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Review

Metal complexes as fluorescent probes for sensing biologically relevant gas molecules

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ABSTRACT

The 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 the 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.

1. Introduction

Nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) are the main examples of biologically active gases which occur naturally in the human body [1]. These gaseous molecules affect physiological and/or patho-physiological functions within the human body. NO, CO and H_2S participate in the regulation of vascular homeostasis 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 progress 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

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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].

2. 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 in 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 based 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 submicromolar level by means of a FRET (Förster Resonance Energy Transfer) mechanism [24]. Metalloprotein-based probes, however, will not be discussed in the present review.

2.1. Transition metal-based fluorescent probes

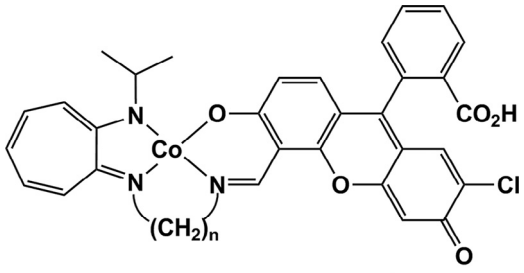
Differently than purely organic NO probes, metal-based probes detect NO directly. Existing transition metal-based fluorescent probes for NO detection have been subdivided into three different categories (depending on the reaction mechanism by which NO recognition occurs) [20,25]: *(a)* fluorophore displacement; *(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.

All the three mechanisms rely on the ability of transition metals with an 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 [26]. 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 [27–34] and the Cu^{2+} reduction approach [35–42].

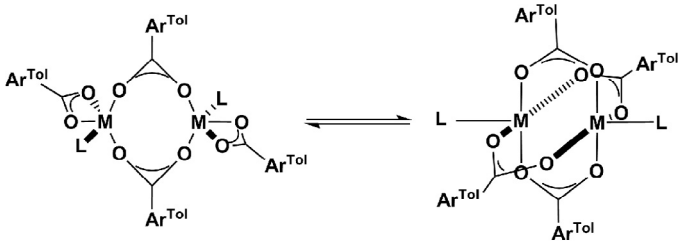
One of the first NO sensing device, belonging to the category *(a)*, is a cobalt complex with a mixed aminotroponiminate salicylaldiminate ligand **(1)** where the two aminotroponiminate moieties bear two dansyl substituents [27] (Fig. 1).

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, $Co(NO)_2(i\text{-}Pr_2ATI)$ [43]. 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, another family of cobalt based NO sensors **(5)** was proposed [29].



(5) **n=** 3, 4

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. Carboxylate-bridged diiron(II) and dicobalt(II) complexes as NO sensors **(6)** have been synthesized and tested [44].



(6)

M= Fe (II), Co (II)

L= a nitrogen base

Again, both the diiron and the dicobalt complexes 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