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Metal complexes as fluorescent probes for sensing biologically relevant gas molecules

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Abstract

Last decades have seen a marked escalation in interest in the biology of naturally occurring gases. Examples of the most significant of these gases are nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S). All of them feature a number of physiological and/or pathophysiological functions within human body. For example, NO regulates vasodilatation in the circulatory system and long-term potentiation in the brain. CO modulates vasorelaxation, vascular smooth muscle cell growth and tissue injury. H_2S relaxes vascular smooth muscle and inhibits smooth muscle cell proliferation. In addition it acts as neuromodulator in the central nervous system. Furthermore it is also well acknowledged that all of them are differently associated with various human diseases. However, for the advancement of our understanding of the physiological and pathological roles played by these signal transductors, there is a pressing need for methods allowing their detection in both aqueous and gaseous media. The aim of this review is to highlight the recent developments in the field of metal complexes as fluorescent probes for the detection of gasotransmitters and to provide a general overview of fluorescent sensors implemented so far for NO, CO and H_2S.

Keywords
NO, CO, H_2S, metal complexes, fluorescent molecular probes, sensing.

Introduction

Nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) are the main examples of biologically active gases which occur naturally in human body [1]. These gaseous molecules effect physiological and/or patho-physiological functions within the human body. NO, CO and H_2S participate in the regulation of vascular homoeostasis and of the central nervous system. While there is plenty of literature on the biological importance and functioning of NO [2-6] and CO [7;8], understanding of H_2S chemistry and of its far-ranging contributions to physiology and pathology is at a somewhat earlier stage and still mostly unknown [1;9-16]. During the last decades, the possibility of dynamic monitoring of these gas molecules in biological samples resulted in an upsurge of interest with the aim to devise highly efficient systems for their detection. Early approaches to measure these molecules in blood plasma and homogenized tissues mainly rely on colorimetry, electrochemistry and chromatography which require sample processing and/or destruction of tissues or cell lysates. Optical devices (mainly fluorescence-based sensors), which overcome most of the limitations of the traditional approaches, have been also presented over the years.

This review deals with the recent progresses in the field of fluorescence-based probes for the detection of biologically relevant gas molecules (e.g. NO, CO, H_2S) focusing on the devices using a metal complex as the molecular recognition element. Sensors are commonly referred to as “turn-off” sensors when they exploit the quenching of the fluorescence intensity upon analyte binding, whereas the “turn-on” sensors undergo the enhancement of the fluorescence intensity upon analyte binding. “Turn-off” sensors are inherently less sensitive than methods exploiting fluorescence enhancement or “turn on” as a result of binding. Furthermore, it is usually difficult to distinguish analyte response from sensor degradation when quenching is relied upon for recognition [17].

1. Sensing nitric oxide (NO)

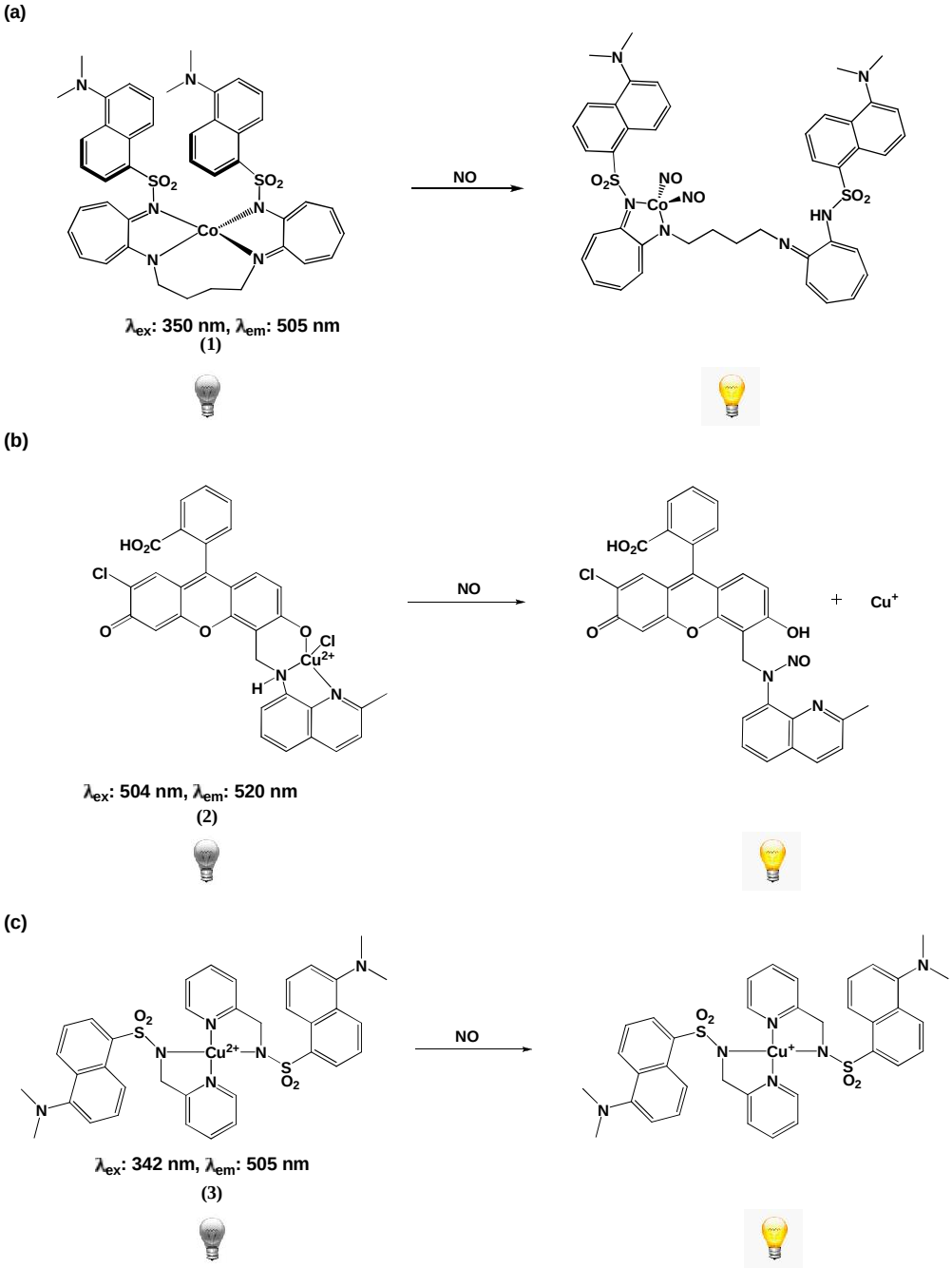
NO plays a key role in a number of different biological processes [3]. At low concentrations, NO regulates vasodilation in the circulatory system and serves as a messenger in the immune and nervous systems [4]. At micromolar concentrations NO can result into neurodegenerative and carcinogenic disorders [5;6]. Furthermore NO is a by-product of high temperature combustion [18] and one of the environmentally hazardous exhaust gases generated by motor vehicles [19]. Emissions of this gas cause environmental problems such as acid rain, destruction of the ozone layer, greenhouse effects and air pollution. With such wide interests in NO, the setting up of efficient methods for detection of NO in both aqueous and gaseous media is still a challenging task. In the literature several fluorescence-based systems for NO detection have been proposed over the last decades. They can be divided into two main groups : *i*) transition metal-based fluorescent probes and *ii*) organic molecules-based fluorescent probes. Probes belonging to the second group (*ii*) make use of organic molecules with electron-rich components, such as 1,2-diaminobenzenes, that react with an oxidation product of NO, such as N_2O_3, to form an electron deficient product, such as a triazole, to modulate the emission of the fluorophore, thus reporting the presence of NO. Probes belonging to the second group (*ii*) have been recently reviewed elsewhere [20] and will not be discussed in the present review.

For a more complete picture of the NO sensors reported in the literature, it is worth mentioning also sensors using a metalloprotein as molecular recognition element (whose cofactors are in turn metal complexes). A number of these sensors base their functioning on the coordination of the target analyte to the metal binding site of the protein [21-23]. In this context, we devised a biosensor which uses fluorescently labeled cytochrome c peroxidase (CcP) from baker's yeast for monitoring nitric oxide (NO) down to the sub-micromolar level, by means of a FRET (Förster Resonance Energy Transfer) mechanism [24]. Metalloprotein-based probes, however, will not be discussed in the present review.

1.1. Transition metal-based fluorescent probes

Differently than purely organic NO probes, metal-based probes detect NO directly. Existing transition metal-based fluorescent probes for NO detection have been subdivided into three different categories (depending on the reaction mechanism by which NO recognition occurs)

[20;25] : *(a)* fluorophore displacement; *(b)* ligand nitrosation; *(c)* and Cu^{2+} reduction by NO. Typical examples of the three mechanisms involved in NO recognition are displayed in **scheme 1**.



Scheme 1

All the three mechanisms rely on the ability of transition metals with a incomplete filled d-shell to quench the fluorophore fluorescence via energy or electron transfer between the d-orbitals of the metal ions and the excited states of the fluorophore. In the first two cases the turn-on response to NO is due to the displacement of the fluorophore from the quenching ability of the metal centre, so that emission of the fluorophore itself is restored. The third approach involves NO-mediated reduction of paramagnetic Cu(II) to diamagnetic d^{10} Cu(I) which finally results in the recovery of the emission of the fluorophore.

Lippard and coworkers reported several studies on different metal complexes as NO sensors, by exploiting both the fluorophore displacement approach [26-33] and the Cu^{2+} reduction approach [34-41].

One of the first NO sensing device implemented by the group of Lippard, belonging to the category *(a)*, is a cobalt complex with a mixed aminotroponiminate salicylaldiminate ligand **(1)** where the two aminotroponiminate moieties bear two dansyl substituents [26].

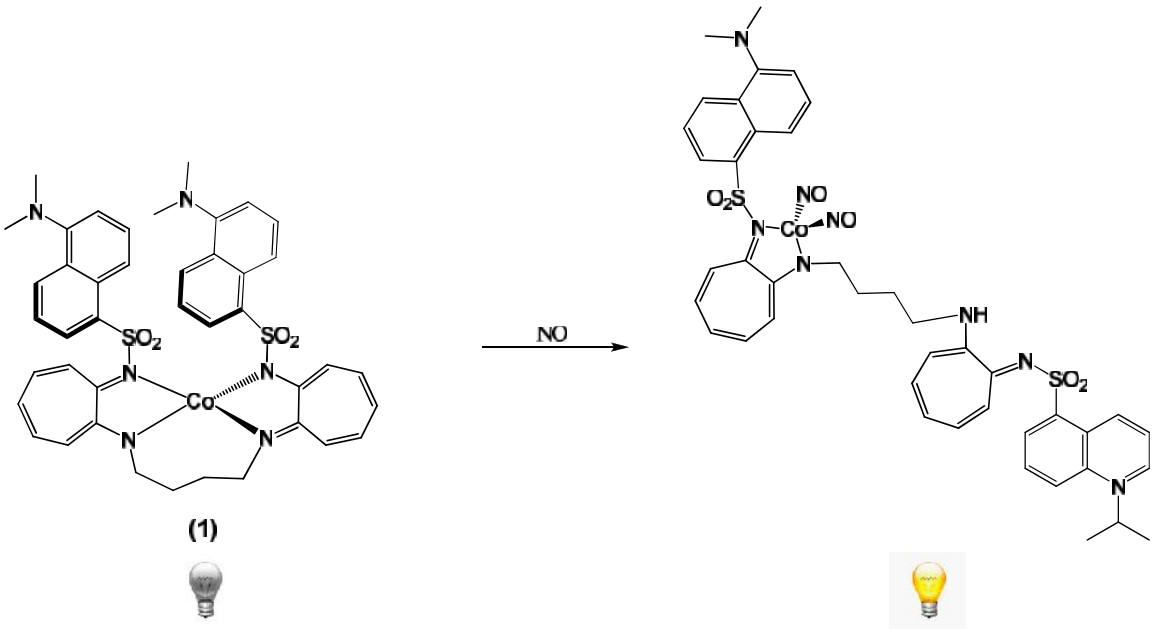
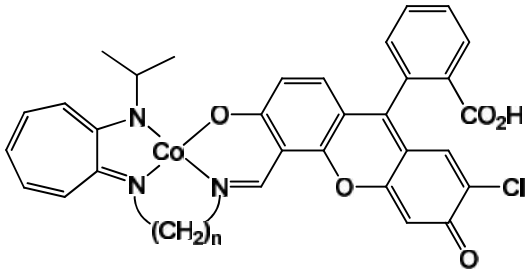


Figure 1. Schematic representation of the NO sensing mechanism by (**1**). Adapted from ref. [26]

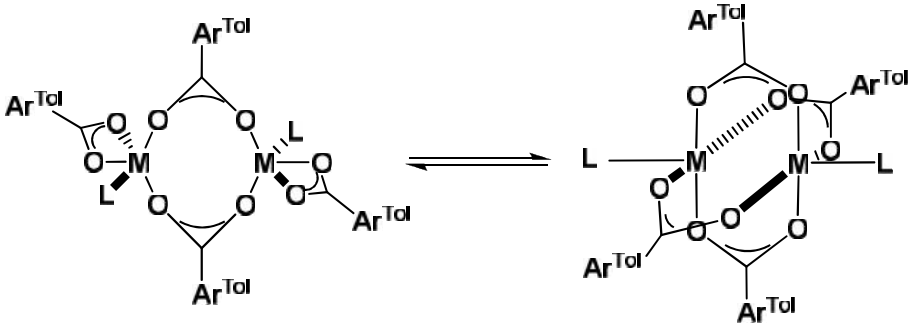
The complex acts as a 'turn-on' NO fluorescence sensor which selectively recognize NO against different NO oxidation products. Upon NO addition the system undergoes a four-fold fluorescence enhancement. The quoted NO detection limit is in the range of 50-100 μM. The mechanism proposed for the fluorescence enhancement in the presence of NO implies formation of a Co-nitrosyl adduct with a tetrahedral geometry, as proposed by IR experiments and by comparison with the crystal structure of a similar adduct, $Co(NO)_2$(*i*-

Pr_2ATI) [42]. Formation of a Co-nitrosyl adduct with a tetrahedral coordination environment around the cobalt is possible when dissociation of one of the arms of the fluorescent ligand from the metal center occurs. This way, in the absence of the quenching metal, the fluorescent ligand recovers its initial fluorescence. A few years later the same research group proposed another family of cobalt based NO sensors **(5)** [28].



(5)

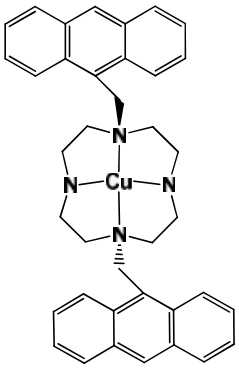
This time the aminotroponiminate moiety was linked to a derivatized fluorescein group with the aim of achieving a water solubility higher than that of the previously implemented probes. Unfortunately, a lower fluorescence enhancement in the presence of NO and poor water solubility were actually found, leading to the conclusion that those systems were not well suited for NO detection in biological systems. The next step of the Lippard group was to synthesize and test carboxylate-bridged diiron(II) and dicobalt(II) complexes as NO sensors **(6)**.[43]



(6)

Again, both the diiron and the dicobalt complexes were found to react with NO leading to an increase in fluorescence emission caused by the ligand displacement approach, but the issue

of enhancing water solubility could not be resolved with these systems. It was concluded that the fluorophore displacement methodology *(a)* is compatible only with organic solvents while fluorescence turn-on can occur even in the absence of nitric oxide in aqueous environments, since water molecules can replace the fluorophore at the metal center. Thus the first generation of the Lippard sensors were not suitable for detection of NO in biological systems. Hence, in the course of the years, a more effective strategy has been devised *(b)*, involving the reduction of a metal center by nitric oxide followed by the nitrosation of the starting ligand which is displaced by the metal center (usually copper). One of the main examples of NO sensors working via the ligand nitrosation approach *(b)* was reported by Ford et al.[44;45] $Cu(DAC)^{2+}$ (where DAC is a derivative of the macrocycle cyclam) is a non-fluorescent specie because of the intramolecular quenching by the paramagnetic Cu(II) centre **(7)**.



(7)

In the presence of NO the system undergoes a clear fluorescence enhancement and a strong emission in the 380-480 nm range characteristic of anthracene luminophores appeared. The NO-triggered fluorescence enhancement is due to Cu^{2+} reduction to Cu^{+} and to the concomitant dissociation of the N-nitrosated ligand from Cu^{+}. A few years later the Lippard group proposed a family of fluorescein-based Cu^{2+} complexes ($CuFL_n$) working with a similar mechanism **(8)** [35;40;46;47].

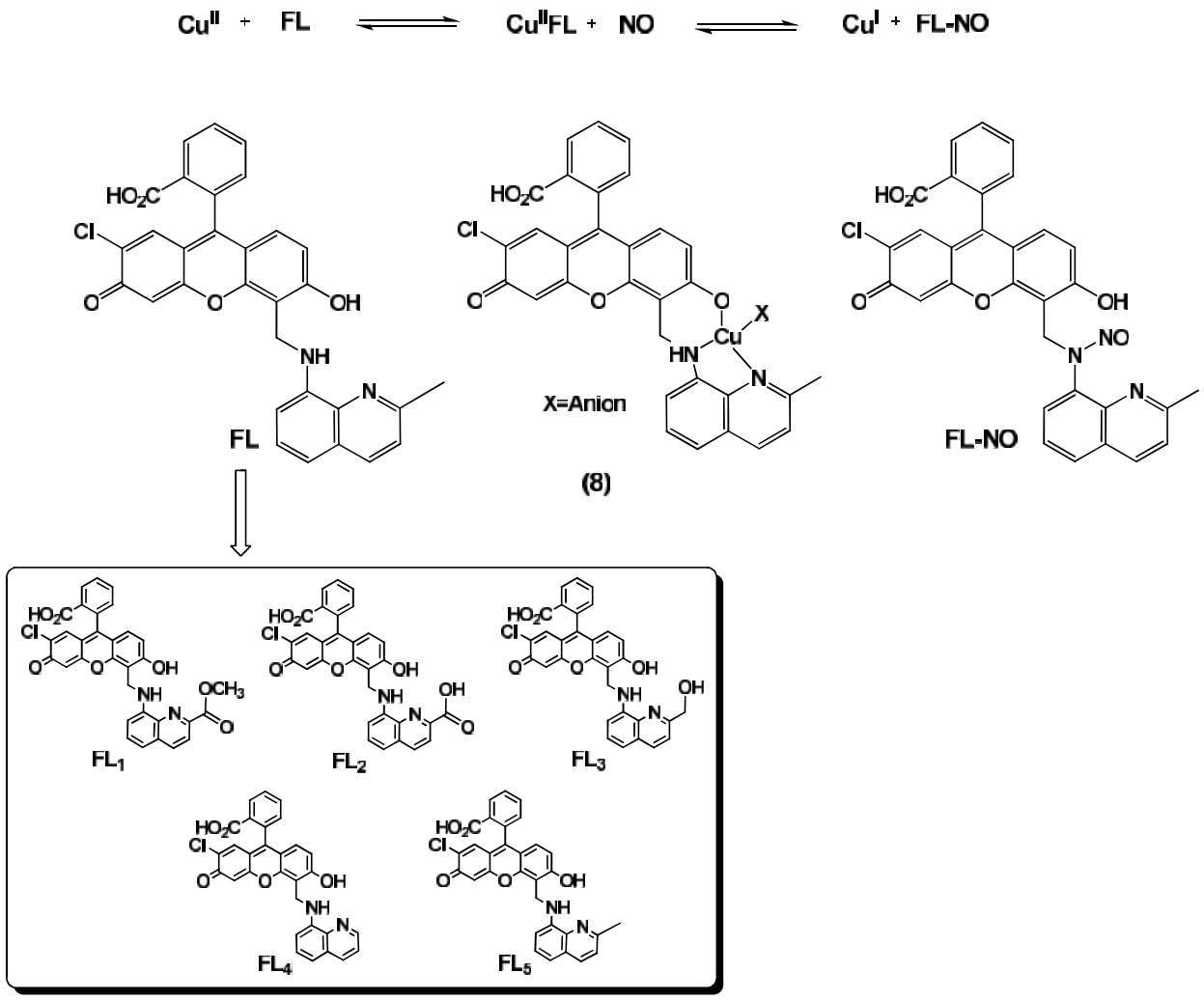
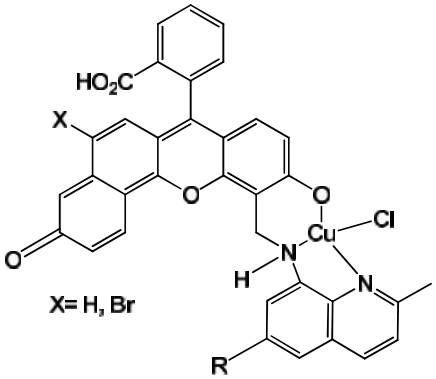


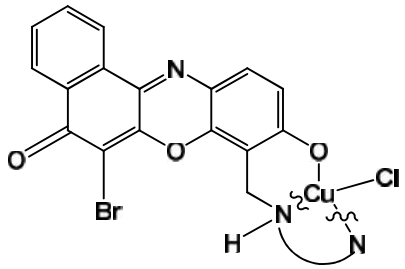
Figure 2. Schematic representation of the NO sensing mechanism by CFL probes

CFL probes react directly and quickly with NO resulting in a consistent turn-on of the fluorescence emission (which spans from a ~3-fold fluorescence enhancement for $CuFL_1$ to a ~30-fold for $CuFL_4$) in buffered solutions (pH = 7), maintaining selectivity for NO over other RNOS. The quoted NO detection limit for the CuFL probes is in the nanomolar range. The family of the CFL probes represent one of the first examples of NO probes able to sense NO in physiological media. In more recent years, to improve the utility of the CFL probes for measuring NO in biological environments, Lippard & coworkers devised scaffolds emitting at longer wavelengths **(9)** [38]. In these constructs the fluorescein group was substituted by a seminaphthofluorescein moiety (SNFL systems).



(9)

Such probes expanded the number of colors available for multi-dye imaging experiments. Upon NO addition these probes exhibited a huge fluorescence enhancement (~ 50 fold) together with high selectivity over other potential RONS in biological systems. The seminaphthofluorescein-based probes were successfully used to visualize endogenously produced NO in live cells. Last generation of the Lippard Cu complexes as probes for NO detection exploits benzoresorufin-based complexes (CuBRNO1-3) **(10)** which work by the nitrosation approach *(b)* [39].



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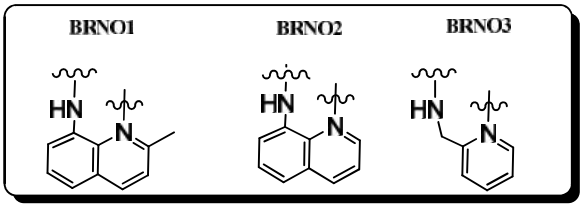
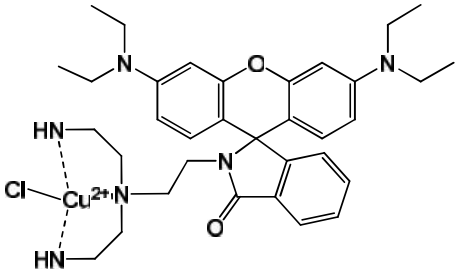


Figure 3. Different chemical structures of (**10**)

The rationale behind the choice of resorufin dyes is that they emit at wavelengths >600 nm with Stokes shifts up to 60 nm. Accordingly, sensors based on resorufin dyes exhibit less background absorption and emission from biological samples and constitute an advantage over previously reported emitters above all for biological imaging purposes. These complexes serve as selective sensors for NO over other ROS but exhibit modest increases in emission intensity (~3 fold emission turn-on). ESI-MS, EPR and electrochemical studies on

the mechanisms by which these complexes respond to NO indicate that the fluorescence enhancement is due to copper reduction to Cu^{+} and to the concomitant displacement of the N-nitrosated ligand from Cu^{+}.

The ligand nitrosation approach *(b)* has been successfully applied by the group of Duan **(11)** [48].



(11)

They prepared a copper(II) complex with a ring-closed rhodamine containing tripodal ligand (CuRBT) which undergoes an extraordinarily high fluorescence enhancement in the presence of NO: 700-fold in aqueous solution. The detection limit was found to be around 1 nM. The system could be successfully employed for measurements of NO in living cells. By ESI-MS experiments and cyclic voltammetry studies authors proposed the working mechanism of the system. Upon NO addition, initial NO coordination to the square planar copper complex occurs followed by formation of NO^{+} through the NO-induced reduction of Cu(II) to Cu(I); then NO^{+} moves towards the amide nitrogen and the spirolactam opens. At this point the concomitant nitrosation of the ligand and the turn-on of the fluorescence response take place. The quoted NO detection limit is 1 nM. One year later the group of Duan proposed a different copper complex as NO sensing device **(12)** [49].

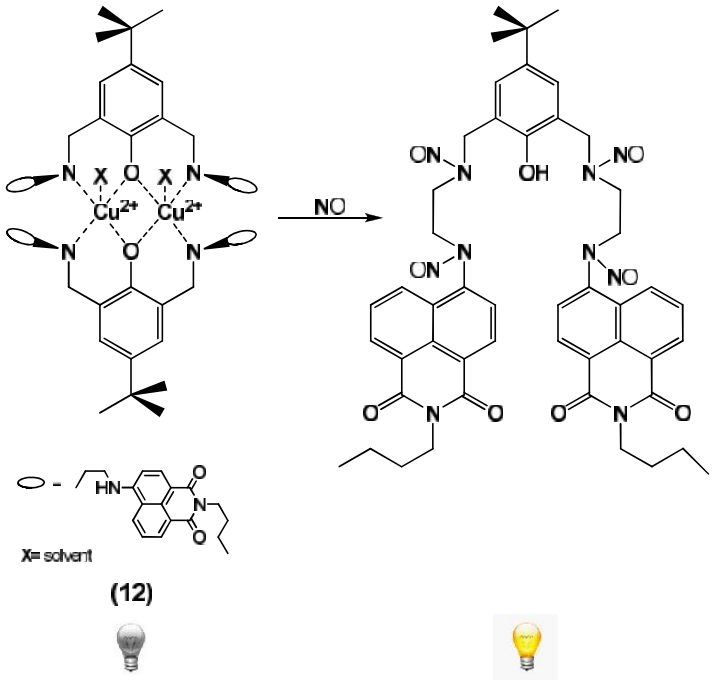


Figure 4. Schematic representation of the NO sensing mechanism by (**12)**. Adapted from ref. [49]

In this work, the copper complex features a naphthalimide moiety as the luminescence active unit (CuQNE). As for the previous system (see above) the proposed mechanism exploits the initial NO coordination to the copper complex followed by formation of NO^+ with concomitant reduction of Cu(II) to Cu(I), restoring the emission of naphthalimide. Then the ligand (QNE) was nitrosated to QNE-NO by NO, resulting in further enhancement of fluorescence. The authors report for this system an approximate 8-fold fluorescence increase in the presence of NO and a detection limit of about 1 nM . Also CuQNE was found suitable for measuring NO in intracellular environments as proven by confocal fluorescence experiments.

As already mentioned before, a consistent number of copper complexes for NO detection relying on the Cu^{2+} reduction approach *(c)* are also present in the literature. The group of Lippard gave a consistent contribution [34-41]. $Cu(Ds\text{-}en)_2$ and $Cu(Ds\text{-}AMP)_2$ (where Ds-en (dansyl-ethylenediamine) and Ds-AMP (dansyl-aminomethylpyridine) **(13)** are the ligands coordinating the copper center) constitute some of the main examples of this class of sensors proposed by Lippard and coworkers [34].

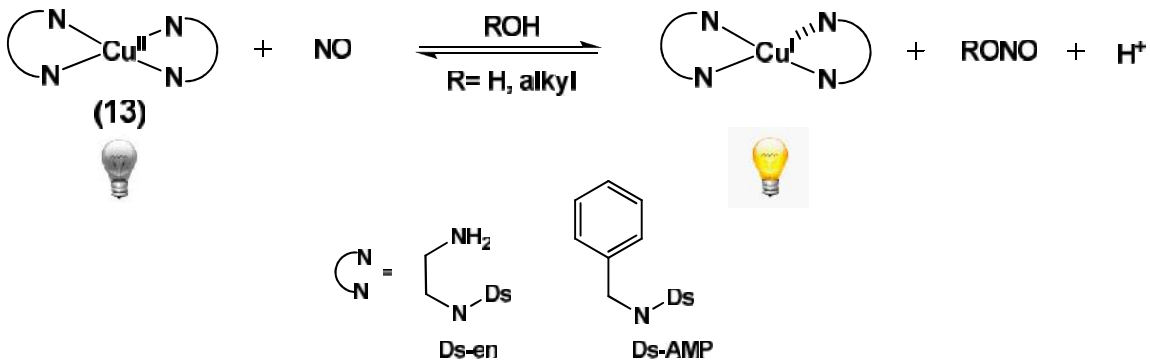


Figure 5. Schematic representation of the NO sensing mechanism by (**13)**. Adapted from ref. [34]

The main difference between the CuFL sensing platform with respect to $Cu(Ds\text{-}en)_2$ and $Cu(Ds\text{-}AMP)_2$ is that in the latter case NO recognition occurs only by Cu^{2+} reduction, whereas the complete release of the organic ligand from the Cu(I) centre does not occur. In the presence of NO the emission intensity of this class of complexes increases by about 8 fold with a detection limit of 10 nM.

Mondal and coworkers synthesized Cu(II) complexes with tridentate N-donor ligands featuring a pendant dansyl fluorophore **(14)** which can be used to sense nanomolar quantities of nitric oxide in both methanol and pH 7.2 buffered-water medium. In the presence of NO they observed a fuorescence enhancement (ranging from 6-fold to 8-fold) and attributed it to the formation of a diamagnetic Cu(I) species after reduction of a paramagnetic Cu(II) center by nitric oxide [50-53].

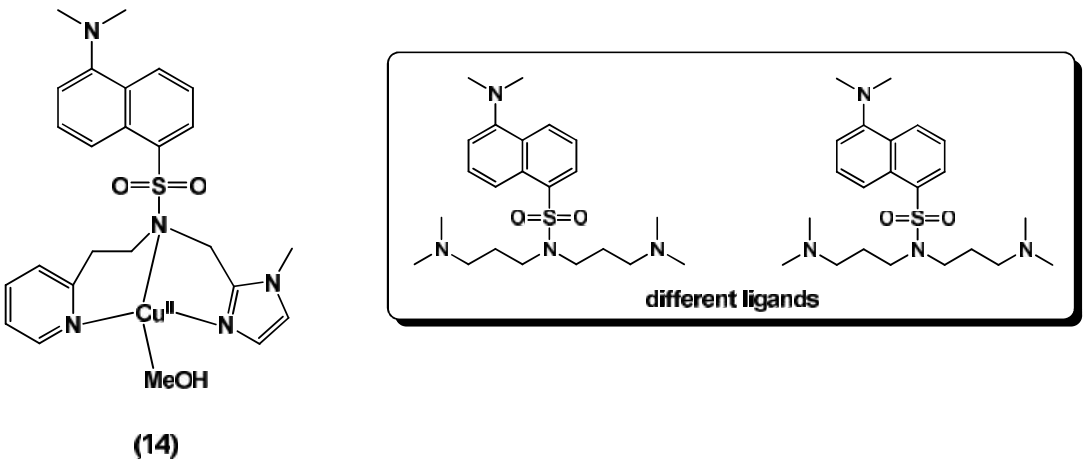


Figure 5. Different chemical structures of (**14**)

In addition to the wide variety of copper complexes, other transition-metal complexes, including those of Fe(II), Ru(II), Rh(I) and Re(I), have been devised over last decades as nitric oxide sensors [46;54-59]. For instance, very recently a series of rhenium(I) polypyridine complexes functionalized with an electron-rich diaminoaromatic moiety **(15)** were reported as a new class of phosphorogenic sensors for NO [58;59]. All the starting diamine complexes were very weakly fluorescent, due to the PET from the diaminoaromatic moiety to the excited rhenium(I) complexes. Upon treatment with NO, the diamine complexes were transformed into the strongly fluorescent triazole derivatives (as evidenced by ESI-MS experiments and cyclic voltammetry studies) with the emission intensity enhanced by ~60 fold. The successful use of some of the rhenium polypyridine complexes as intracellular NO sensors was also demonstrated by the authors.

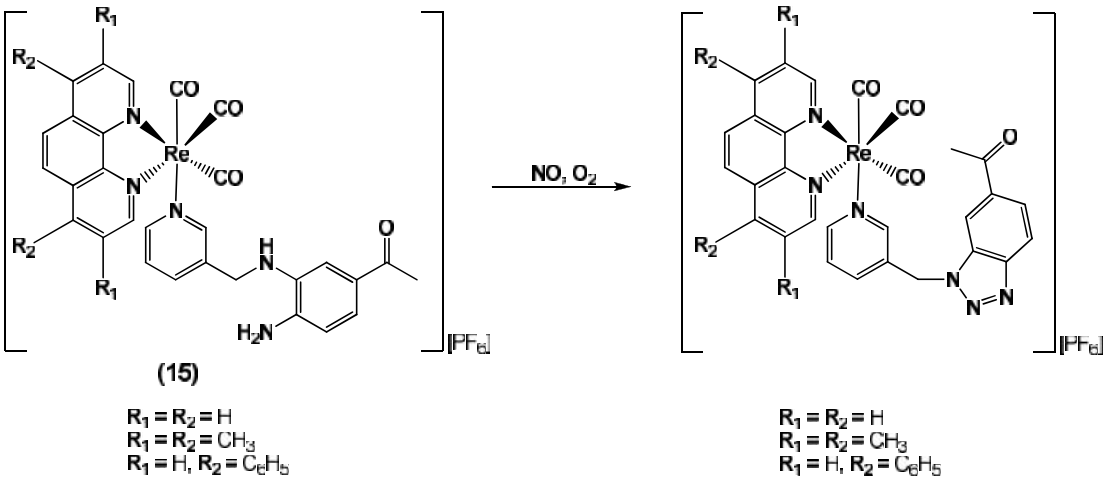


Figure 7. Schematic representation of the NO sensing mechanism by (**15)**. Adapted from ref. [58]

2. **Sensing carbon monoxide (CO)**

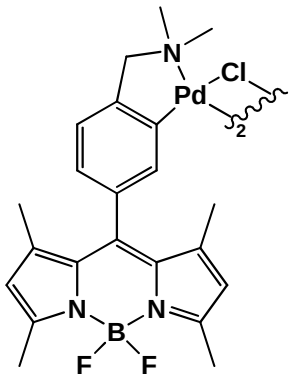
Like NO, CO is also an important signalling molecule. Many of the biological properties of CO are similar to those of NO. In addition CO inhibits proliferation of vascular smooth muscle cells and has anti-apoptotic activity [1]. On the other hand CO is well known for its high toxicity and its common presence in domestic and work settings. The traditional methods to detect CO make use of electrochemical cells, solid-state sensors, and thermocouples. Electrochemical sensors based on metal oxide semiconductors generally possess reasonably good resolution and measuring ranges. However, these sensors are very

sensitive to temperature and pressure and this may constitute a limitation for measurements on real samples [60].

As already mentioned above, optical methods offer several advantages over other analytical procedures, such as the use of very simple and inexpensive instrumentation. Since in the literature there are only a few examples of transition-metal fluorescence based probes, herein we review also the UV-vis based probes [20;60].

2.1. Metal complexes as fluorescence based CO sensors

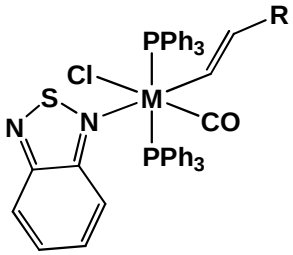
In 2012 the group of Chang proposed a cyclopalladated species as a CO fluorescent sensor **(16)** [61].



(16)

In the presence of CO authors report a fluorescence enhancement (~10 fold) in aqueous buffer. The proposed mechanism exploits the fact that the presence of palladium quenches the fluorescence of the borondipyrromethene difluoride (BODIPY) core whereas upon binding of CO, a carbonylation reaction concomitantly reduces palladium to Pd(0) and forms a more fluorescent species. Furthermore, the cyclopalladated species was found to have good selectivity to CO over other biologically relevant reactive oxygen, nitrogen, and sulfur species, including H_2O_2, tert-butyl hydroperoxide (*t*BuOOH), hypochlorite (OCl^-), superoxide (O^{2-}), NO, peroxynitrite ($ONOO^-$), and H_2S. By confocal fluorescence experiments authors demonstrated that their probe can be successfully used to visualize CO in living cells.

In 2015 Wilton-Ely reported a series of ruthenium and osmium vinyl complexes of the general formula $[M(CH=CHR)Cl(CO)(BTD)(PPh_3)_2$ containing the BTD chromophore (BTD=2,1,3-benzothiadiazole) and several different vinyl ligands **(17)** [60;62].



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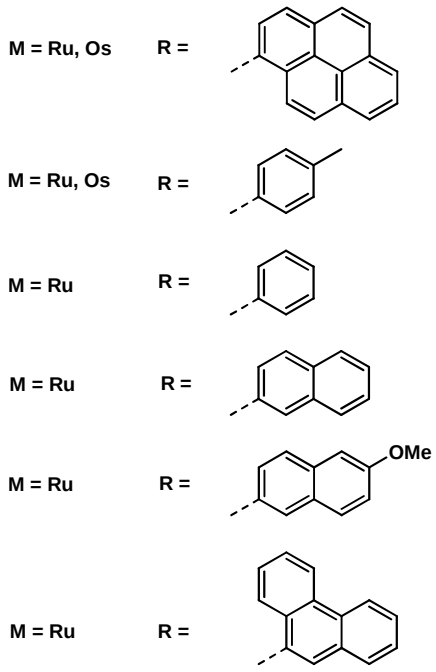
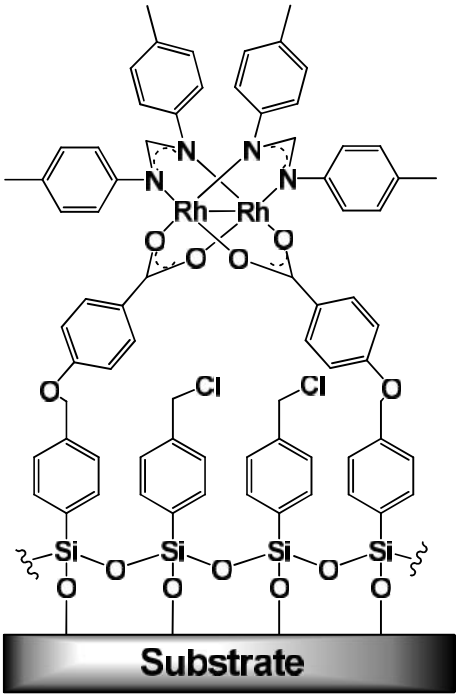


For these compounds, authors reported a clear fluorescence enhancement (20-fold) in the presence of CO (both in chloroform solutions and in gas phase), which were ascribed to the displacement of the BTD ligand upon coordination of the CO group. Different color modulations and sensing features were reported by the authors in the presence of CO when changing the metal center and the vinyl ligands (with different donor-acceptor properties). The pyrenylvinyl ruthenium complex was reported as the best performing CO sensor in the set of compounds investigated. Considering the combination of sensitivity (till 0.005 ppm of CO), selectivity (against other gases e.g. CO_2, N_2, O_2, Ar, SO_2, NO_x and H_2S), simple synthesis, and low cost of their systems, the authors proposed them as attractive and efficient chemosensors for the simple chromogenic and fluorogenic detection of CO.

2.2. Metal complexes as UV-vis based CO sensors with potential environmental applications

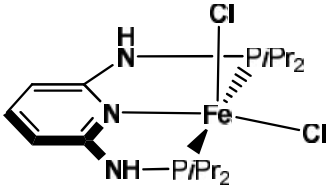
One of the first examples makes use of bimetallic rhodium complexes covalently immobilized on glass substrates **(18)** [63].



(18)

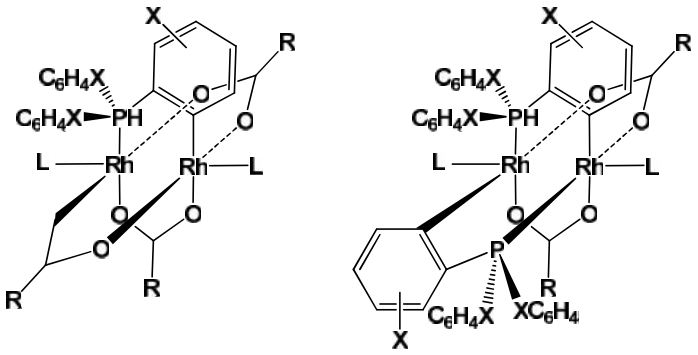
Bimetallic rhodium complexes undergo immediate color change in the presence of ppm levels of CO in air. The sensor is highly selective against unsaturated hydrocarbons and does not respond to air saturated with water vapor. In the presence of gaseous CO authors report a significant absorption intensity increase of the initial UV-vis spectrum of the system. They rationalize this optical behavior by an enhancement of ligand-to-metal charge transfer (LMCT) promoted by η^1-coordination of CO to the metal complex. CO binding is reversible since heating or purging the system with air, Ar or N_2 results in full system recovery. Authors report selectivity to CO of their system against N_2, CO_2, NOx, N_2O, O_2, CH_4, H_2. The detection limit quoted for the system is of 2.5 ppm of CO.

Another example was proposed by Kirchner and coworkers [64]. This time the complex which acts as molecular recognition element is a coordinatively unsaturated iron PNP pincer complex [Fe(PNP-iPr)Cl_2] **(19)**.



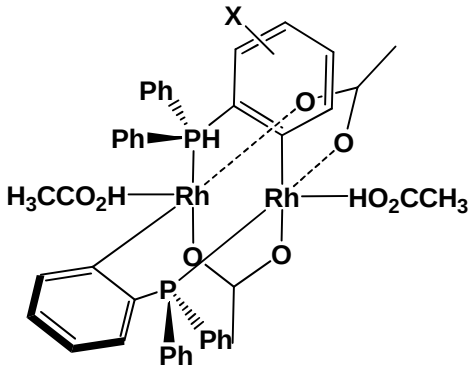
(19)

This iron complex is able to bind reversibly and in a selective manner CO. Heating the system under vacuum results in the complete recovery of the pure sample; the cycle can be repeated several times with a concomitant and clear color change from yellow to red. The formation of the hexa-coordinate derivative CO adduct was proven by time-resolved IR spectroscopy, NMR, UV-vis and X-Ray powder diffraction. The system works as an efficient CO sensor in the solid state (by exposing the solid compound to 1 atm of gaseous CO) but also in DMSO solution suggesting possible applications as CO sensor and as crystalline switch. Selectivity of the iron PNP pincer complex to CO was proven against different gases like NO and SO_2. More recently the group of Sancenon proposed a family of binuclear rhodium complexes as sensitive and selective CO sensors **(20)** both in chloroform solution and in gas phase [65;66].



(20)

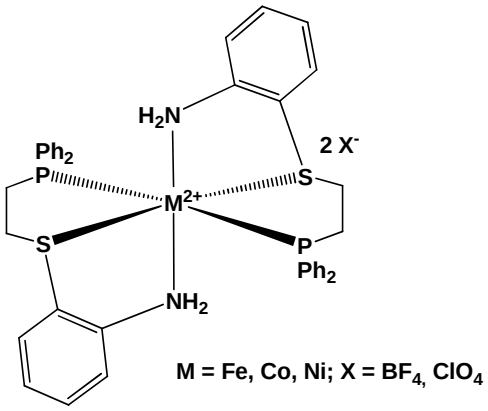
In particular they showed as the compound of formula cis-$[Rh_2(C_6H_4PPh_2)_2(O_2CCH_3)_2](HO_2CCH_3)_2$ **(21)** prepared by Cotton et al. in 1985 [67] works very efficiently as a chromogenic probe for carbon monoxide.



(21)

Color modulations are due to coordination of CO at axial positions. A clear color change to the naked eye at 50 ppm of CO (concentrations at which it becomes toxic) was observed. Preliminary experiments were performed in chloroform solutions; in a second instance the complex was absorbed on silica gel to measure CO in air samples. Authors report that the system is selective to CO (against different gases like SO_2, NO, NO_2) and fully reversible.

Long and coworkers prepared a series of P-S-N complexes **(22)** and reported that the iron and the cobalt complexes act as efficient CO chromogenic sensors by forming the corresponding octahedral monocarbonyl complexes [68].



(22)

When acetonitrile solutions of the P-S-N complexes were exposed to 1 atm of CO, CO binding occurs and results in a clear color change from purple to orange. They also report that CO binding to the isolated complexes is fully reversible.

3. Sensing hydrogen sulfide (H_2S)

Traditionally, H_2S was considered a toxic and harmful gas (the critical concentration is 300 ppm). More recently, in sharp contrast to its toxic image, it was recognized to occur naturally in human body [1;15;69]. The concentration of H_2S required to give physiological responses has been reported to be in the range 10µM- 1mM, although the intracellular H_2S levels generated in response to physiological stimuli are still controversial [70;71]. In recent years the understanding of its reactivity has increased a lot and this molecule has been recognized to be involved in various physiological and pathological functions within the human body. However the complex contributions of H_2S to both healthy and disease states,

and a large part of the underlying molecular events, remain unknown [72]. Therefore, efficient methods to sensitively and selectively detect H_2S in living systems are still a challenging task [16;20;69;72-80].

Current classification of the existing fluorescent probes for H_2S is based on the mechanism of the reaction by which analyte recognition occurs [20;81]. Existing fluorescence-based probes have been subdivided in four different categories: *i*) azide-to-amine reduction [82-89]; *ii*) nucleophilic addition [90-93]; *iii*) copper displacement [94-98]; *iv*) nitro-to-amine reduction [99;100].

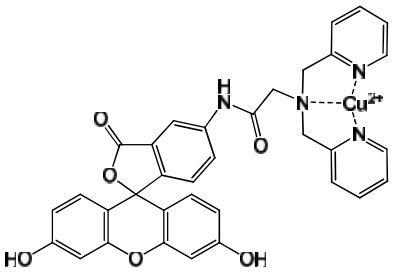
All the sensors belonging to the above categories are based on the use of organic molecules which change their fluorescence intensity upon interaction with H_2S. Sensors belonging to category *iii* constitute an exception since in this case the sensing molecule is a metal complex. In this case recognition builds on the displacement of the metal from the fluorophore's environment to generally produce fluorescence turn-on changes via H_2S mediated precipitation of Mt-S [101-108].

As already mentioned above, probes belonging to the groups *i*), *ii*), *iiii*) do not contain a metal center, thus are outside the scope of the present review. For recent reviews on them, please see the works of Kumar and coworkers [20], that of Guo and coworkers [25] and that of Jiang and coworkers [109].

In addition to the above mentioned approaches for H_2S detection, a fifth way to achieve H_2S recognition by using a metal complex as molecular recognition element has been recently devised: a coordinative-based approach [110-114].

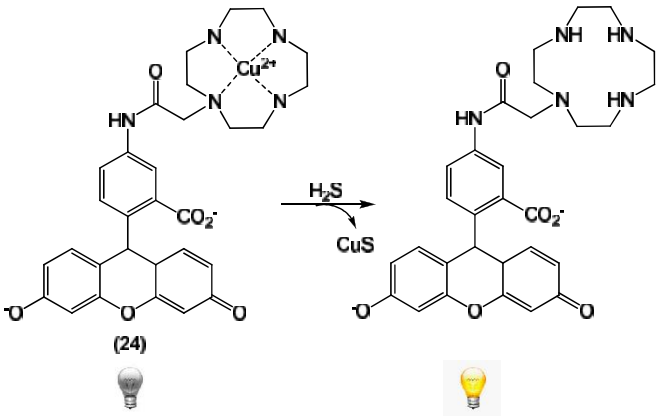
3.1. Copper displacement approach

One of the first H_2S sensing device implemented by exploiting this approach has been set up by the group of Chang [115]. They reported that a dipicolylamine (DPA) fluorescein complex with Cu^{2+} (DPA-AF+Cu^{2+}) **(23)** showed a selective turn-on fluorescence response to sulfide anion.



(23)

The selective signal is based on the decomplexation of Cu^{2+} ions from the (DPA)_fluorescein moiety due to the precipitation of a stable complex of Cu^{2+} with sulfide anions. The S^{2-}triggered-Cu^{2+} removal allows the probe to detect 10 µM H_2S in aqueous solution at pH 7.4, and it could be used for H_2S detection in physiological media. However this system was also not selective since it showed fluorescence enhancement upon addition of 10 mM GSH. Thus in 2011 Nagano and coworkers designed and synthesized a new family of probes based on a fluorescein framework conjugated with an azamacrocyclic Cu^{2+} complex **(24)**.[116]



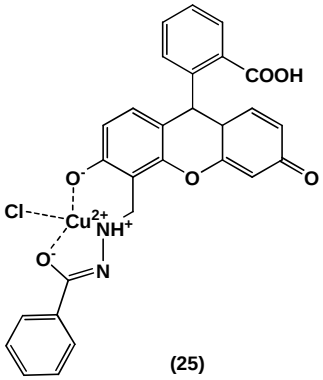
(24)

Figure 8. Schematic representation of the H_2S sensing mechanism by (**24)**. Adapted from ref. [116]

Initially, fluorescence of the azamacrocyclic ring (cyclen) is quenched by the paramagnetic Cu^{2+} center. Reaction with a sulfide source (Na_2S or NaHS) results in the precipitation of CuS and release of the unbound cyclen which displays fluorescence enhancement. The system implemented by Nagano undergoes a large and immediate increment of fluorescence intensity by 50-fold upon addition of 10 µM H_2S, whereas almost no fluorescence increase is observed upon addition of 10 mM GSH. The high potential of the azamacrocyclic Cu^{2+} complex as H_2S sensor was proven by employing it for fluorescence imaging measurements

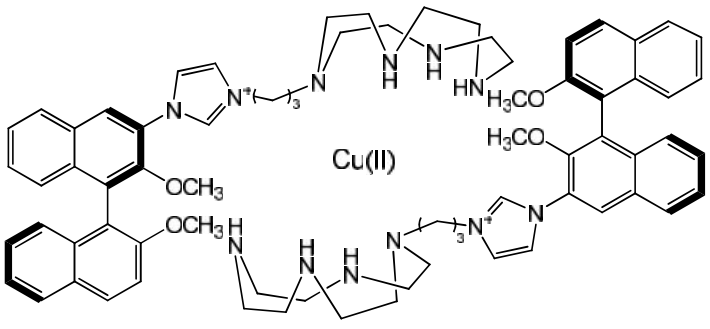
of H_2S in intracellular environments. Use of different macrocycles such as tryazacyclononane (TACN) or tetraazacyclotetradecane (cyclam) or trimethylcyclen (TMCyclen) resulted in less efficient H_2S sensing [116].

The group of Zeng synthesized a related fluorescein-based scaffold which showed the usual fluorescence quenching when binding Cu(II) **(25)** [117].



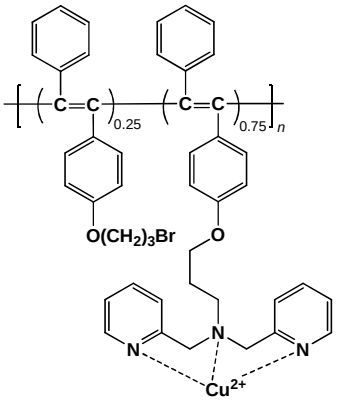
(25)

The complex resulted highly specific for hydrogen sulfide over other interferents (e.g. different inorganic sulfur compounds, reactive oxygen species (ROS) or reactive nitrogen species (RNS)), and following the usual scheme for this class of H_2S sensors, its reaction with H_2S restored the free dye. The probe displayed 25–30 fold fluorescence enhancement after adding 20 µM H_2S to the sample and the detection limit was quoted at 1.7 µM. Interestingly, when adding subsequently Cu(II) and H_2S to the solution of the sensing system, a switchable change in the fluorescence intensity was observed. Such a reversible interconversion can be repeated more than 10 times by adding alternatively Cu(II)/H_2S, indicating that the system behaves as a reversible fluorescence on–off–on probe for H_2S. In addition the authors showed that the system can be used for detection of H_2S in intracellular media by live-cell imaging experiments. By a similar approach, Yu and coworkers synthesized a multifunctional fluorescent Cu(II) sensor based on a cyclen-appended BINOL derivative **(26)** [118].



(26)

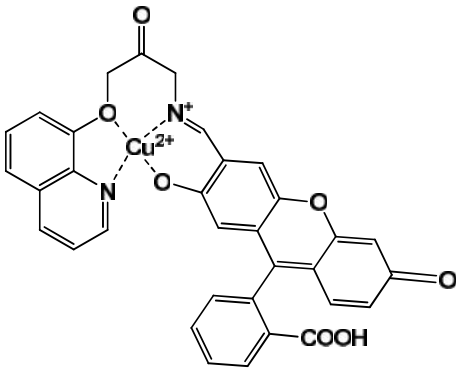
Also the present system works as “ON-OFF-ON” fluorescence switch when subsequently adding $Cu^{2+}$and S^{2-} along with reversible formation-separation of the complex in water solution. The detection limit was estimated to be 16 μM. Furthermore the system showed high selectivity over competitive biothiols, commonly tested anions and inorganic sulfur compounds. The group of Li successfully prepared a new disubstituted polyacetylene bearing pyridine moieties in the side chains **(27)** which upon binding of Cu^{2+} acted as a well-performing H_2S sensor via the copper displacement approach [119].



(27)

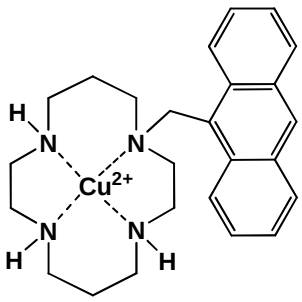
The strong green fluorescence of disubstituted polyacetylene could be completely quenched by Cu^{2+} even at a very low concentration ($2.0 * 10^{-6}$ mol/L) and restored upon addition of sulfide anion, with the detection limit down to 5.0 *10-7mol/L. High selectivity against a number of possible competing species was observed.

Later, a 8-hydroxyquinoline-appended fluorescein Cu^{2+} derivative was proposed by the group of Zeng by exploiting the same copper displacement approach **(28)** [120].



(28)

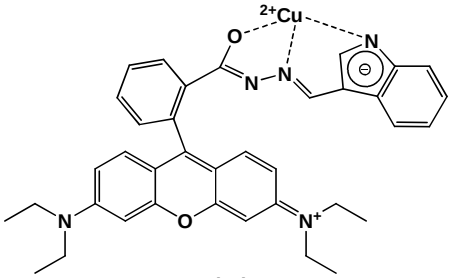
High selectivity is claimed for the implemented device against other common ions and other forms of sulfate. By experiments in living cells authors reported clear evidence that their sensor has potential biological applications for sulfide detection. In 2014 the group of Parra proposed an anthracene-functionalised cyclam–copper(II) complex **(29)** for the detection of HS^- by making use of the same approach.



(29)

The latter system behaves quite similarly to the above discussed copper sensors for H_2S detection [121]. The probe recognizes selectively H_2S over other anions, biothiols and common oxidants such as H_2O_2. Real-time fluorescence imaging experiments demonstrated that the system can be used to successfully detect HS^- in intracellular environments.

A slightly different approach was used in the setting up of an indole functionalized rhodamine Cu^{2+} derivative **(30)** as H_2S sensor which enables naked eye detection [122].



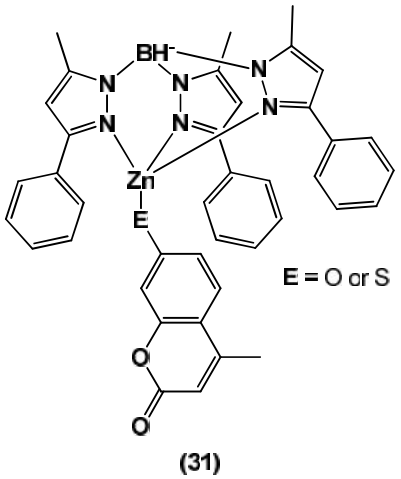
(30)

Indole and rhododamine (the two fluorophores) were chosen for designing the receptor which bases on a FRET-based phenomenon. Binding of Cu^{2+} to the indole functionalized rhodamine results in the opening of the spyrolactam ring of the rhodamine derivative, whose absorption spectra shows a significant spectral overlap with the emission spectra of the indole moiety and makes the FRET process possible. Furthermore an increased absorbance in the NIR (near- infrared) region of the UV-vis spectra was also observed. A concomitant change from colorless to blue was also observed when Cu^{2+} binds to the indole functionalized rhodamine. When adding S^{2-} to the solution containing the copper complex, the usual precipitation of copper was observed and the fluorescence of the functionalized rhodamine restored. Authors reported that their indole functionalized rhodamine Cu^{2+} derivative could be successfully used also for sulfide sensing in intracellular environments.

3.2. Coordinative-based approach

Over the last decades different examples of transition metal complexes featuring H_2S or HS^- binding to the metal center have been isolated and fully characterized [123-128]. Drawing upon the consideration that fluorescent sensors for H_2S developed so far are one-pot-devices because of the irreversibility of the reaction by which H_2S recognition occurs, a coordinative-based approach was recently proposed by us and others [110-114]. By a coordinative-based approach one may, in principle, remove H_2S from the metal center of the sensor and ensure a reversible H_2S binding process. This is advantageous for measurements on real samples allowing reusability of the sensing device.

In 2009 Galardon and coworkers reported the first HS^- coordination complex as a probe for the target analyte: a thiolato complex of zinc ($Tp^{Ph,Me}Zn(MUS)$) **(31)**, where MUS stands for 7-mercapto-4-methylcoumarin, as a 'turn-on' specific sensor for H_2S.[110]



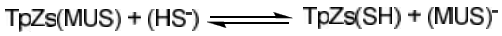


Figure 9. Schematic representation of the H_2S sensing mechanism by (**31)**. Adapted from ref. [110]

In the presence of HS^- its recognition occurs thanks to MUS^- release and HS^- binding to the zinc centre which results in the concomitant color change of the sample solution from colorless to yellow. Furthermore the fluorescence intensity of the zinc complex is higher than that of free MUSH, thus the complex acts as 'turn-off' H_2S sensor. The detection limit for H_2S was quoted down to 1 μM.

More recently our research group reported a simple copper porphyrin complex **(32)** as a 'turn on', sensitive and selective fluorescent probe for the detection of H_2S in aqueous media via a coordinative-based approach [113].

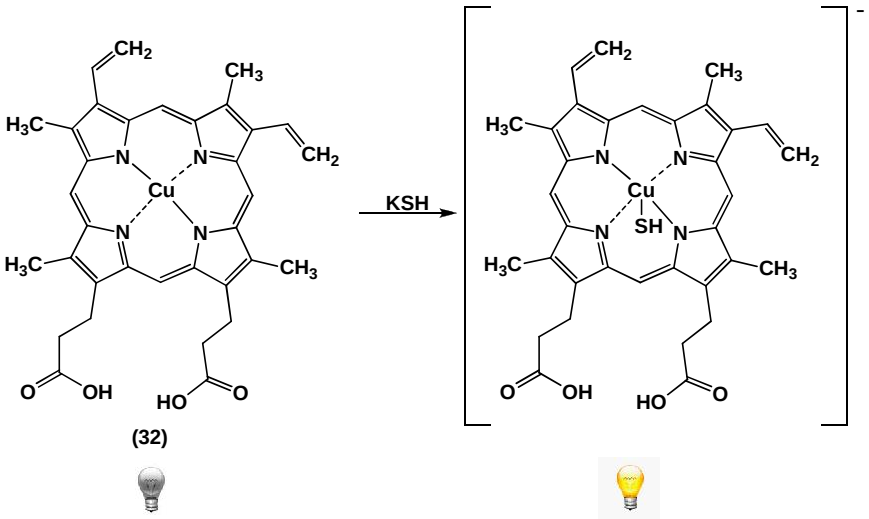


Figure 10. Schematic representation of the H_2S sensing mechanism by (**32)**.

The probe selectively and sensitively detect HS^- anions in basic water over other anions, biothiols and common oxidants such as H_2O_2. ^1H NMR and ESI MS experiments provided evidence that the turn-on of the fluorescence in the presence of H_2S is due to binding of the target analyte to the copper center. Extending our studies to metalloproteins, we reported that cobalt containing peptide deformylase (Co-PDF) can be implemented as a FRET-based H_2S sensor by the same coordinative-based approach [112]. We also reported the X-ray structure of the Co-PDF hydrosulfide adduct (see figure 11). The Co-PDF system operates as a 'turn-off' devise.

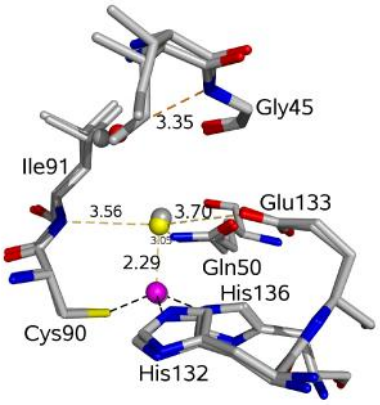


Figure 11. Coordination of hydrosulfide to Co-PDF (hydrosulfide in yellow and water in red). Water molecules alternating with hydrosulfide in the Co-PDF adduct are omitted for clarity.

Conclusions

Different strategies have been designed for the development of fluorescent metal complexes for the sensitive and selective detection of NO, CO and H_2S in solution and in intracellular environments. As for NO detection via transition metal complexes three different strategies have been devised over the decades: *(a)* fluorophore displacement; *(b)* ligand nitrosation; *(c)* and Cu^{2+} reduction by NO. The first approach resulted not suitable for the design of sensors working in biological environments because of the poor water solubility of most of the implemented systems. In addition, the possibility that water molecules can displace the fluorophore from the metal center causing fluorescence turn-on even in the absence of NO constitutes also a limitation when exploiting the first approach for the implementation of sensors for bioimaging purposes. The other two strategies resulted more effective in devising sensors for measurements of NO in living cells. The main difference between the ligand nitrosation approach and the Cu^{2+} reduction approach is that in the latter case NO recognition occurs only by Cu^{2+} reduction whereas the complete release of the organic ligand from the Cu(I) centre does not occur. Implementation of fluorescent transition metal complexes as CO sensors is at an earlier stage than that of NO sensors and research in this field is still in progress. Research efforts in the implementation of fluorescent transition metal complexes as H_2S sensors started much later than that on NO and CO sensors as a consequence of the recent discovery that H_2S is involved in various physiological and pathological functions within the human body. The two main strategies to devise transition metal complexes as H_2S sensors exploit the copper displacement approach and the coordinative-based approach. In both cases H_2S binds to the metal center but in the first case subsequent precipitation of the Mt-S occurs whereas in the second case removal of the target analyte can be possible, ensuring reversibility of the binding process, which in turns results in the reusability of the sensor. For sensing applications on real samples reusability of the sensor is of course highly desiderable.

We expect that the design strategies described here will trigger the development of new and improved probes to meet specific research needs and for practical applications. We foresee significant advances in this area in the near future.

Reference List

(1) Li, L.; Moore, P. K. Biochem.Soc.Trans. 35 (2007) 1138-1141.
(2) Koshland, D. E., Jr. Science 258 (1992) 1861.
(3) Culotta, E.; Koshland, D. E., Jr. Science 258 (1992) 1862-1865.
(4) Moncada, S.; Palmer, R. M.; Higgs, E. A. Pharmacol.Rev. 43 (1991) 109-142.
(5) Thomsen, L. L.; Miles, D. W. Cancer Metastasis Rev 17 (1998) 107-118.
(6) Lala, P. K. Cancer Metastasis Rev 17 (1998) 1-6.
(7) Durante, W.; Johnson, F. K.; Johnson, R. A. J Cell Mol.Med. 10 (2006) 672-686.
(8) Wagener, F. A.; Volk, H. D.; Willis, D.; Abraham, N. G.; Soares, M. P.; Adema, G. J.; Figdor, C. G. Pharmacol.Rev 55 (2003) 551-571.
(9) Lin, V. S.; Chang, C. J. Curr.Opin.Chem Biol 16 (2012) 595-601.
(10) Reiffenstein, R. J.; Hulbert, W. C.; Roth, S. H. Annu.Rev Pharmacol.Toxicol. 32 (1992) 109-134.
(11) Smith, R. P. Can.Med.Assoc.J. 118 (1978) 775-776.
(12) Smith, R. P. Am Sci 98 (2010) 6-9.
(13) Chen, C. Q.; Xin, H.; Zhu, Y. Z. Acta Pharmacol.Sin. 28 (2007) 1709-1716.
(14) Li, L.; Moore, P. K. Trends Pharmacol.Sci. 29 (2008) 84-90.
(15) Wang, R. Physiol Rev 92 (2012) 791-896.
(16) Liu, J.; Sun, Y. Q.; Zhang, J.; Yang, T.; Cao, J.; Zhang, L.; Guo, W. Chem Eur. J. 19 (2013) 4717-4722.
(17) White, B. R.; Liljestrand, H. M.; Holcombe, J. A. Analyst 133 (2008) 65-70.
(18) Ball, J. C.; Hurley, M. D.; Straccia, A. M.; Gierczak, C. A. Environ.Sci.Technol. 33 (1999) 1175-1178.
(19) Dooly, G.; Fitzpatrick, C.; Lewis, E. Energy 33 (2008) 657-666.
(20) Kumar, N.; Bhalla, V.; Kumar, M. Coordin Chem Rev 257 (2013) 2335-2347.
(21) Barker, S. L.; Kopelman, R.; Meyer, T. E.; Cusanovich, M. A. Anal.Chem. 70 (1998) 971-976.
(22) Barker, S. L.; Clark, H. A.; Swallen, S. F.; Kopelman, R.; Tsang, A. W.; Swanson, J. A. Anal.Chem. 71 (1999) 1767-1772.
(23) Barker, S. L.; Zhao, Y.; Marletta, M. A.; Kopelman, R. Anal.Chem. 71 (1999) 2071-2075.
(24) Strianese, M.; De Martino F.; Pavone, V.; Lombardi, A.; Canters, G. W.; Pellecchia, C. J.Inorg.Biochem. 104 (2010) 619-624.
(25) Liu, Z. P.; He, W. J.; Guo, Z. J. Chem Soc Rev 42 (2013) 1568-1600.
(26) Franz, K. J.; Singh, N.; Lippard, S. J. Angew.Chem.Int.Ed. 39 (2000) 2120-2122.
(27) Franz, K. J.; Singh, N.; Spingler, B.; Lippard, S. J. Inorg.Chem 39 (2000) 4081-4092.
(28) Hilderbrand, S. A.; Lippard, S. J. Inorg.Chem 43 (2004) 4674-4682.
(29) Hilderbrand, S. A.; Lim, M. H.; Lippard, S. J. J Am.Chem Soc. 126 (2004) 4972-4978.
(30) Lim, M. H.; Lippard, S. J. Inorg.Chem 43 (2004) 6366-6370.
(31) Kozhukh, J.; Lippard, S. J. J Am Chem Soc 134 (2012) 11120-11123.
(32) Victor, E.; Kim, S.; Lippard, S. J. Inorg.Chem 53 (2014) 12809-12821.
(33) Lim, M. H.; Kuang, C.; Lippard, S. J. Chembiochem. 7 (2006) 1571-1576.
(34) Lim, M. H.; Lippard, S. J. J Am.Chem Soc. 127 (2005) 12170-12171.
(35) Lim, M. H.; Xu, D.; Lippard, S. J. Nat Chem Biol 2 (2006) 375-380.
(36) Smith, R. C.; Tennyson, A. G.; Lim, M. H.; Lippard, S. J. Org.Lett. 7 (2005) 3573-3575.
(37) McQuade, L. E.; Ma, J.; Lowe, G.; Ghatpande, A.; Gelperin, A.; Lippard, S. J. Proc Natl Acad Sci USA 107 (2010) 8525-8530.
(38) Pluth, M. D.; Chan, M. R.; McQuade, L. E.; Lippard, S. J. Inorg.Chem 50 (2011) 9385-9392.
(39) Apfel, U. P.; Buccella, D.; Wilson, J. J.; Lippard, S. J. Inorg.Chem 52 (2013) 3285-3294.

(40) Lim, M. H.; Wong, B. A.; Pitcock, W. H.; Mokshagundam, D.; Baik, M. H.; Lippard, S. J. J Am Chem Soc 128 (2006) 14364-14373.
(41) Ghosh, M.; van den Akker, N. M.; Wijnands, K. A.; Poeze, M.; Weber, C.; McQuade, L. E.; Pluth, M. D.; Lippard, S. J.; Post, M. J.; Molin, D. G.; van Zandvoort, M. A. PLoS.One. 8 (2013) e75331.
(42) Franz, K. J.; Singh, N.; Lippard, S. J. unpublished results 2015.
(43) Hilderbrand, S. A.; Lippard, S. J. Inorg Chem 43 (2004) 5294-5301.
(44) Tsuge, K.; DeRosa, F.; Lim, M. D.; Ford, P. C. J Am.Chem Soc. 126 (2004) 6564-6565.
(45) Khin, C.; Lim, M. D.; Tsuge, K.; Iretskii, A.; Wu, G.; Ford, P. C. Inorg.Chem. 46 (2007) 9323-9331.
(46) Lim, M. H.; Lippard, S. J. Acc.Chem.Res. 40 (2007) 41-51.
(47) McQuade, L. E.; Pluth, M. D.; Lippard, S. J. Inorg Chem 49 (2010) 8025-8033.
(48) Hu, X. Y.; Wang, J.; Zhu, X.; Dong, D. P.; Zhang, X. L.; Wu, S. O.; Duan, C. Y. Chem Commun 47 (2011) 11507-11509.
(49) Hu, X. Y.; Zhang, X. L.; Song, H. L.; He, C.; Bao, Y. M.; Tang, Q.; Duan, C. Y. Tetrahedron 68 (2012) 8371-8375.
(50) Sarma, M.; Kalita, A.; Kumar, P.; Singh, A.; Mondal, B. J Am Chem Soc 132 (2010) 7846-7847.
(51) Sarma, M.; Singh, A.; Gupta, G. S.; Das, G.; Mondal, B. Inorg Chim Acta 363 (2010) 63-70.
(52) Mondal, B.; Kumar, P.; Ghosh, P.; Kalita, A. Chem Commun 47 (2011) 2964-2966.
(53) Kumar, P.; Kalita, A.; Mondal, B. Dalton Trans 41 (2012) 10543-10548.
(54) Soh, N.; Katayama, Y.; Maeda, M. Analyst 126 (2001) 564-566.
(55) Katayama, Y.; Takahashi, S.; Maeda, M. Anal Chim Acta 365 (1998) 159-167.
(56) Ortiz, M.; Torrens, M.; Mola, J. L.; Ortiz, P. J.; Fragoso, A.; Diaz, A.; Cao, R.; Prados, P.; de, M. J.; Otero, A.; Antinolo, A.; Lara, A. Dalton Trans. (2008) 3559-3566.
(57) Patra, A. K.; Rose, M. J.; Murphy, K. A.; Olmstead, M. M.; Mascharak, P. K. Inorg.Chem. 43 (2004) 4487-4495.
(58) Choi, A. W.; Yim, V. M.; Liu, H. W.; Lo, K. K. Chem Eur J 20 (2014) 9633-9642.
(59) Choi, A. W.-T.; Poon, C. S.; Liu, H. W.; Cheng, H. K.; Lo, K. K.-W. New J.Chem. 37 (2013) 1711-1719.
(60) Toscani, A.; Marin-Hernandez, C.; Moragues, M. a. E.; Sancenon, F. ; Dingwall, P.; Brown, N. J.; Martinez-Manez, R. ; White, A. J. P.; Wilton-Ely, J. D. E. T. Chem.Eur.J. 21 (2015) 14529-14538.
(61) Michel, B. W.; Lippert, A. R.; Chang, C. J. J Am Chem Soc 134 (2012) 15668-15671.
(62) Moragues, M. E.; Toscani, A.; Sancenon, F.; Martinez-Manez, R.; White, A. J. P.; Wilton-Ely, J. D. E. T. J Am Chem Soc 136 (2014) 11930-11933.
(63) Gulino, A.; Gupta, T.; Altman, M.; Lo Schiavo, S.; Mineo, P. G.; Fragala, I. L.; Evmenenko, G.; Dutta, P.; van der Boom, M. E. Chem Commun (2008) 2900-2902.
(64) ito-Garagorri, D.; Puchberger, M.; Mereiter, K.; Kirchner, K. Angew.Chem.Int.Ed. 47 (2008) 9142-9145.
(65) Moragues, M. E.; Esteban, J.; Ros-Lis, J. V.; Martinez-Manez, R.; Marcos, M. D.; Martinez, M.; Soto, J.; Sancenon, F. J Am Chem Soc 133 (2011) 15762-15772.
(66) Esteban, J.; Ros-Lis, J. V.; Martinez-Manez, R. ; Marcos, M. D.; Moragues, M.; Soto, J.; Sancenon, F. Angew.Chem.Int.Ed. 49 (2010) 4934-4937.
(67) Chakravarty, A. R.; Cotton, F. A.; Tocher, D. A.; Tocher, J. H. Organometallics 4 (1985) 8-13.
(68) Tate, C. W.; deMello, A.; Gee, A. D.; Kealey, S.; Vilar, R.; White, A. J. P.; Long, N. J. Dalton Trans 41 (2012) 83-89.
(69) Lin, V. S.; Lippert, A. R.; Chang, C. J. Proc.Natl.Acad.Sci.U.S.A 110 (2013) 7131-7135.

(70) Yang, G. D.; Wu, L. Y.; Jiang, B.; Yang, W.; Qi, J. S.; Cao, K.; Meng, Q. H.; Mustafa, A. K.; Mu, W. T.; Zhang, S. M.; Snyder, S. H.; Wang, R. Science 322 (2008) 587-590.
(71) Papapetropoulos, A.; Pyriochou, A.; Altaany, Z.; Yang, G.; Marazioti, A.; Zhou, Z.; Jeschke, M. G.; Branski, L. K.; Herndon, D. N.; Wang, R.; Szabo, C. Proc.Natl.Acad.Sci.U.S.A 106 (2009) 21972-21977.
(72) Yu, C. M.; Li, X. Z.; Zeng, F.; Zheng, F. Y.; Wu, S. Z. Chem Commun 49 (2013) 403-405.
(73) Wang, X.; Sun, J.; Zhang, W.; Ma, X.; Lv, J.; Tang, B. Chem.Sci. 4 (2013) 2551-2556.
(74) Zhou, G.; Wang, H.; Ma, Y.; Chen, X. Tetrahedron 69 (2013) 867-870.
(75) Chen, S.; Chen, Z. J.; Ren, W.; Ai, H. W. J.Am.Chem Soc. 134 (2012) 9589-9592.
(76) Chen, T.; Zheng, Y.; Xu, Z.; Zhao, M.; Xu, Y.; Cui, J. Tetrahedron Lett 54 (2013) 2980-2982.
(77) Mao, G. J.; Wei, T. T.; Wang, X. X.; Huan, S. Y.; Lu, D. Q.; Zhang, J.; Zhang, X. B.; Tan, W.; Shen, G. L.; Yu, R. Q. Anal.Chem 85 (2013) 7875-7881.
(78) Quek, Y. L.; Tan, C. H.; Bian, J.; Huang, D. Inorg.Chem 50 (2011) 7379-7381.
(79) Tropiano, M.; Faulkner, S. Chem Commun. 50 (2014) 4696-4698.
(80) Takashima, I.; Kinoshita, M.; Kawagoe, R.; Nakagawa, S.; Sugimoto, M.; Hamachi, I.; Ojida, A. Chem Eur. J 20 (2014) 2184-2192.
(81) Lin, V. S.; Chang, C. J. Curr.Opin.Chem Biol 16 (2012) 595-601.
(82) Chen, S.; Chen, Z. J.; Ren, W.; Ai, H. W. J.Am.Chem Soc. 134 (2012) 9589-9592.
(83) Lippert, A. R.; New, E. J.; Chang, C. J. J.Am.Chem Soc. 133 (2011) 10078-10080.
(84) Peng, H.; Cheng, Y.; Dai, C.; King, A. L.; Predmore, B. L.; Lefer, D. J.; Wang, B. Angew.Chem Int.Ed Engl. 50 (2011) 9672-9675.
(85) Yu, F.; Li, P.; Song, P.; Wang, B.; Zhao, J.; Han, K. Chem Commun. 48 (2012) 2852-2854.
(86) Das, S. K.; Lim, C. S.; Yang, S. Y.; Han, J. H.; Cho, B. R. Chem Commun. 48 (2012) 8395-8397.
(87) Montoya, L. A.; Pluth, M. D. Chem Commun. 48 (2012) 4767-4769.
(88) Zheng, K.; Lin, W.; Tan, L. Org.Biomol.Chem 10 (2012) 9683-9688.
(89) Wu, Z.; Li, Z.; Yang, L.; Han, J.; Han, S. Chem Commun. 48 (2012) 10120-10122.
(90) Qian, Y.; Karpus, J.; Kabil, O.; Zhang, S. Y.; Zhu, H. L.; Banerjee, R.; Zhao, J.; He, C. Nat.Commun. 2 (2011) 495.
(91) Liu, C.; Pan, J.; Li, S.; Zhao, Y.; Wu, L. Y.; Berkman, C. E.; Whorton, A. R.; Xian, M. Angew.Chem Int.Ed Engl. 50 (2011) 10327-10329.
(92) Liu, C.; Peng, B.; Li, S.; Park, C. M.; Whorton, A. R.; Xian, M. Org.Lett. 14 (2012) 2184-2187.
(93) Zhao, Y.; Zhu, X.; Kan, H.; Wang, W.; Zhu, B.; Du, B.; Zhang, X. Analyst 137 (2012) 5576-5580.
(94) Sasakura, K.; Hanaoka, K.; Shibuya, N.; Mikami, Y.; Kimura, Y.; Komatsu, T.; Ueno, T.; Terai, T.; Kimura, H.; Nagano, T. J.Am.Chem Soc. 133 (2011) 18003-18005.
(95) Choi, M. G.; Cha, S.; Lee, H.; Jeon, H. L.; Chang, S. K. Chem Commun.(2009) 7390-7392.
(96) Hou, F.; Huang, L.; Xi, P.; Cheng, J.; Zhao, X.; Xie, G.; Shi, Y.; Cheng, F.; Yao, X.; Bai, D.; Zeng, Z. Inorg.Chem 51 (2012) 2454-2460.
(97) Wang, M. Q.; Li, K.; Hou, J. T.; Wu, M. Y.; Huang, Z.; Yu, X. Q. J.Org.Chem 77 (2012) 8350-8354.
(98) Cao, X.; Lin, W.; He, L. Org.Lett. 13 (2011) 4716-4719.
(99) Wu, M. Y.; Li, K.; Hou, J. T.; Huang, Z.; Yu, X. Q. Org.Biomol.Chem 10 (2012) 8342-8347.
(100) Xuan, W.; Pan, R.; Cao, Y.; Liu, K.; Wang, W. Chem Commun. 48 (2012) 10669-10671.
(101) Lin, V. S.; Chang, C. J. Curr.Opin.Chem Biol 16 (2012) 595-601.
(102) Sasakura, K.; Hanaoka, K.; Shibuya, N.; Mikami, Y.; Kimura, Y.; Komatsu, T.; Ueno, T.; Terai, T.; Kimura, H.; Nagano, T. J.Am.Chem Soc. 133 (2011) 18003-18005.
(103) Choi, M. G.; Cha, S.; Lee, H.; Jeon, H. L.; Chang, S. K. Chem Commun. (2009) 7390-7392.

(104) Hou, F.; Huang, L.; Xi, P.; Cheng, J.; Zhao, X.; Xie, G.; Shi, Y.; Cheng, F.; Yao, X.; Bai, D.; Zeng, Z. Inorg.Chem 51 (2012) 2454-2460.
(105) Zhang, D.; Jin, W. Spectrochim.Acta A Mol.Biomol.Spectrosc. 90 (2012) 35-39.
(106) Santos-Figueroa, L. E.; de la Torre, C.; El Sayed, S.; Sancenon, F.; Martinez-Manez, R.; Costero, A. M.; Gil, S.; Parra, M. Eur J Inorg Chem 2014 (2014) 41-45.
(107) Ye, Z.; An, X.; Song, B.; Zhang, W.; Dai, Z.; Yuan, J. Dalton Trans. 43 (2014) 13055-13060.
(108) Strianese, M.; Milione, S.; Bertolasi, V.; Pellecchia, C.; Grassi, A. Inorg Chem 50 (2011) 900-910.
(109) Guo, Z.; Chen, G. Q.; Zeng, G. M.; Li, Z. W.; Chen, A. W.; Wang, J. J.; Jiang, L. B. Analyst 140 (2015) 1772-1786.
(110) Galardon, E.; Tomas, A.; Roussel, P.; Artaud, I. Dalton Trans (2009) 9126-9130.
(111) Strianese, M.; De Martino F.; Pellecchia, C.; Ruggiero, G.; D'Auria, S. Protein Pept.Lett. 18 (2011) 282-286.
(112) Strianese, M.; Palm, G. J.; Milione, S.; Kuhl, O.; Hinrichs, W.; Pellecchia, C. Inorg.Chem 51 (2012) 11220-11222.
(113) Mirra, S.; Milione, S.; Strianese, M.; Pellecchia, C. Eur J Inorg Chem (2015) 2272-2276.
(114) Strianese, M.; Mirra, S.; Bertolasi, V.; Milione, S.; Pellecchia, C. New J.Chem. 39 (2015) 4093-4099.
(115) Choi, M. G.; Cha, S.; Lee, H.; Jeon, H. L.; Chang, S. K. Chem Commun (2009) 7390-7392.
(116) Sasakura, K.; Hanaoka, K.; Shibuya, N.; Mikami, Y.; Kimura, Y.; Komatsu, T.; Ueno, T.; Terai, T.; Kimura, H.; Naganot, T. J Am Chem Soc 133 (2011) 18003-18005.
(117) Hou, F.; Cheng, J.; Xi, P.; Chen, F.; Huang, L.; Xie, G.; Shi, Y.; Liu, H.; Bai, D.; Zeng, Z. Dalton Trans 41 (2012) 5799-5804.
(118) Wang, M. Q.; Li, K.; Hou, J. T.; Wu, M. Y.; Huang, Z.; Yu, X. Q. J.Org.Chem. 77 (2012) 8350-8354.
(119) Zhang, L.; Lou, X.; Yu, Y.; Qin, J.; Li, Z. Macromolecules 44 (2011) 5186-5193.
(120) Hou, F. P.; Huang, L.; Xi, P. X.; Cheng, J.; Zhao, X. F.; Xie, G. Q.; Shi, Y. J.; Cheng, F. J.; Yao, X. J.; Bai, D. C.; Zeng, Z. Z. Inorg.Chem. 51 (2012) 2454-2460.
(121) Santos-Figueroa, L. E.; de la Torre, C.; El Sayed, S.; Sancenon, F.; Martinez-Manez, R.; Costero, A. M.; Gil, S.; Parra, M. Eur J Inorg Chem 2014 (2014) 41-45.
(122) Kar, C.; Adhikari, M. D.; Ramesh, A.; Das, G. Inorg Chem 52 (2013) 743-752.
(123) Mudalige, D. C.; Ma, E. S.; Rettig, S. J.; James, B. R.; Cullen, W. R. Inorg.Chem. 36 (1997) 5426-&.
(124) Pleus, J.; Waden, H.; Saak, W.; Haase, D.; Pohl, S. J.Chem.Soc., Dalton Trans. (1999) 2601-2610.
(125) Rombach, M.; Vahrenkamp, H. Inorg.Chem. 40 (2001) 6144-6150.
(126) Pavlik, J. W.; Noll, B. C.; Oliver, A. G.; Schulz, C. E.; Scheidt, W. R. Inorg.Chem. 49 (2010) 1017-1026.
(127) Galardon, E.; Tomas, A.; Selkti, M.; Roussel, P.; Artaud, I. Inorg.Chem. 48 (2009) 5921-5927.
(128) Galardon, E.; Roger, T.; Deschamps, P.; Roussel, P.; Tomas, A.; Artaud, I. Inorg.Chem. 51 (2012) 10068-10070.

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Metal complexes as fluorescent probes for sensing biologically relevant gas molecules

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