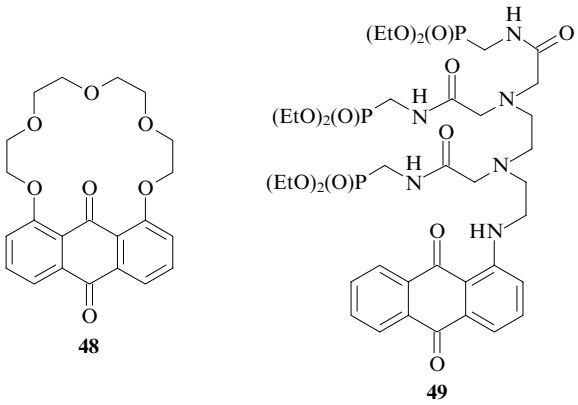
Structures 46, 47



A crown ether fused to 1,8-dihydroxyanthraquinone (compound **48**) is a fluorescent sensor for Pb^{2+} ions.[86] The complex formation changes the energy of excited states and is accompanied by a 10-fold increase in the fluorescence intensity and a 35 nm bathochromic shift of the emission band maximum.

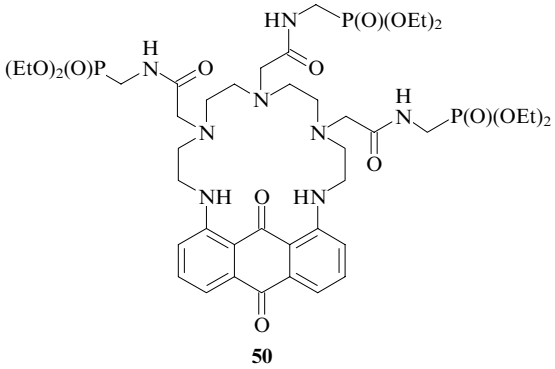
The water-soluble 1-aminoanthraquinone-based ligand **49** synthesized by our research team[62] can be used as a sensor for lead ions owing to a colour change from red to yellow-pink due to the 42 nm hypsochromic shift of the absorption band. The limit of detection is 1.3 mg litre^{-1} for naked-eye detection and 0.07 mg litre^{-1} (480 nm) for spectrophotometric detection; however, the selectivity is not sufficiently high.

Structures 48, 49



Pentaazamacrocyclic ligand **50** containing a 1,8-disubstituted anthraquinone moiety and three (diethoxyphosphoryl)methyl groups can also be used for analysis of aqueous solutions and is more selective than open-chain analogue **49**.[87] The macrocycle gives the absorption maximum at 570 nm, which is responsible for the blue colour of its aqueous solutions. The addition of 1 equiv. of Pb^{2+} ions causes the appearance of pink colour as a result of a 45 nm hypsochromic shift.

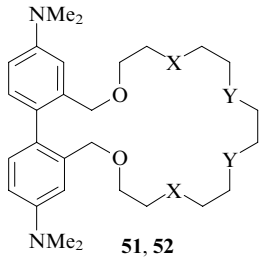
Structure 50



Costero *et al.*[88] studied the complex formation of 4,4′-bis(dimethylamino)biphenyl derivatives with various metal ions. It was found that diazacrown ethers **51** and **52** can produce a pronounced fluorescent response to the complex formation with Pb^{2+} due to a 50 nm bathochromic shift of the emission band maximum. However, these compounds form stable complexes with many transition metals, which precludes their use as chemosensors for lead ions.

Compound **26**, which is a chemosensor for copper ions, has low sensitivity to the presence of lead ions. Meanwhile, a close analogue of this macrocycle, compound **53** , behaves in a different way: after the addition of a small amount of lead ions, the fluorescence intensity decreases, and the band maximum remains invariable. At higher metal concentration, the fluorescence is enhanced and the maximum shifts to shorter wavelengths.[64] The authors attributed these findings to the fact that an aggregate containing several betaine molecules is first formed, and at higher concentra-

Structures 51, 52



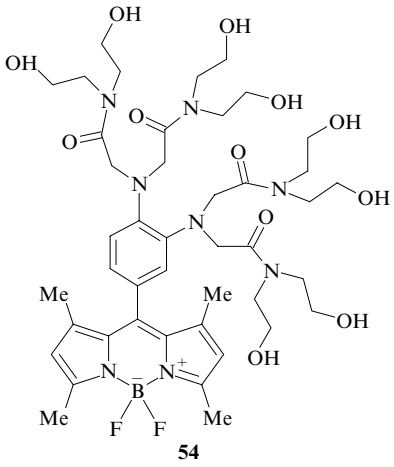
51, **52**

X = NMe, Y = O (**51**);
X = O, Y = NMe (**52**)

tions of lead ions, the complex **53**: Pb^{2+} = 1 : 2 is formed (Scheme 8).

Chemosensor **54**, which contains the signalling BODIPY moiety and an intricate receptor comprising amine, hydroxy and amide donor groups, is also suitable for analysis of aqueous samples. The free ligand absorbs at 497 nm and does not fluoresce due to fluorescence quenching by the PET mechanism. Upon complexation with lead ions, the absorption maximum almost does not change; however, emission at 510 nm appears.[89] This ligand having 12 donor groups forms a complex with a ligand to metal ratio of 1 : 2.

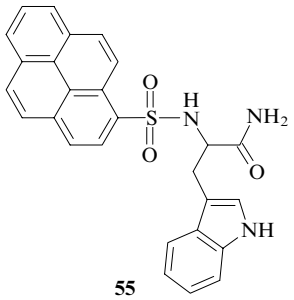
Structure 54



54

The pyrene-containing chemosensor **55** is used for detection of lead cations in water owing to the increase in the fluorescence intensity (by a factor of 7 upon the addition of 25 equiv. of metal ions).[90] Irradiation at 342 nm of the solution being analyzed induces emission at 378 and 395 nm. Other metal cations do not interfere with lead determination. However, although no marked emission enhancement in the UV region occurs upon the addition of a mercury salt, emission at 475 nm caused by excimer formation is observed. Thus, this chemosensor is suitable for both lead and mercury determination.

Structure 55



55

4. Detection of Cd^{2+} cations

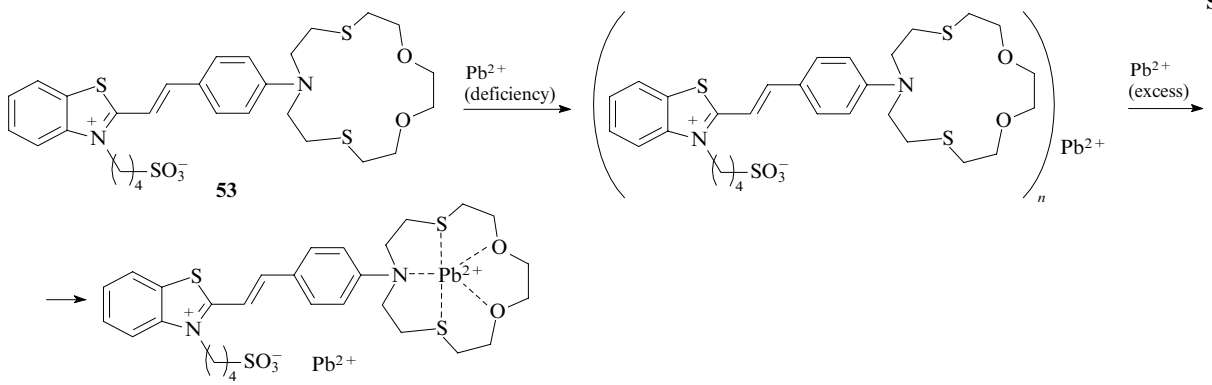
Cadmium is a heavy metal widely used in industrial production. Due to man-made pollution, cadmium can be found in air, water and plants. The main source of cadmium in the body is food. Potable water may contain cadmium as it is present as an impurity in zinc and other metals used in water supply systems. For potable water, the MPC of cadmium is 0.003 mg $litre^{-1}$.[40] There are rather few examples of effective optical chemosensors for cadmium ions. Zinc ions often interfere with determination of cadmium, because the coordination properties of these two ions are similar. The search for selective receptor groups is especially topical in this field. For example, compound **56** based on calixarene proved to be selective to Cd^{2+} and Zn^{2+} ions as compared with other cations.[91] The excimer fluorescence quenching can be used for ratiometric measurement of both cations; however, it is impossible to discriminate cadmium and lead using this ligand.

Note that related chemosensor **57** proved to be somewhat more selective to Cd^{2+}.[92] The complexation with Cd^{2+} decreases the pyridyltriazole fluorescence intensity and gives rise to a band with a maximum at 480 nm corresponding to the formation of excimers. It was demonstrated that two complexes with metal to ligand ratios of 1 : 1 and 2 : 1 are formed.

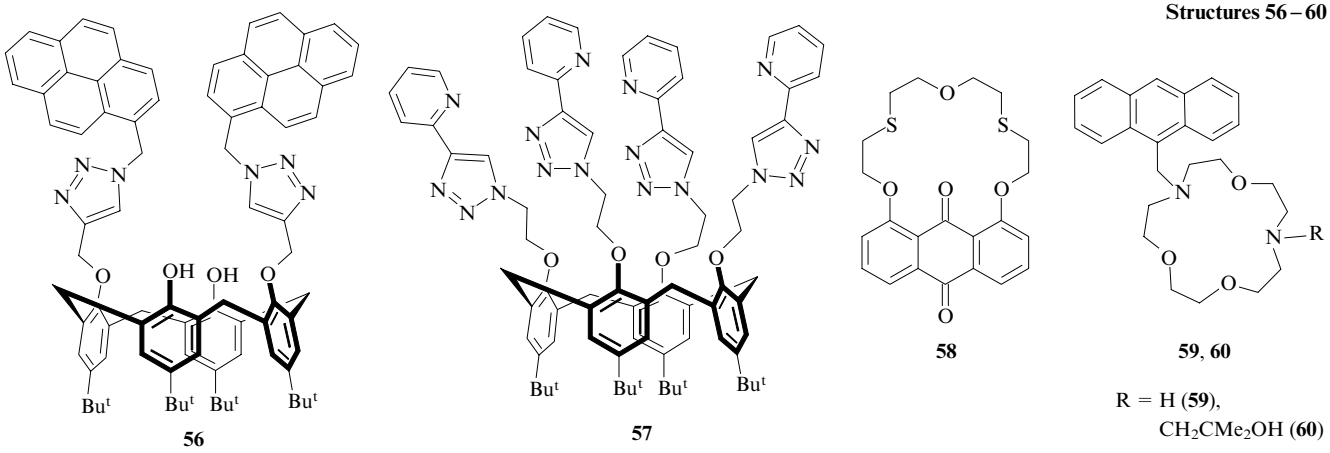
Dithiacrown ether based on 1,8-dihydroxyanthraquinone **58** is suitable for selective detection of Cd^{2+} and Hg^{2+} ions based on the increase in the fluorescence intensity.[93] This compound gives no response in the presence of Zn^{2+} but cadmium determination is still interfered with by mercury.

The intensity of fluorescence of diazacrown ethers **59** and **60** increases due to the PET effect only in the presence

Scheme 8



Structures 56–60



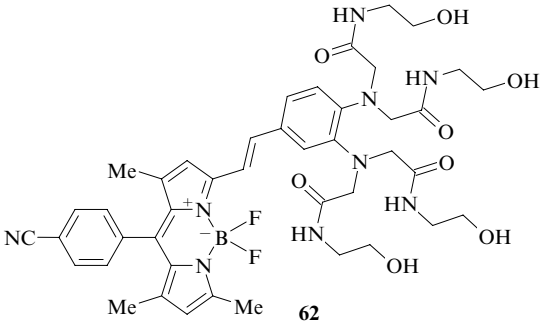
56 **57** **58** **59**, **60**

of Cd^{2+}, although they form stable complexes also with other cations, in particular, with Zn^{2+}.[94]

The use of crown ether fused to a conjugated system of bonds for the design of promising sensor **61** for cadmium ion has been reported.[95] This compound comprises two potential ionophores — the macrocycle and the *exo*-pyridine nitrogen atom. Cadmium ions are coordinated initially only to the pyridine nitrogen atom; this gives the complex $[Cd^{2+}(\mathbf{61})_2]$, which is converted to $[Cd^{2+}(\mathbf{61})]$ on further addition of cadmium cations (Scheme 9). The free ligand has a fluorescence maximum at 430 nm, while the coordinated species absorb at about 500 nm.

Cheng *et al.*[96] synthesized chemosensor **62** containing a polyamide receptor based on *o*-phenylenediamine. The

Structure 62



62

complex formation with Cd^{2+} induces a considerable fluorescence enhancement (by a factor of almost 200) without a change in the position of the emission band maximum. This ligand forms a complex with a metal to ligand ratio of 2 : 1 and serves as a highly sensitive and selective sensor for cadmium. Note that the ionophore structure in chemosensor **62** is identical to the structure of the receptor group in detector **54**, which has been proposed for selective determination of lead cations. The causes for this change in the selectivity upon replacement of the signalling group which is not involved in the metal coordination remain obscure.

5. Detection of Hg^{2+} cations

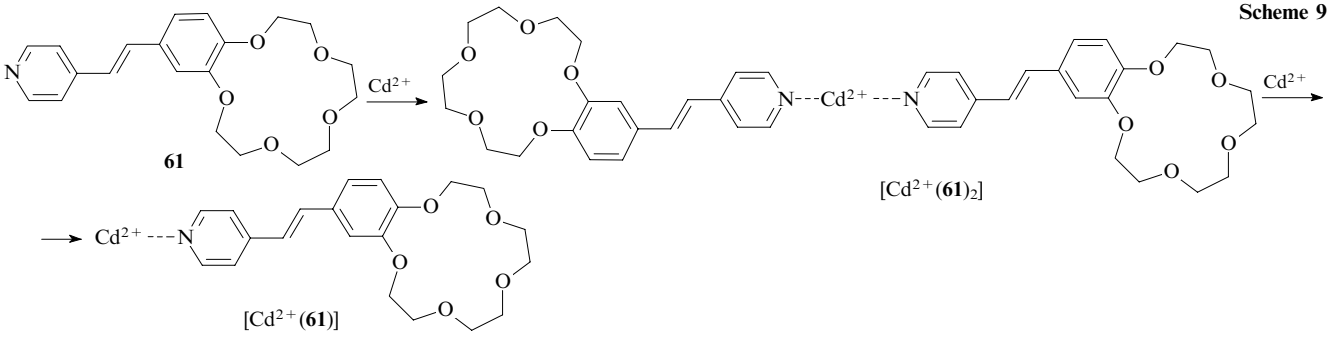
Mercury is one more highly toxic metal having adverse impact on the environment and human health. Therefore, the Hg^{2+} contents in food, water and the environment must be strictly controlled.

The detection of mercury ions is substantially facilitated by its specific coordination properties: selective complex formation can be easily achieved by using soft donor groups. Lots of molecular detectors for Hg^{2+} ions have been developed in recent years.[97] We will give a few examples.

Azobenzene derivative **63** contains two amino groups able to be coordinated to Hg^{2+}. This coordination gives rise to a metal-induced intramolecular charge transfer where the free amino group serves as the electron donor. As a consequence, the addition of Hg^{2+} to a solution of compound **63** in acetonitrile induces a 100 nm bathochromic shift of the absorption maximum and red colouring of the solution. The colour change is specific to Hg^{2+} ions.[98]

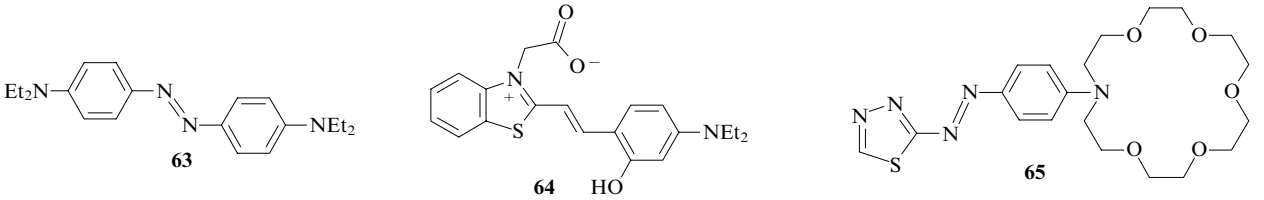
Hemicyanine dye **64** comprising an aniline electron-donating group and a benzothiazolium electron-withdrawing group can be used to perform selective colorimetric detection of Hg^{2+} in aqueous solutions at neutral pH.[99] The addition of Hg^{2+} to ligand **64** leads to a hypsochromic shift of the absorption band and a change of the solution colour from pink to green. In addition, mercury ions cause the quenching of fluorescence of dye **64**.

Scheme 9



61 $[Cd^{2+}(\mathbf{61})_2]$ $[Cd^{2+}(\mathbf{61})]$

Structures 63–65



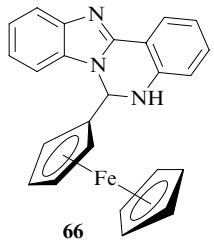
N-Aryl dithiaazacrown ether derivatives **26** and **53**, which are considered above as sensors for copper and lead ions, can also be used to determine mercury ions, as their coordination to mercury is followed by a large hypsochromic shift of the chromophore absorption band (by 135 and 130 nm, respectively). Copper coordination to ligand **26** leads to a 62 nm hypsochromic shift, while in the case of ligand **53**, only the fluorescence spectrum changes.[64] The dimeric and monomeric complexes occur in equilibrium (Scheme 10), the absorption maximum of the dimeric complex being at 470 nm and that of the monomeric complex being at 396 nm due to differences in mercury coordination.

Yet another colorimetric sensor is the thiadiazolyl 1-aza-18-crown-6 ether derivative **65**.[100] This ligand can detect mercury cations in water because upon complex formation, the absorption band maximum of free ligand at 491 nm decreases and two closely speced bands at 536–574 nm appear. This sensor can also be used to detect lead: in this case, complexation gives rise to an absorption band at 378 nm, the solution colour being changed from orange to pale yellow.

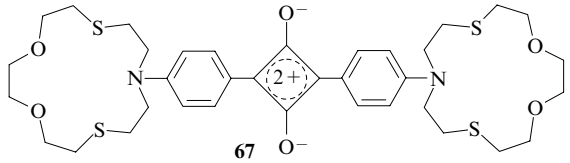
Colorimetric and fluorescent multisignal sensor **66** is devoid of a macrocyclic moiety.[101] It was shown that this ligand is suitable for determination of mercury and lead ions in 50% aqueous ethanol. After the addition of Hg^{2+}, the almost colourless solution becomes dark-red, while after the addition of Pb^{2+}, the solution becomes light-green. Other metals do not exert such influence on the solution colour, although the addition of copper induces a light-brown colour. It was found that the metal to ligand ratio in the mercury complex of this ligand is 1 : 1, while that in the lead complex is 1 : 2. The complex formation affects also the fluorescence of compound **66**: the addition of 7 equiv. of mercury cations decreases the fluorescence intensity by 72%, while the addition of 10 equiv. of lead cations increases the intensity by 16%.

In some colorimetric sensors, the chromophore is represented by squaraine, which has high absorption in the visible and near-IR spectral regions. A solution of chemosensor **67** in a acetonitrile–water mixture (1 : 4) is coloured violet. Coordination to Hg^{2+} violates the charge delocalization in the chromophore, and the solution becomes colourless.[102] The addition of Ag^{+} ions induces a colour change to green.

Structure 66

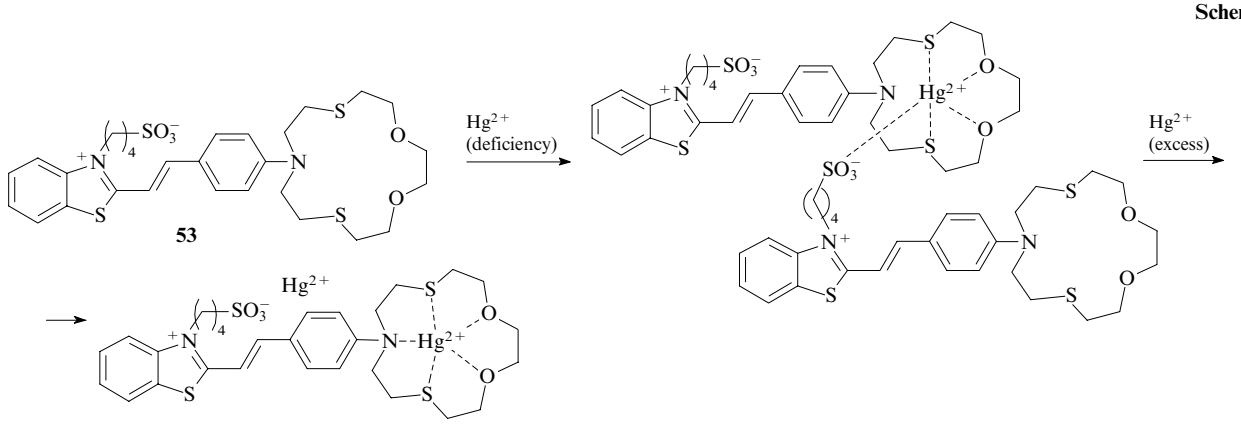


Structure 67



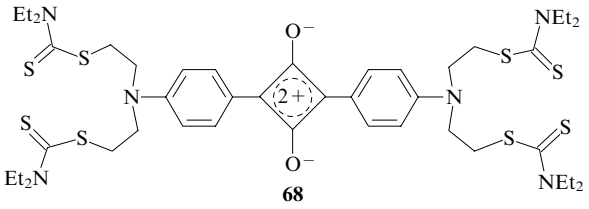
In the case of chemosensor **68** based on squaraine, a colour change from violet to blue was observed for its solution in an AcOH–H_2O mixture (2 : 3 by volume) upon the addition of Hg^{2+} ions.[103] This is explained by the fact that at a relatively high water content in the solvent mixture, squaraine forms aggregates, and the monomer absorption band at 640–650 nm disappears to be replaced by an absorption band for the aggregate, which is shifted by ~100 nm to the blue region. The addition of Hg^{2+} leads to deaggregation of the dye molecules giving rise to an absorption band with a maximum at 636 nm. In addition,

Scheme 10



a 700-fold enhancement of fluorescence is observed. The complex thus formed was found to have a metal to ligand ratio of 2 : 1, each mercury cation being coordinated to four sulfur atoms.

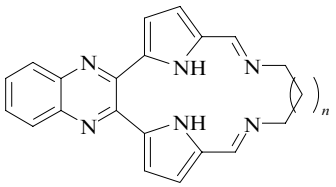
Structure 68



68

The fluorescence of dipyrolylquinoxaline macrocycles **69a**,**b** in aqueous solutions is quenched by the addition of Hg^{2+} ions.[104, 105] Both macrocycles show fluorescence maxima at 506 nm, and mercury coordination induces a hypsochromic shift to 460 nm and a 4- and 8-fold decrease in the fluorescence intensity, respectively. This response of chemosensors **69** is specific to Hg^{2+}, and the presence of other cations does not affect the optical response.

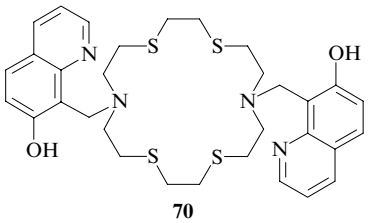
Structures 69



69a,**b** $n = 1$ (**a**), 2 (**b**)

Ho *et al.*[106] synthesized tetrathiadiazacrown ether **70**, which contains two 7-hydroxyquinoline moieties. The complex formation with Hg^{2+} causes a hypsochromic shift of the long-wavelength absorption maximum from 403 to 352 nm and the intensity of the emission band at 520 nm increases 25-fold. This response to Hg^{2+} ions is selective and is not affected by the presence of other cations.

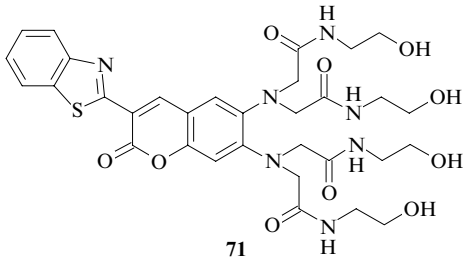
Structure 70



70

Fluorescent sensor **71** containing a coumarin fluorophore is suitable for ratiometric determination of Hg^{2+} in neutral aqueous solutions.[107] Indeed, the coordination of Hg^{2+} results in a considerable hypsochromic shift of the emission band maximum (from 567 to 475 nm), and the change in the fluorescence intensity ratio at these wavelengths ensures an almost 30-fold ratiometric response. Chemosensor **71** can be also used as a colorimetric one owing to the 50 nm hypsochromic shift of the absorption band maximum. The researchers[107] assume that compound **71** forms a 1 : 1 complex with Hg^{2+} in which the cation has a tetrahedral environment composed of two amine nitrogen atoms and two deprotonated amide nitrogen atoms. It is worth noting that today chemosensor **71** demonstrates the best ratiometric response to the presence of Hg^{2+} ions;[8] moreover, the determination of mercury is not interfered with by the presence of 20 equiv. of common transition metals.

Structure 71

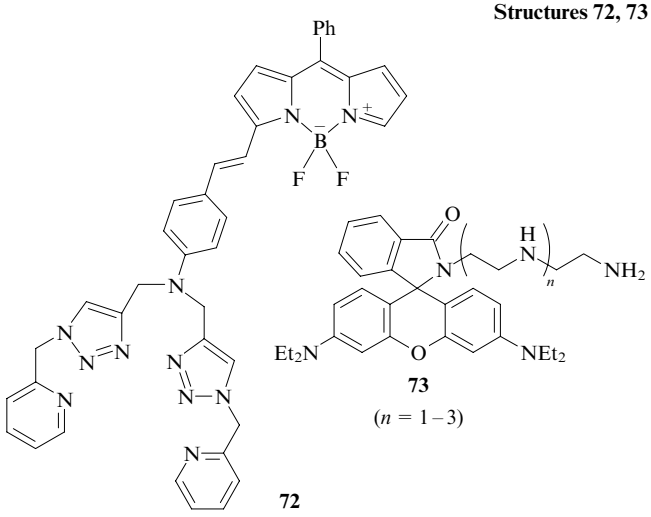


71

Multisignal colorimetric and fluorescent sensor **72** for mercury cations was developed based on a BODIPY derivative.[108] The coordination of mercury results in a hypsochromic shift of the absorption band from 606 to 577 nm caused by the inhibition of the intramolecular charge transfer from nitrogen to the BODIPY moiety, inducing blue to purple change in the solution colour. The complex formation with mercury also increases the fluorescence intensity at 650 nm (by a factor of 65 upon the addition of 1.5 equiv. of the metal cations).

Sensor **73** with a rhodamine signalling group almost does not fluoresce in the free state (*cf.* analogous sensors described above), and after the addition of mercury ions, ring opening occurs to give the acyclic amide form, resulting in a 350-fold fluorescence enhancement (band maximum at 580 nm).[109] Copper(II) cations induce a similar response but the sensitivity to mercury is 300 times higher.

Structures 72, 73

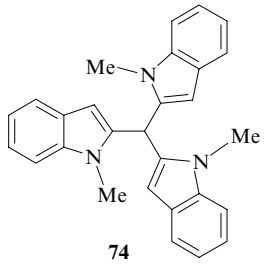


73 ($n = 1–3$)

72

Tris(*N*-methylindol-2-yl)methane (**74**) also proved to be an effective sensor for ratiometric determination of mercury ions.[110] The free ligand has an emission band at 500 nm; the addition of mercury results in a regular weakening of this band and the appearance of a band at 570 nm. The intensity ratio depends on the amount of mercury added. The addition of copper cations quenches the fluorescence of chemosensor **74**. In both cases, 1 : 1 complexes are formed. Other metals do not affect the fluorescence of compound **74**.

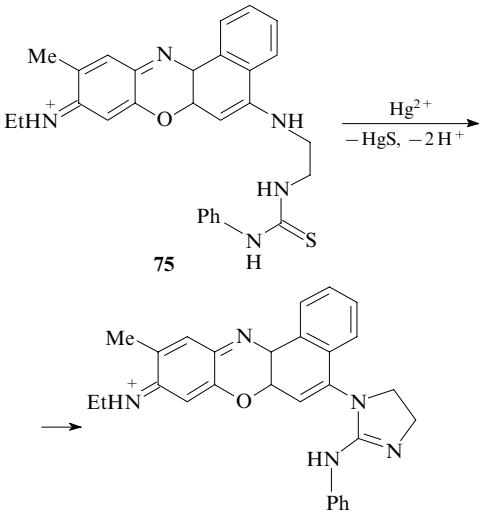
Structure 74



74

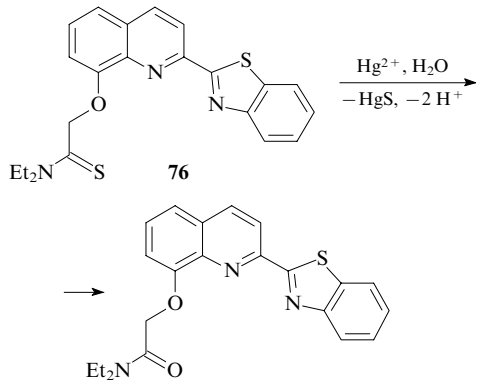
The chemodosimetric approach is used rather often to detect mercury cations, because Hg^{2+} ions can participate in some specific reactions. Lee *et al.*[111] developed a derivative of the Nile blue dye **75** for selective and highly sensitive determination of Hg^{2+} in aqueous solutions. Compound **75** proved to be efficient for both colorimetric and fluorimetric detection over a broad pH range (2–9). The operation of this dosimeter is based on the conversion of the thiourea moiety to a cyclic guanidine derivative (Scheme 11). The solution colour turns from blue to red and the fluorescence maximum undergoes a hypsochromic shift from 652 to 626 nm.

Scheme 11



One more relevant reaction involving Hg^{2+} is the transformation of thiocarbonyl compounds to carbonyl compounds (Scheme 12). The thioamide group in chemodosimeter **76** quenches the fluorescence of the hydroxyquinoline moiety. Upon the addition of 1 equiv. of Hg^{2+} to a water–acetonitrile solution of compound **76**, the intensity of fluorescence with a maximum at 479 nm increases 170-fold.[112] Other cations almost do not enhance the fluorescence; however, Cd^{2+} and Ag^{+} decrease the fluorescence intensity in the **76**–Hg^{2+} system by 10%.

Scheme 12



V. Synthetic approaches to molecular detectors

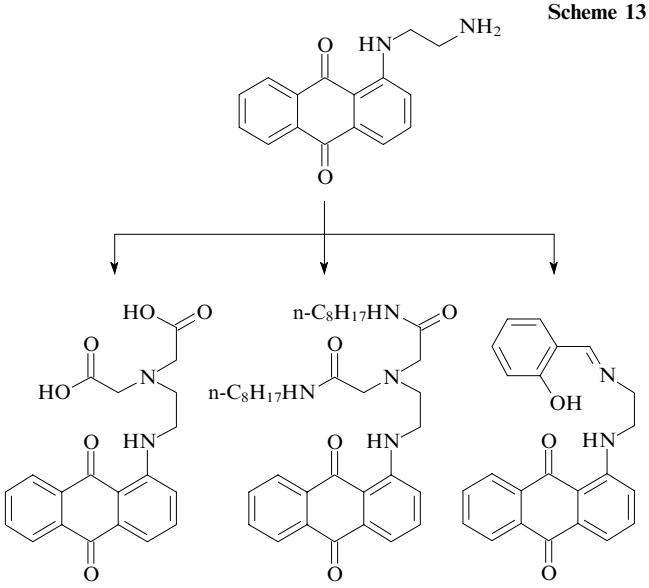
The previous Section presents examples of molecular sensors used to detect metal cations. These examples are only a minor portion of the whole diversity of sensors known to date. The development of a sensor starts with the synthesis, and this stage often determines the success of the whole project. Since the structures of molecular detectors are fairly complex and, as a rule, they comprise a signalling group and numerous electron-donating groups, the synthetic routes include many stages and make use of various methods of organic chemistry. Perhaps, only syntheses of natural compounds and pharmaceutical agents employ an equally broad range of synthetic methods. Almost all new reactions find use in this field. We will mention only some most popular and general approaches and give examples of application of reactions catalyzed by transition metal complexes.

The most facile and widely used method for the synthesis of molecular sensors is covalent bonding of a known ionophore and signalling group into a single molecule. This can be done by linking these moieties either directly or *via* some spacer, either an aliphatic or conjugated group. Most often, classical methods of organic chemistry are used such as nucleophilic and electrophilic substitution and addition. Compounds with a variety of functional groups are used for this purpose: amines, alcohols, thiols, carbonyl compounds and carboxylic acid derivatives. The overall yield of the desired product upon a multistage synthesis required to obtain sophisticated molecules can be moderate, which substantially complicates the search for effective molecules.

Polyamines are convenient for the design of the ionophore moiety of chemosensors. By means of N-functionalization of amino groups, it is easy to increase the number of donor atoms in the ligand and adjust the ligand structure to the coordination properties of an analyte. This approach was used to synthesize many detectors. Alkylation and the Michael reaction are most useful in these synthetic charts. For example, N-alkylation can be performed for halides containing acid, ester, amide and pyridine groups. Thus, it is possible to obtain a set of potential chemosensors by functionalization of one starting polyamine. For example, colorimetric chemosensors for Cu^{II} and Ni^{II} ions were obtained by modification of 1-(2-aminoethylamino)anthraquinone (Scheme 13).[61, 113]

The 'click-chemistry' techniques popular in recent years are also useful for the synthesis of chemosensors, because two parts of a chemosensor can thus be linked under mild conditions and in high yield. For example, it enables fast synthesis of libraries of potential sensors by a single reaction using a set of different receptor and signalling subunits. This procedure was used[114] to search for a fluorescent sensor for the protein hydrolysis enzyme by functionalization of oligopeptide by various available fluorophores (Scheme 14).

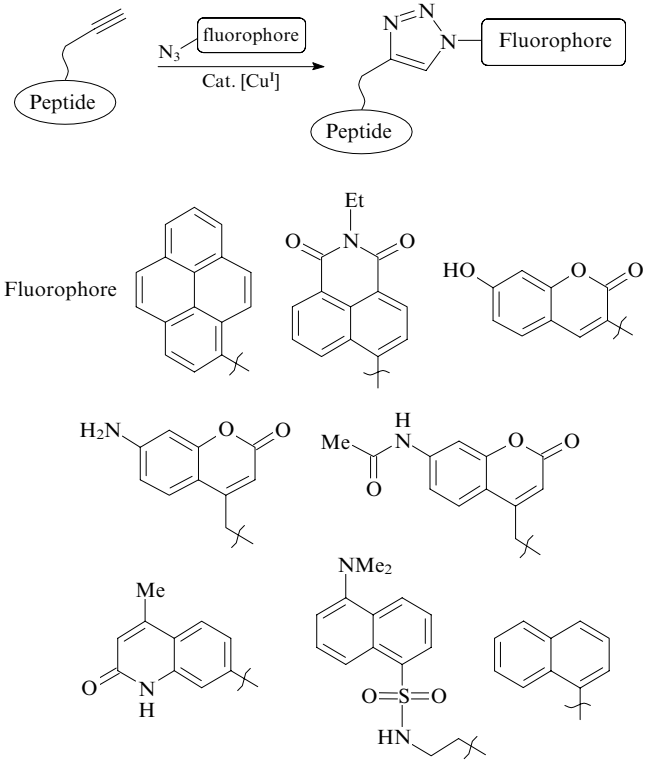
Scheme 13



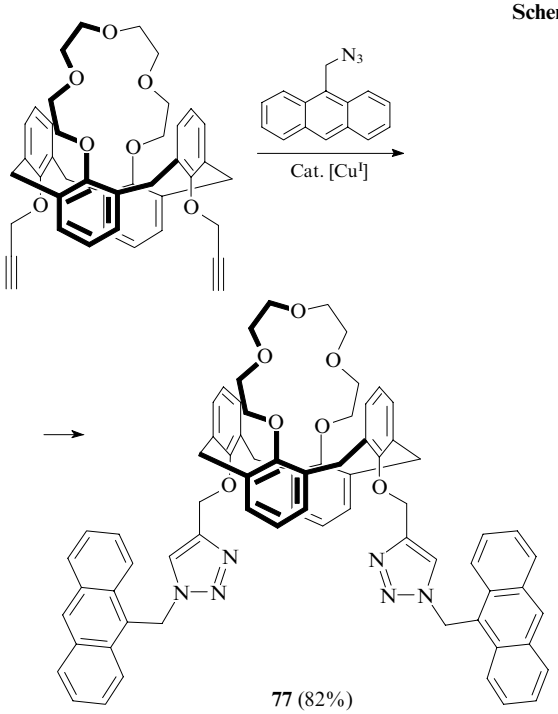
When using this approach, one should bear in mind that triazole is a good donor group for metal cations; therefore, it can considerably change the complexing properties of the receptor moiety being introduced. For example, fluorescence of chemosensor **77** obtained by Scheme 15 is quenched by Hg^{2+}, Cu^{2+}, Cr^{3+} and Pb^{2+} ions coordinated by two triazole moieties.[115]

Palladium-catalyzed amination of aryl halides is of obvious interest for the synthesis of chemosensors, as almost all currently applied signalling groups are aromatic compounds. This reaction was used for the synthesis of chemosensors **78**–**80** containing azacrown-ether and anthracene moieties (Scheme 16).[116, 117] The introduction

Scheme 14



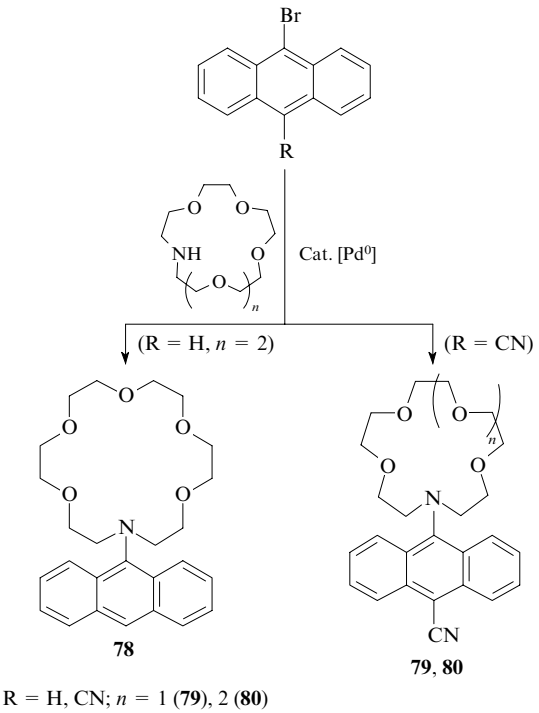
Scheme 15



77 (82%)

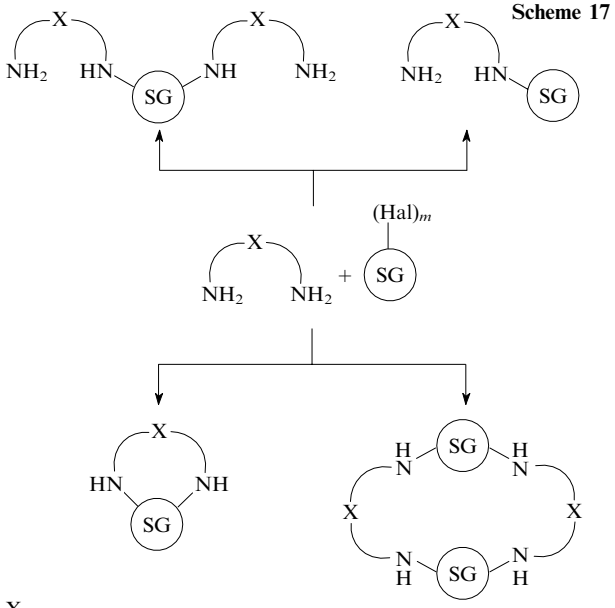
of a donor nitrogen atom gives rise to an intramolecular charge transfer band in the absorption and fluorescence spectra of these ligands. This band completely disappears upon protonation of the nitrogen atom. The addition of alkali metal ions affects the band intensity in different ways. The addition of Na^+ ions to a solution of ligand **80** in acetonitrile induces an increase in the intensity of the ICT band in the absorption spectrum, while the addition of K^+ ions decreases the intensity. Note that the ligand showed higher affinity for sodium ions.[117]

Scheme 16



R = H, CN; n = 1 (**79**), 2 (**80**)

Scheme 17



X = $CH_2(CH_2NHCH_2)_nCH_2$, $CH_2(CH_2CH_2NHCH_2)_nCH_2CH_2$ (n = 0–2); SG is signalling group; Hal = Cl, Br, I; m = 1, 2

Beletskaya *et al.*[118] demonstrated the possibility of selective palladium-catalyzed arylation of the primary amino group of linear polyamines without the use of protecting groups. This opens up the way to the selective functionalization of the polyamine receptor and can be used in the synthesis of detectors of diversified structures (Scheme 17).

Examples of chemosensors with the 1-aminoanthraquinone signalling group that we prepared by this reaction were discussed in the previous Section.

Thus, the design and synthesis of optical molecular sensors is an important area of modern organic synthesis and often determines the progress in this field.

VI. The use of molecular detectors in ion-selective optical chemical devices

Chemosensors and chemodosimeters are used for qualitative and quantitative determination of analytes in solutions. However, for analysis of environmental, industrial or medicinal samples in laboratory, in the field or even at home, it is more convenient to work with analytical sensor devices. Each chemical sensor device (CSD) is designed for the solution of a particular range of practical problems and functions under specified conditions. Optical chemosensors are used as operating sensing elements (OSE) in ion selective optical chemical sensor devices (OCSD).[119] For a successful solution of this problem, appropriate instrumentation, methods of chemosensor immobilization and the detecting molecule itself are selected. Thus, the efficiency of OCSD depends not only on the nature of the molecular detector but also on the engineering solution that forms the basis of device operation.[119]

The action of any OCSD is based on the physicochemical phenomena that occur between the OSE of the device and the analyte and give rise to a measurable light signal. This process can be accomplished within different engineering solutions and the molecular detector can be used either in solution or in the immobilized form.

Solutions of chemosensors can be used in flow injection analysis.[120, 121] In our opinion, most promising are microfluid instruments in which the flow rate of the reagent solution does not exceed 1 ml h^{-1}. Fluorescent chemosensors, which are distinguished by high sensitivity, selectivity and response rate, are beyond doubt most promising as OSE in these devices. For example, this method was used to determine lead ions in water by the above-described sensor **41**.[122] The chemosensor and the analyte were injected into the device through two glass microchannels. Optimization of the microcapillary length ensured the possibility of complete complexation. Fibre-optic technology was used to record the optical response of the system. The fluoroionophore was excited by using two optical fibres connected to a light emitting diode (λ = 365 nm). The chemosensor emission was recorded using an optical fibre connected to a photomultiplier.

Note that optimization of OCSD of this type is fairly complicated and requires detailed investigation of the thermodynamics and kinetics of complex formation.[123]

In most cases, chemosensors used in the OCSD are attached to a solid matrix. The solid-phase sensing elements can be used in the design of fibre optical CSD, integrated optical CSD and devices with planar sensing elements.[124] They also find use in the development of test methods of analysis and for analyte determination outside the laboratory by unskilled personnel.[125]

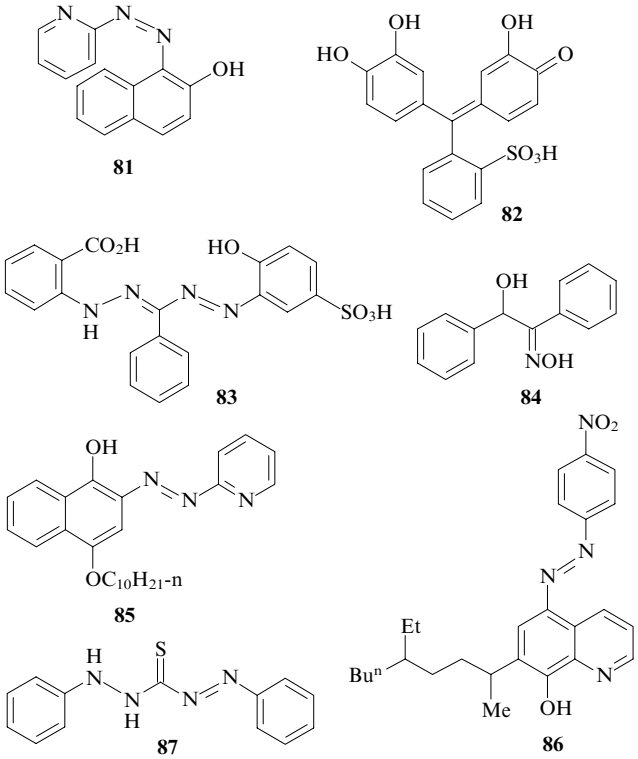
The solid-phase OSE have several obvious advantages. Their manufacture requires small amounts of reagents and they do not contaminate the analyte solution. They can be more easily embedded into existing analytical instruments and are suitable for the repeated use.

In the development of solid-phase OSE, organic and inorganic polymers are used most often as matrices. The choice of the polymer is of high importance for elaboration of effective analytical methods. The polymeric matrix not only affects the sensitivity, selectivity and the response time of OSE but can also change the optical response of the chemosensor. In ionic OCSD, preference is given to hydrophilic polymers.[126] Most often, they are used as films or membranes. However, optimized procedures for the preparation of fine polymer granules may provide even better results.[127]

An example of polymeric sensing materials is provided by films for determination of Cu^{2+} ions. They were prepared by immobilization into polymeric matrices of diverse dyes such as 1-(2-pyridylazo)-2-naphthol (**81**),[128] pyrocatechol violet (**82**),[129] zincon (**83**),[130] cupron (**84**),[131] 4-decyloxy-2-(2-pyridylazo)-1-naphthol (**85**)[132] and hydrophobic derivative of 8-hydroxyquinoline **86**.[133] The sensor material obtained by immobilization of dithizone **87** into the triacetyl cellulose membrane was most efficient.[134] The limit of detection of Cu^{2+} ions was 0.2 μmol $litre^{-1}$, the linear response being observed at copper ion concentrations from 0.83 to 16.28 μmol $litre^{-1}$. Depending on the analyte concentration, the response time was 5 to 8 min.

Most sensors based on indicator dyes are non-selective. The selectivity of determination can be increased by adding an appropriate receptor (for example, an ion exchanger). Most popular are the systems based on the simultaneous extraction and ion exchange mechanism. These sensors are composed of a receptor, a pH-indicator dye and ionic

Structures 81–87



81 **82** **83** **84** **85** **86** **87**

additives.[135–138] An alternative procedure is based on immobilization of fluorescent dyes sensitive to the potential and the ion receptors.[139,140] The use of chemosensors for the design of OSE of this type is promising for increasing the sensitivity and selectivity, extending the range of quantifiable concentrations of the analyte and optimization of analysis conditions (the choice of optimal pH, elimination of the salt effect, *etc.*). The design of OSE based on chemosensors can be performed using known procedures for the production of indicator films and membranes. As an example, consider the OSE for Hg^{2+} ions obtained by immobilization of porphyrin derivatives **88**,[141] **89**[142] and corrole **90**.[143]

Among inorganic matrices, silicate materials are used most often. For example, aluminon immobilization on silica gel particles of different diameter gave a series of materials. Finely granulated Silasorb 300 proved to be the most suitable base for the design of OSE for the determination of copper.[144]

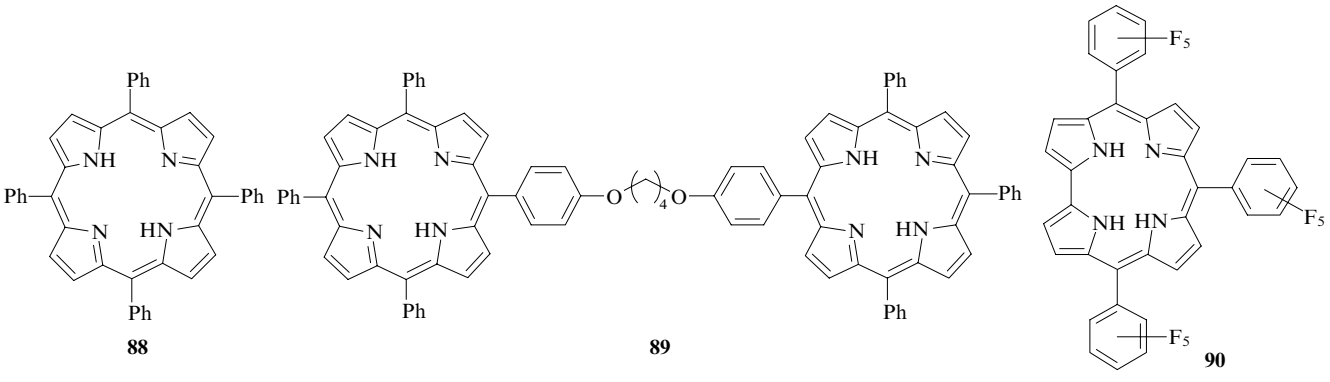
However, most of the OSE based on classical inorganic materials and polymers have inadequate sensitivity for detection of toxic metals, which are often present in the samples in trace amounts. In addition, this immobilization substantially retards the kinetics of reaction with the analyte.

Note that until recently, the attention in the development of chemical sensorics was focused on the advancing of instrumentation (invention of new types of optical fibres, miniature and cheap light sources and detectors), the use of new detection methods (for example, lifetimes in luminescent methods of analysis), *etc.*, but in recent years, more and more publications have been devoted to the development of new materials based on chemosensors. Considerable progress in the manufacture of periodically organized mesoporous materials[145] and achievements of nanotechnologies not only considerably increased the efficiency of OSE but also opened up easier ways for embedding them into already designed devices and facilitated miniaturization of OCSD. We will consider several new approaches to the design of solid-phase OSE based on chemosensors that appeared in the last decade.

In recent years, keen attention has been devoted to the manufacture of multilayer materials suitable for the use in OCSD. Highly sensitive OSE can be produced by the formation of monolayers of optical chemosensors on a liquid and solid surface by the Langmuir[146] or the Langmuir–Blodgett method.[147] For example, copper ions can be detected by multilayered sensors manufactured by the Langmuir–Blodgett method using 8-aminoquinoline derivative **91**[148] or lipid **92**.[149]

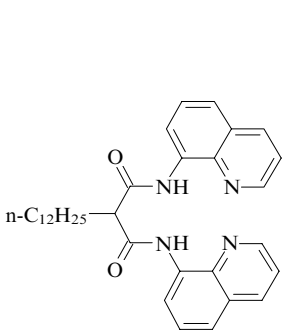
Note that both the complexing properties of the receptor group and the optical characteristics of the chemosensor signalling group may considerably change in the case where an analyte is detected in a monolayer. This imposes additional requirements on the selection of the molecular chemosensor and complicates the development of effective monolayer OSE. For example, chemosensor **93** can be used for determination of mercury ions in chloroform and acetonitrile.[150] However, the monolayer formed from **93** on the surface of deionized water is able to detect mercury ions only if the surface pressure does not exceed 4–6 mN m^{-2}. At higher pressure, the aggregation of chemosensor molecules leads to the loss of complexing properties. It is of interest that the behaviour of the monolayer depends on whether the aqueous subphase contains alkali or alkaline earth metal ions, which do not form stable

Structures 88–90

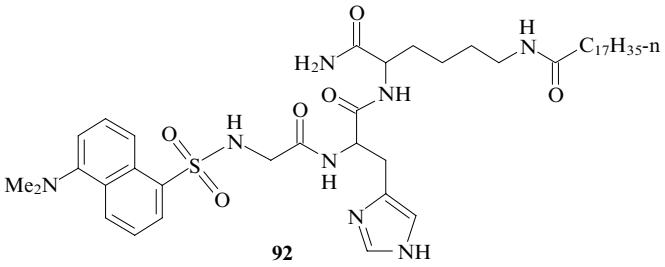


88 **89** **90**

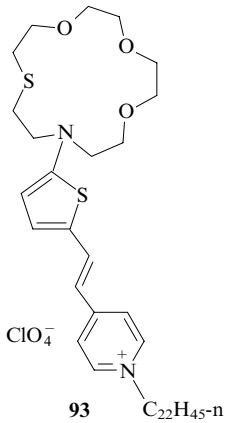
Structures 91–93



91



92



93

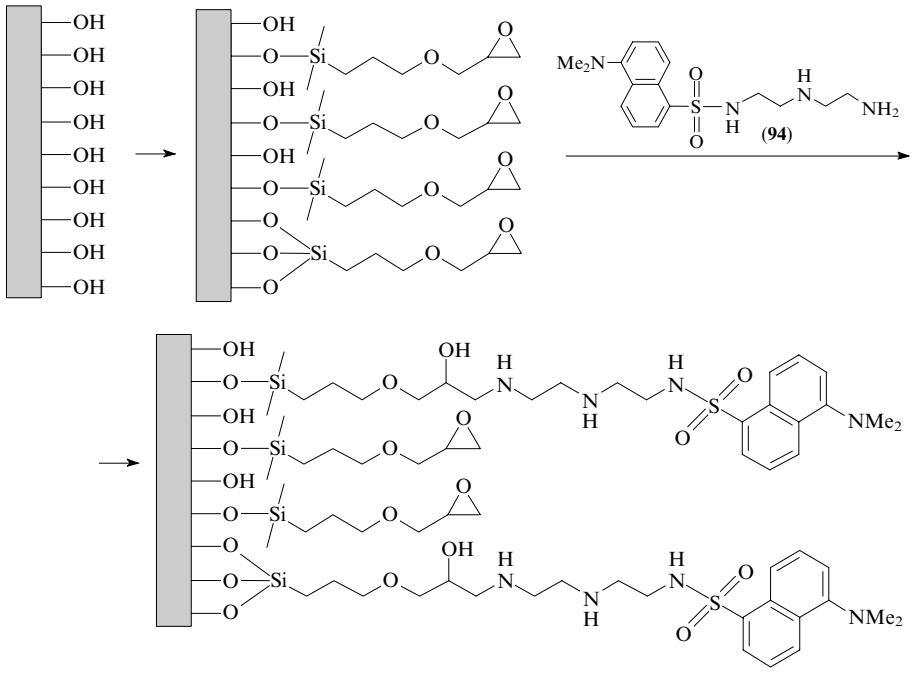
complexes with ligand **93** but affect the aggregation of the ligand molecules in the monolayer.

The monolayers obtained by the Langmuir–Blodgett method are thermodynamically unstable and are easily destroyed under the action of external factors. Therefore, the technique of self-assembling monolayers is more promising for the design of effective OSE.[151,152] Of principal importance in the development of this field were studies demonstrating the possibility to manufacture a self-assembling monolayer of a fluorophore on the surface of glass that does not quench fluorescence.[153] More recently, a selective chemosensor based on calixarene was covalently bonded to the monolayer self-assembled on the glass surface and used to determine Na^+ ions in methanol.[154] Two-dimensional self-assembling materials on the glass surface are manufactured most often using the sol–gel process. This ensures covalent binding of the chemosensor to either the glass surface or a linker pre-organized as a monolayer. The latter technique is much more convenient for the synthesis of chemosensors functionalized by an additional group, which is necessary for the manufacture of a covalently bonded monolayer.

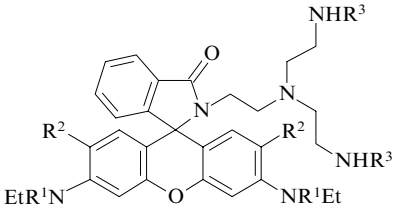
A self-assembled fluorescent film for detection of copper ions was obtained by immobilization of dansyl chemosensor **94** on the surface of a glass plate.[155] For this purpose, the glass surface was modified by a self-assembled monolayer containing an epoxide group. The reaction of this film with chemosensor **94** gave a fluorescent film (Scheme 18). Fluorescence measurements have shown that using this film, Cu^{2+} ions can be determined in the presence of Pb^{2+}, Zn^{2+}, Ni^{2+} and Co^{2+} ions. The sensitivity of determination was high (detection limit of 7.6×10^{-5} mol litre^{-1}), and the fluorescent film could be regenerated several times, which makes it suitable for determination of copper(II) ions in waste waters of production plants and in contaminated soils.

A monolayer of chemosensor **95** on the surface of glass plates modified by *N*-hydroxysuccinimide was obtained for detection of lead ions in acetonitrile.[156] The limit of detection of Pb^{2+} by this highly selective OSE is 10^{-4} mol litre^{-1}. Furthermore, it can be regenerated by washing with a 0.1 M NaOH solution and used in several successive determinations.

Scheme 18



Structures 95, 96



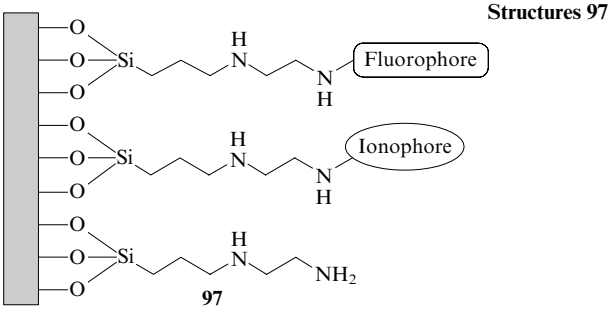
95, **96**

95: $R^1 = R^3 = H$, $R^2 = Me$;
96: $R^1 = Et$, $R^2 = H$, $R^3 = C(O)(CH_2)_5SH$

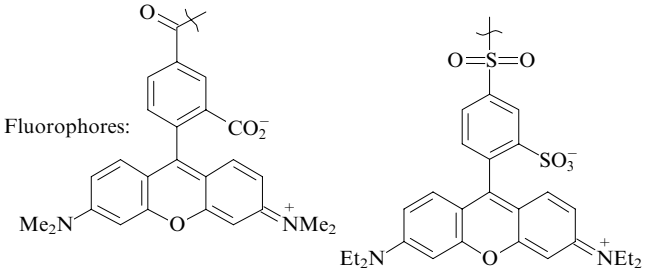
Recently, it was demonstrated that Cu^{2+} ions can be detected by a monolayer of chemosensor **96** deposited on an ultrathin platinum film attached to glass.[157] Unlike films on the glass surface, this was a classical monolayer, *i.e.*, it was attached to the surface without forming covalent bonds. These films are not destroyed in alkaline media due to hydrolysis of the Si–O bonds. It is of interest that whereas chemosensor **96** detects Cu^{2+} ions only in organic solvents and cannot be used in water–methanol solutions, the fluorescent monolayer can be used to detect Cu^{2+} in aqueous solutions with a concentration of 10^{-5} mol litre^{-1}. It can be readily regenerated by washing with aqueous NaOH.

Detection by a two-dimensional self-assembled fluorophore monolayer has a number of significant advantages over chemosensor immobilization in a polymer matrix. The two-dimensional organization ensures high concentration of the chemosensor on the surface and its fast reaction with the analyte, which explains the high sensitivity and fast response of the OSE. In addition, covalently bound monolayers are much more stable and can provide the durable operation of OCSD. This method is especially convenient for the manufacture of matrices of sensing elements and is widely used in the analysis of biological analytes. In the detection of heavy metal ions, matrix system **97** based on two fluorophores and four simple ionophores was used for

Structures 97



97



Ionophores: *p*-Pr^{i}C$_6$H$_4$NHC(O), n-C$_6$H$_{13}$NHC(O), *p*-Pr^{n}C$_6$H$_4$C(O), n-C$_6$H$_{13}$C(O)

selective recognition of Cu^{2+}, Co^{2+}, Pb^{2+} and Ca^{2+} ions.[158] By using microcontact printing, a miniature sensing device was manufactured. Due to simplicity of formation of combinatorial libraries of fluorescent monolayers on the glass surface, this approach is promising for the development of new selective detection systems by high-throughput screening and for the manufacture of differential sensor devices based on several types of low-selectivity molecular detectors.[159]

Yet another type of effective OSE was designed after the discovery of periodically organized mesoporous materials (POMM) in the mid-1990s. These materials are obtained by the sol–gel technique in the presence of an organic template reagent. Currently methods have been developed for the production of a multitude of inorganic and hybrid materials of various chemical composition as powders, monoliths, thin films, membranes and fibres. For the production of optical chemical sensors, silicate hybrid materials are mainly used.[145] The use of POMM markedly increases the rate of analyte diffusion and improves the sensitivity and the response time of the immobilized chemosensor as compared with functional materials obtained by the traditional sol–gel technique (without using a template) or by polymerization of organic monomers. In the OSE of this type, the chemosensor molecule may be covalently bonded to the inorganic matrix or be retained by electrostatic, hyrophilic/hydrophic interactions and/or hydrogen bonds. The first method is used more often, as the chemosensor is washed out from the porous matrix faster than from the above-described polymeric materials. The covalent binding of a chemosensor molecule can be accomplished either by a one-pot sol–gel process from appropriate molecular precursors or by surface modification of an inorganic POMM with a functional component (post-modification). Post-modification is used most often for functionalization of nano-sized silica gel,[160, 161] silicate nanotubes[162] and monolithic POMM.[163–165] The one-stage process is used in the production of film type materials[166] and functionalized nano-sized powders.[167]

Non-covalent binding of the chemosensor molecule to the POMM surface can also be rather strong if the molecule is held by the electrostatic interactions of charged groups,[165, 168] hydrophilic/hydrophobic interactions in the case of diphilic chemosensors[169] or hydrogen bonds.[170, 171]

The covalent bonding of the chemosensor to the POMM surface requires, as a rule, modification of its molecule by introducing an additional functional (most often, trialkoxysilyl) group capable of a condensation reaction with the inorganic precursor or material. The synthesis of these organic derivatives may be fairly complicated. Therefore, a simplified two-stage immobilization procedure was developed. The first stage was modification of the inorganic matrix by a commercially available organosilane containing a reactive functional group (amine, thiol, isocyanate group or iodine atom). This is done using either of the above methods — direct co-condensation of precursors of the organic and inorganic components or post-modification of an inorganic material. The resulting hybrid material is used to immobilize a chemosensor molecule having suitable reaction sites.[158, 165, 168, 172, 173]

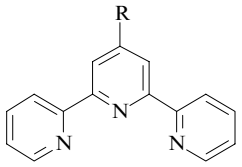
The combination of traditional factors of supramolecular chemistry such as the number, topology and arrangement of donor groups in the molecular detector with preorganization of the solid-phase matrix can bring about

synergistic effects and properties not inherent in any of the system components, for example, enhancement (or appearance) of the selectivity and sensitivity as compared with traditional molecular systems.[171] Thus, POMM are very important for the development of effective OSE; we will consider particular examples in a separate review devoted to nano-sized sensor systems.

In the development of quick test methods, cellulose is among the most convenient polymer matrices. Paper test strips are widely used to determine various analytes and can be adjusted for simultaneous analysis of several analytes.[174] As an example, consider the test strips developed for determination of Hg^{2+} ions. The simplest way to manufacture these strips is to immerse the paper into a solution of an appropriate chemosensor (usually in an organic solvent) and to dry it in air. This gives test strips based on the above-considered chemosensor **63**.[98] They can be used to determine Hg^{2+} ions in aqueous solutions if the ion concentration exceeds $2\,10^{-5}$ mol litre^{-1}. The Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, Ag^+, Ni^{2+} and Co^{2+} cations do not interfere with the determination.

Note that paper immobilization of a chemosensor is not always efficient and can result in the loss of its functional properties observed in solution.[175] More stable test strips may be obtained by using immobilization on polymer films. Shunmugam *et al.*[176] proposed terpyridine (**98a**) and its derivatives **98b**,**c** and a polymer based on methyl methacrylate (MMA) modified by terpyridine moiety (**98d**) as sensors for mercury ions. Treatment of paper with polymer **98d** gave test strips for determination of Hg^{2+} ions in aqueous solutions at concentrations higher than 2 μg litre^{-1}.[176]

Structures 98

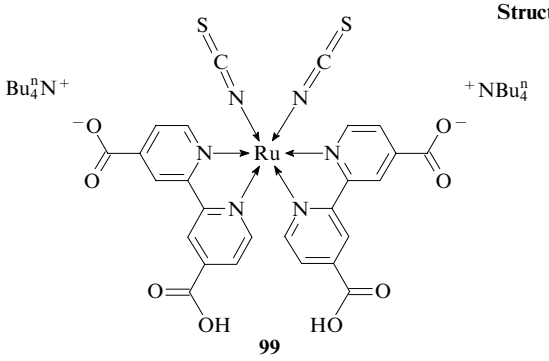


98a–d

R = H (**a**), OBu^n (**b**), $(OCH_2CH_2)_nOMe$ (**c**), MMA-based polymer(**d**)

The use of nanotechnology techniques for the deposition of a functional film of a chemosensor on the paper surface markedly increases the sensitivity of determination. Effective immobilization of the chemosensor is possible after coating filter paper nanofibres by titania or silica thin films obtained by the sol–gel process. The filter paper modified by a thin silicate film can be used for immobilization of (3-sulfanylpropyl)trimethoxysilane, which can be used to determine Hg^{II} ions.[177] The cellulose nanowires coated by titania were modified by ruthenium dye N719 (**99**) sensitive to Hg^{2+} ions. High concentration of the chemosensor on the test strip surface provides determination in very dilute solutions, which is especially important for analysis of toxic metal cations. For example, the multilayer system $N719/TiO_2$ can be used in 50 μM aqueous solutions of Hg^{2+} ions; this indicates that test strips manufactured by this method are much more sensitive than the $N719/TiO_2$ films deposited on a smooth glass surface. These materials make it possible not only to detect mercury(II) ions but also to perform their adsorption from aqueous solutions because, owing to great surface area, they contain considerable amounts of the chemosensor.

Structure 99



99

A chemosensor can also be immobilized on a cellulose membrane surface from an aqueous suspension of the chemosensor if it has been prepared as a nano-sized powder.[178] The amount of the deposited chemosensor can be easily controlled. Using this process, it is possible to manufacture highly stable test strips for the determination of metal ions over a broad concentration range.

* * *

The review covers the use of optical molecular detectors for the detection of heavy metal ions in solutions and methods of immobilization of sensors for the design of ion selective optical devices. In recent years, considerable progress has been made in increasing the selectivity and sensitivity of detection of heavy metal ions in solutions owing to the advent of new effective receptors and development of new ways of transduction. Many effective molecular detectors for determination of low concentrations of toxic elements in aqueous solutions and biological media were designed. Development of new methods of chemosensor immobilization is in progress. These works represent a key point for increasing the efficiency of the operating sensing elements and extend the options for their embedding into already designed devices. The experience accumulated in this area clearly demonstrates the complexity of the problem and gives interesting examples of manufacture of practically valuable materials. In conclusion, we would like to note that many issues have yet been unsolved and require intense investigations by multidisciplinary research teams.

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