

Bioinorganic Chemistry of Hydrogen Sulfide: Detection, Delivery, and Interactions with Metalloproteins

Joshua J. Woods & Justin J. Wilson
Cornell University, Ithaca, NY, USA

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1 INTRODUCTION

For the majority of the twentieth century, the gaseous small molecule hydrogen sulfide (H₂S) has been known for its toxicity and characteristic rotten egg smell. Only after a series of investigations on the metabolism of sulfur-containing amino acids was it discovered that H₂S is produced endogenously in mammals.^{1–8} Following this revelation, H₂S is now recognized to be the third gasotransmitter, a small gaseous molecule that mediates cellular signaling processes, joining carbon monoxide (CO) and nitric oxide (NO; see *Nitrogen Monoxide (Nitric Oxide): Bioinorganic Chemistry*) in this role.⁹ The biological activity of H₂S and related polysulfides (H₂S_n) is highly diverse, and within the last two decades, they have received significant attention for their ability to regulate cell death signaling,^{10,11} cancer biology,¹² the cardiovascular system,^{13,14} the nervous system,^{15,16} and metabolism.^{17,18} It has been hypothesized that a number of the observed biological actions of H₂S stem from its interaction with biologically relevant metals and metalloproteins.^{19–21} Thus, in-depth investigations of the coordination chemistry of H₂S and HS[−] in simple transition metal complexes have shed light on these interactions and highlighted the diverse reactivity of this gas and related sulfur species with metal ions (see *Sulfur: Inorganic Chemistry*).^{22–35} In addition to its roles in maintaining normal

biological function, H₂S has received significant attention for its therapeutic potential for the treatment of pathological conditions such as ischemic-reperfusion injury, stroke, and Alzheimer's disease.^{36–39} As such, there has been a significant amount of research devoted to developing molecules to detect and deliver H₂S in biological systems.⁴⁰ These compounds have been invaluable for studying the biological activity of this gas. This article will focus on the role of inorganic chemistry in the biology of H₂S. Specifically, a description of the nature of chemical interactions of H₂S with metalloproteins and the use of metal complexes for both the detection and delivery of this gasotransmitter will be provided. The body of work presented in this review highlights the significance of bioinorganic H₂S chemistry and will motivate future work in this area.

2 PROPERTIES AND ENDOGENOUS PRODUCTION OF H₂S

H₂S is weakly acidic with pK_a values of 7.02 and >17 at 25 °C.^{41,42} In pH 7.4 aqueous solution, approximately 72% of the total H₂S exists in the form of HS[−]_(aq) and 28% as H₂S_(aq). Despite early speculation to the contrary,^{43,44} the dianionic S^{2−} does not exist in aqueous solution.⁴⁵ H₂S is slightly hydrophobic with a water-octanol partition coefficient of 0.64 at pH 7.4, thereby enabling it to efficiently permeate cell membranes.⁴⁶ The anion HS[−] is a potent nucleophile that readily reacts with reactive oxygen, nitrogen, and sulfur species (ROS, RNS, and RSS, respectively) in addition to biologically relevant metals and metalloproteins.^{20,47} This high nucleophilicity has been implicated as a key feature of the biological chemistry of H₂S and has also been leveraged in molecular strategies to detect this gasotransmitter in solution. In complex biological systems, sulfur can attain oxidation states ranging from −2 in H₂S to +6 in SO₄^{2−}. With the sulfur atom of H₂S in its lowest oxidation state, this molecule can be easily oxidized under biological conditions, giving rise to other biologically relevant RSS (see *Sulfur: Organic Polysulfanes*).⁴⁸ Its high nucleophilicity and ability to undergo a wide range of redox reactions make studying the biological chemistry of H₂S particularly challenging.

Enzymatic production of H₂S relies primarily on the activity of cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE), and the combined action of cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3MST).^{49,50} H₂S can also be produced nonenzymatically through metabolism of naturally occurring polysulfides, bacterial reduction of sulfur-containing species in the intestinal tract, and catalytic reduction of sulfur-containing amino acids in blood.^{51–53} A summary of the major production pathways for enzymatic production of H₂S is given in Figure 1. CBS is expressed primarily

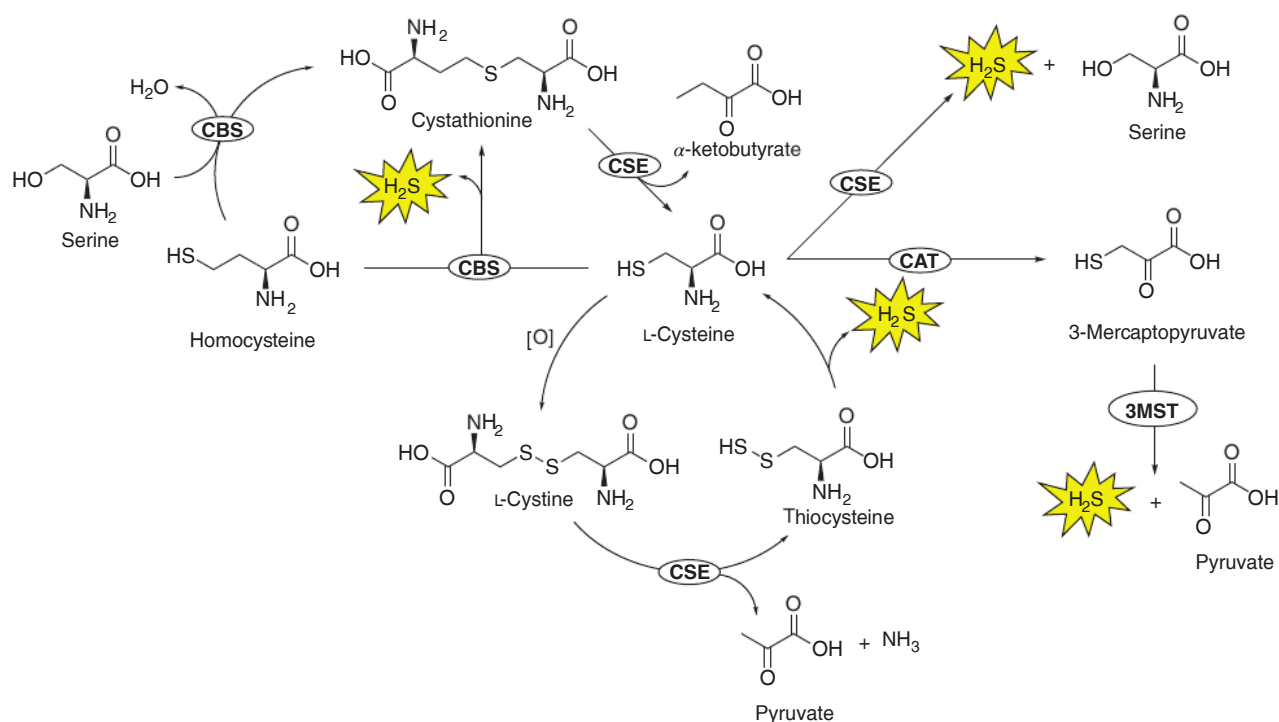


Figure 1 Summary of the major H_2S production pathways by cystathionine- β -synthase (CBS), cystathionine- γ -lyase (CSE), and the combined action of cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3MST)

in the central nervous system and liver,⁵⁴ whereas CSE is more broadly distributed throughout the rest of the body. CSE knockout ($\text{CSE}^{-/-}$) mice have decreased circulating H_2S levels compared to the wild-type mice.⁵⁵ Canonically, CBS catalyzes the pyridoxal 5'-phosphate (PLP) dependent condensation of L-homocysteine and L-serine to generate L-cystathionine,⁵⁶ and CSE promotes cleavage of L-cystathionine to yield L-cysteine, ammonia, and α -ketobutyrate. Both enzymes are able to produce H_2S through a number of different pathways starting from cysteine or homocysteine.^{10,57–59} CBS is allosterically activated by *S*-adenosyl-L-methionine (AdoMet), which binds to the regulatory C-terminal domain.⁶⁰ It has been suggested that CBS is further regulated by NO and CO, which can bind to the heme center located in the N-terminal domain.^{61–66} In contrast to CBS, the biological regulation of CSE is poorly understood. It has been suggested that H_2S production by CSE increases in the presence of calcium and/or calmodulin.⁵⁵ Other studies have found that elevated Ca^{2+} levels decrease H_2S production.⁶⁷ Unlike CBS, which is constitutively expressed within cells, the expression of CSE is highly inducible; its expression in tissues is modulated by a range of stimuli including endoplasmic reticulum (ER) stress, oxidative stress, NO, and nutrient deprivation.⁶⁸

CAT and 3MST generate H_2S through a sequential two-step reaction process. L-cysteine is converted to

3-mercaptopyruvate by CAT, which in turn is converted to pyruvate by 3MST with the release of H_2S .⁶⁹ This pathway was first discovered in $\text{CBS}^{-/-}$ mice, where the brain levels of H_2S were relatively unchanged compared to those in wild-type mice.⁷⁰ Rather little is understood of the activity and regulation of H_2S production via this pathway, although it has been shown that CAT is highly regulated by cellular Ca^{2+} levels.⁷¹ In the structure of 3MST, a central cysteine residue (Cys248) is required for enzyme function.⁶⁹

3 INTERACTIONS WITH METALLOPROTEINS

3.1 Hemeproteins and Synthetic Heme Systems

Heme-containing systems are interesting platforms that can bind to and activate a number of small molecules including O_2 , CO, and NO. The interactions of these and related small molecules with both natural and synthetic heme systems have been studied in great detail (see *Cytochrome Oxidase; Iron: Heme Proteins & Dioxygen Transport & Storage; Iron: Heme Proteins, Mono- & Dioxygenases; Iron: Heme Proteins, Peroxidases, Catalases & Catalase-Peroxidases*).^{72–74} Consequently, the chemistry of H_2S with hemeproteins, which has been recently reviewed,^{10,20,26,75} has received significant attention compared to other metalloproteins. The nature of these

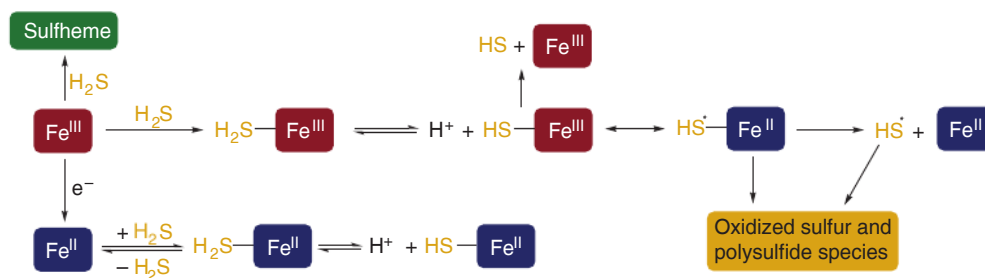


Figure 2 Possible pathways for H_2S interactions with heme proteins

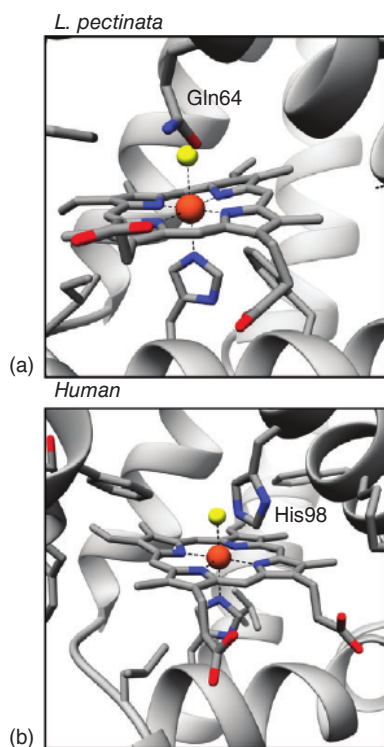


Figure 3 X-ray crystal structures of sulfide-bound (a) HbI from *L. pectinata*¹⁰⁷ and (b) human hemoglobin¹⁰³ (PDB: 1MOH, 5UCU). [(a) Based on Rizzi, M., Wittenberg, J. B., Coda, A., Ascenzi, P., & Bolognesi, M. (1996). Structural bases for sulfide recognition in *Lucina pectinata* hemoglobin I. *Journal of Molecular Biology*, 258(1), 1–5. (b) Source: Based on V. Vitvitsky, P. K. Yadav, S. An, J. Seravalli, Structural and Mechanistic Insights into Hemoglobin-catalyzed Hydrogen Sulfide Oxidation and the Fate of Polysulfide Products, U. S. Cho, R. Banerjee, *J. Biol. Chem.* 2017, 292, 5584–5592]

reactions, summarized in Figure 2, is highly dependent on the surface accessibility of the heme center, the polarity of the local protein environment, and the identity and position of distal residues within the active site.^{76,77}

A multitude of studies involving neuroglobins,^{78,79} hemoglobins,^{80–83} myoglobins,^{84–86} metalloenzymes,^{87–90}

and synthetic heme systems^{91–101} have highlighted the diverse reactivity of H_2S with heme centers. H_2S or HS^- can bind ferric heme (Fe^{III}) and, in some cases, reduce the ferric center to ferrous (Fe^{II}) iron to generate hydrothiyl (HS^{\cdot})– Fe^{II} type complexes.^{93,96} These compounds undergo further reactions to generate oxidized sulfur and polysulfide species (Figure 2).^{83,84,86,88,99,102,103} Such polysulfides have been implicated in the S-sulfhydration of various proteins, which mediates many of the biological roles of H_2S .^{103–106}

Ferric heme can reversibly bind $\text{H}_2\text{S}/\text{HS}^-$ for transport or storage to prevent sulfide toxicity.^{84,107,108} For example, it has been speculated that neuroglobin plays a protective role by binding sulfide under conditions of elevated brain sulfide levels.⁷⁹ In addition, H_2S has been shown to attenuate lipid peroxidation in atherosclerotic lesions to prevent a proinflammatory response. It was hypothesized that this result was due to the ability of H_2S to prevent formation of oxidized hemoglobin,¹⁰⁹ illustrating how the cardioprotective effects of this gas may arise from its interaction with metalloproteins. Ferrous heme may also bind sulfide but with significantly lower affinity than the corresponding Fe^{III} species (Figure 2).^{75,95,108}

One of the best-characterized examples of $\text{H}_2\text{S}/\text{HS}^-$ binding to naturally occurring hemoproteins can be found in studies of the hemoglobin I (HbI), II (HbII), and III (HbIII) proteins isolated from the mollusk *Lucina pectinata*.¹¹⁰ These mollusks exist in a symbiotic relationship with autotrophic bacteria that oxidize H_2S . HbI is a sulfide-reactive hemoglobin that is functionally devoted to sulfide transport. Nucleophilic attack of H_2S on oxygen-bound HbI displaces the bound superoxide anion. The resulting ferric hemoglobin sulfide transports the bound sulfide to the autotrophic bacteria. By contrast, HbII and HbIII only bind H_2S in the absence of O_2 . On the basis of these results, it was hypothesized that HbI is selectively used to transport H_2S , whereas HbII and HbIII facilitate delivery of O_2 .¹⁰⁸ X-ray crystallographic analysis of sulfide-bound HbI revealed the importance of a glutamine residue (Gln64) at the distal ligand-binding site (Figure 3a). It is hypothesized that this residue is important in facilitating the relatively fast sulfide association rate, in addition

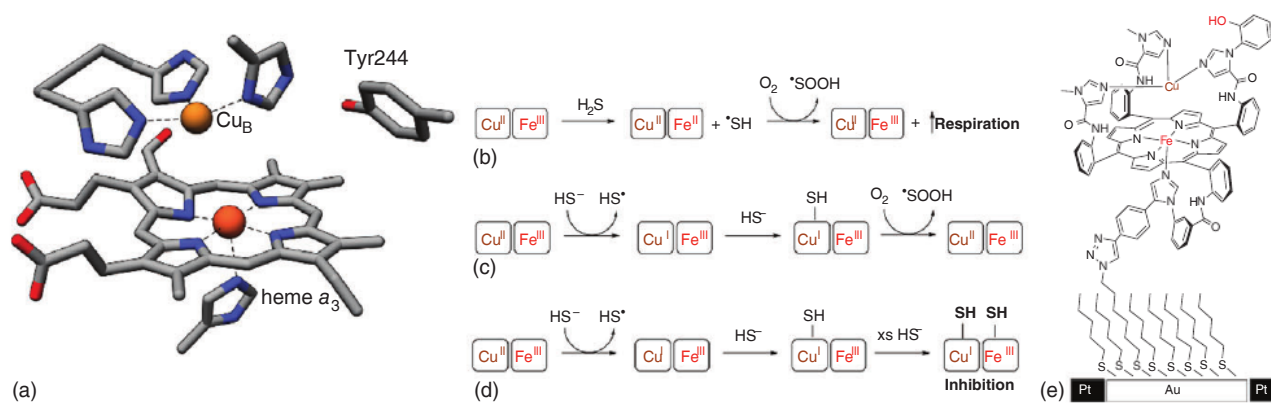


Figure 4 (a) Structure of the active site of human CcO (PDB 5Z62).¹¹⁷ [Based on Zong, S., Wu, M., Gu, J., Liu, T., Guo, R., & Yang, M. (2018). Structure of the intact 14-subunit human cytochrome c oxidase. *Cell Research*]. (b–d) Proposed interactions between CcO and (b) low (≤ 1 equiv.), (c) moderate (2–3 equiv.), and (d) high (> 4 equiv.) H₂S concentrations. (e) Structure of the CcO model complex, attached to a rotating gold electrode, that was used to probe the reaction between CcO and H₂S

to stabilizing the bound sulfide through hydrogen-bonding interactions. Four distal phenylalanine residues, which are unique to HbI, create a hydrophobic pocket that stabilizes the iron-bound sulfide and protects it against oxidation or solvation.^{107,111} In human hemoglobin-sulfide, the distal histidine residue (His98; Figure 3b) participates in hydrogen-bonding interactions similar to Gln64 in HbI.¹⁰³ It was hypothesized that ferric human hemoglobin acts similar to *L. pectinata* HbI to transport H₂S in the blood.¹¹² Given that human hemoglobin binds H₂S with considerably lower affinity and is subsequently reduced to generate ferrous hemoglobin and RSS,⁸⁴ this transport mechanism is unlikely.

In addition to hemoglobin and myoglobin, the heme proteins cytochrome *c* (Cc)¹⁰² and cytochrome *c* oxidase (CcO)¹¹³ have received significant attention for their reactivity with H₂S, as well as the other two gasotransmitters, CO and NO.^{102,114–116} CcO is the final enzyme of the mitochondrial electron transport chain that uses electrons supplied by Cc to reduce O₂ to water. The protons that are produced from this reaction are translocated across the mitochondrial membrane to generate an electrochemical potential that is used for downstream production of adenosine triphosphate (ATP). The active site of this transmembrane metalloenzyme contains a heme center (a₃) and a Cu^{II} center (Cu_B; Figure 4a).

The ability of H₂S to attenuate the activity of CcO has been known since 1929.¹¹⁸ The nature of the interaction between CcO and H₂S is complex and the biological consequences of this interaction are highly concentration dependent.^{113,119,120} At low concentrations (~ 1 equiv.), H₂S reduces heme a₃, but the low binding affinity of H₂S for the ferrous heme ($\sim 12.5 \mu\text{M}$) prevents sulfide binding to the Fe^{II} center (Figure 4b). This reduction event, which leads to production of RSS and increased O₂ consumption,

may suggest that H₂S and related RSS act as substrates for mitochondrial energy production in conditions of low energy supply, such as hibernation.^{113,121–124} At slightly higher H₂S concentrations (2–3 equiv.), the Cu^{II} site is reduced and reversibly binds H₂S. This interaction is reversed by O₂, which oxidizes the Cu^I center, releasing the bound H₂S (Figure 4c).¹²⁰ When a large excess of H₂S (> 4 equiv.) is supplied, reduction of the Cu^{II} center and subsequent binding of H₂S induces a conformational change that allows for another equivalent of H₂S to bind heme a₃, which results in irreversible inhibition of CcO (Figure 4d).^{119,121} A functional small-molecule model of the CcO active site (Figure 4e) was employed to gain further insight on the interactions of this enzyme with H₂S.¹²⁰ This model complex, which faithfully captures the coordination environments and proximities of the copper Cu_B center, heme a₃, and the putative redox-active Tyr244, was found to be well suited as a mimic for the CcO active site, which exhibited reactivity with H₂S that strongly supported hypotheses formulated based on previous studies using the intact enzyme.

In addition to metal reduction and coordination, an alternative mode of interaction of H₂S with hemes arises from its direct incorporation into one of the heme pyrrole rings to furnish sulfheme derivatives. This activity was observed in early investigations of the interaction between H₂S and hemoglobin or myoglobin.^{125–128} The three general classes of sulfheme derivatives, sulfheme A (an episulfide), sulfheme B (a ring-opened episulfide), and sulfheme C (a thiochlorin) are shown in Figure 5.^{129–134} In comparison to natural heme proteins, sulfheme proteins have significant differences in their ligand-binding properties, which arise predominately from electronic rather than steric effects.^{128,129} The exact mechanisms of sulfheme formation are unclear but have been suggested to involve

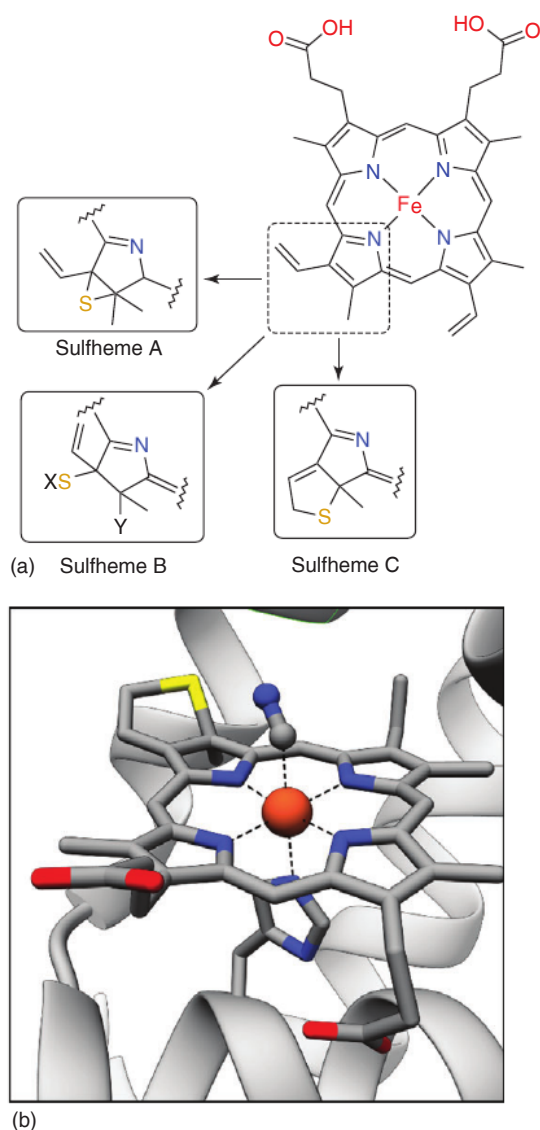


Figure 5 (a) Diagram of three sulfheme products formed through covalent addition of sulfide to the porphyrin ring. (b) X-ray crystal structure of cyanide-bound myoglobin containing sulfheme C (PDB: 1YMC).¹²⁹ [(b) Based on Evans, S. V., Sishta, B. P., Mauk, A. G., & Brayer, G. D. (1994). Three-dimensional structure of cyanomet-sulfmyoglobin C. *Proceedings of the National Academy of Sciences*, 91(11), 4723–4726]

oxoferryl ($\text{Fe}^{\text{IV}}=\text{O}$) intermediates.^{10,89,135} The secondary coordination sphere, specifically a His residue in the distal position of the enzyme active site, has been shown to be important for the production sulfheme species in some cases.^{77,135} For example, human hemoglobin, which contains this distal residue, forms sulfheme derivatives whereas HbI from *L. pectinata*, which contains distal Gln instead, does not. Site-directed mutagenesis of this Gln residue to a His residue allowed this protein to convert to the sulfheme form upon exposure to H_2S .⁷⁷ By contrast, CcO, which

contains His residues near the active site, does not form sulfheme in the presence of H_2S . In this particular case, it has been hypothesized that these His residues do not have the proper orientation and therefore cannot interact with the heme center to promote sulfheme formation.⁷⁶ Sulfheme derivatives of the metalloenzymes catalase and lactoperoxidase have also been observed.^{89,136} Given their poor affinity for O_2 and inability to be converted back to normal hemoproteins,^{125,137,138} it is unlikely that sulfheme species play a role in cellular signaling, but instead mediate the toxic effects of this gas. For example, elevated sulfheme levels induce a toxic condition known as sulfhemoglobinemia due to their inability to adequately bind O_2 .¹³⁹

3.2 Zinc-Containing Proteins

The interactions between spectroscopically silent Zn-containing proteins and H_2S have received relatively little attention compared to those for other metalloproteins.¹⁰ Proteins containing the zinc finger (ZF) motif are particularly important, as evidenced by their high abundance in eukaryotic cells. ZFs are small, folded domains that are stabilized by coordination to a structural Zn^{II} ion with a combination His and Cys residues. This class of proteins plays an important role in eukaryotic cells as transcription factors that regulate gene transcription.¹⁴⁰ Although Zn^{II} is not redox active, Cys-containing ZF domains undergo S-sulfhydration in response to H_2S exposure.^{141–143} The mechanism of S-sulfhydration of the specific ZF protein tristetraprolin was investigated. A key discovery from this study was that this process occurs only in the presence of O_2 .¹⁴² The Zn^{II} center is thought to facilitate the S-sulfhydration by shifting the redox potential of the Cys and enabling its oxidation by O_2 and subsequent sulfhydration by H_2S .

In addition to being a key structural requisite for ZFs, Zn^{II} plays a catalytic role in several enzymes, which may also react with H_2S . For example, the Zn-containing enzyme phosphodiesterase 5 is inhibited by nanomolar concentrations of H_2S .¹⁴⁴ The mechanism of this inhibition has not been fully elucidated, but the direct coordination of H_2S to the catalytic Zn^{II} center could not be ruled out. Similarly, the inhibition of carbonic anhydrase by H_2S arises from the direct coordination of this gasotransmitter to the His_3Zn active site found in most isoforms of this enzyme.^{145–147} A model complex of the dinuclear Zn^{II} enzyme CS_2 hydrolase, which is found in archaeobacteria, was shown to produce H_2S and CO_2 via hydrolysis of CS_2 ,¹⁴⁸ suggesting that CS_2 is a biologically relevant source of H_2S .¹⁴⁹

Lastly, H_2S regulates proteins with alternative functions. For example, H_2S is also known to interact with metallothioneins, Cys-rich proteins that bind Zn^{II} and detoxify heavy metal ions. In this capacity, H_2S prevents Cd^{II} -induced toxicity by stabilizing the Zn^{II} -containing

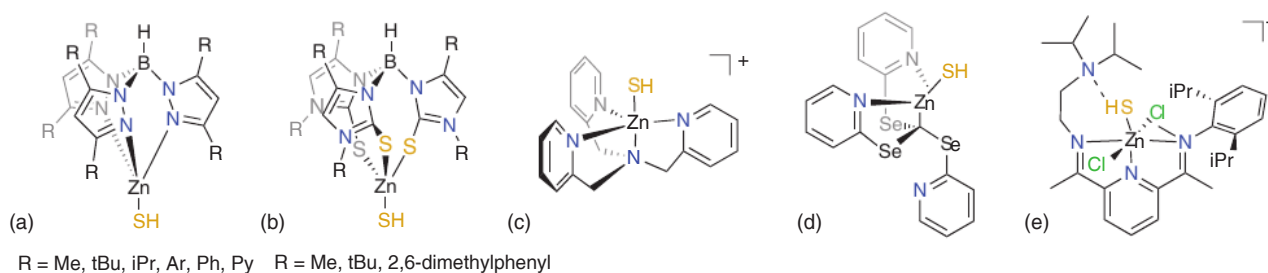


Figure 6 General structures of reported Zn-SH coordination compounds

isoform of metallothionein-1.¹⁵⁰ Zn proteins also have a potential role for transport of H₂S. The giant tubeworm *Riftia pachytila*, which inhabits sulfide-rich environments and lives in a symbiotic relationship with sulfide-oxidizing bacteria,¹⁵¹ uses a unique form of hemoglobin that contains 12 Zn^{II} centers in a hollow cavity that bind and capture H₂S for transport through the bloodstream.¹⁵²

The reactivity of the ZF and catalytic Zn^{II} proteins with H₂S has prompted the evaluation of small-molecule complexes to model this chemistry.¹⁴⁷ The tris-pyrazolylborate ligand system has been used extensively to mimic the His₃ coordination environment of Zn-containing proteins (Figure 6a). Reactions of these model complexes with H₂S have confirmed that SH⁻ can coordinate directly to the Zn^{II} center. These studies have demonstrated the importance of bulky, nonpolar ligands to stabilize the resulting Zn-SH complex.^{153–157} Other Zn-SH complexes supported by the tris(thioimidazole)hydroborate (Figure 6b),^{158,159} tris(2-pyridylmethyl)amine (Figure 6c),^{160,161} tris(2-pyridylseleno)methyl (Figure 6d),¹⁶² and a substituted pyridinediimine ligand (Figure 6e)¹⁶³ have also been reported.

3.3 Cobalamin

In addition to the metalloprotein examples discussed above, H₂S also reacts with other redox-active biomolecules. Of particular relevance to the field of bioinorganic chemistry, one of the more interesting reaction partners of H₂S is vitamin B₁₂, or cobalamin, a Co-containing molecule that is essential for DNA synthesis and metabolism (Figure 7a; see *Cobalamin Biosynthesis and Insertion*).¹⁶⁵ Only a handful of reports have explored the reactivity of H₂S with cobalamin derivatives and as such, relatively little is known about the biological implications of the reactivity between these molecules. H₂S can displace strongly nucleophilic ligands, such as OH⁻ or CN⁻, from the Co^{III} center of cobalamin to furnish stable Co^{II} derivatives and RSS.^{164,166,167} Under anaerobic conditions the generated Co^{II} species readily react with methyl iodide to generate methylcobalamin, which can be cleanly

converted back to Co^{III} aquocobalamin in the presence of light, demonstrating that the reaction between cobalamin and H₂S is reversible.^{164,168} Kinetic studies have suggested that the reaction between H₂S and cobalamin under anaerobic conditions proceeds via initial binding of H₂S to the Co^{III} center followed by reduction to Co^{II} through an inner-sphere electron transfer reaction. Addition of a second equivalent of H₂S to the Co^{II} sulfide complex produces polysulfide derivatives (Figure 7b). In the presence of O₂, the reaction products are much more diverse and include [Co^{II}-S-S-Co^{II}] type species and sulfur-modified corrinoids.^{164,167} Given the ability of cobalamin and its derivatives to bind H₂S, it has been demonstrated that administration of the vitamin B₁₂ analogue cobinamide in rabbits prevents sulfide poisoning in vivo by decreasing plasma H₂S levels.¹⁶⁹

4 METAL COMPLEXES FOR H₂S DETECTION

4.1 Common H₂S Detection Methods

Given the growing importance of H₂S in biology and bioinorganic chemistry, methods for quantification and detection of H₂S in biological systems have become the focus of intensive study. The spectrophotometric methylene blue (MB) assay is one of the oldest, albeit very reliable, method for sulfide detection and quantification.^{170–172} In this assay, MB is generated through the FeCl₃-catalyzed reaction between *p*-dimethylamino aniline and H₂S. The characteristic absorbance of MB at 670 nm allows for direct quantification of H₂S. The MB assay requires the use of acidic aqueous solutions. These conditions, however, can extract acid-labile sulfur from other biological sources, thereby complicating analysis of H₂S in biological or pH-sensitive systems. Thus, the use of this assay is limited in measuring H₂S production from donors that are activated under acidic conditions, such as phosphinodithioates.^{173–175} An alternative procedure involving precipitation of H₂S as zinc sulfide prior to performing the MB reaction can be used to circumvent

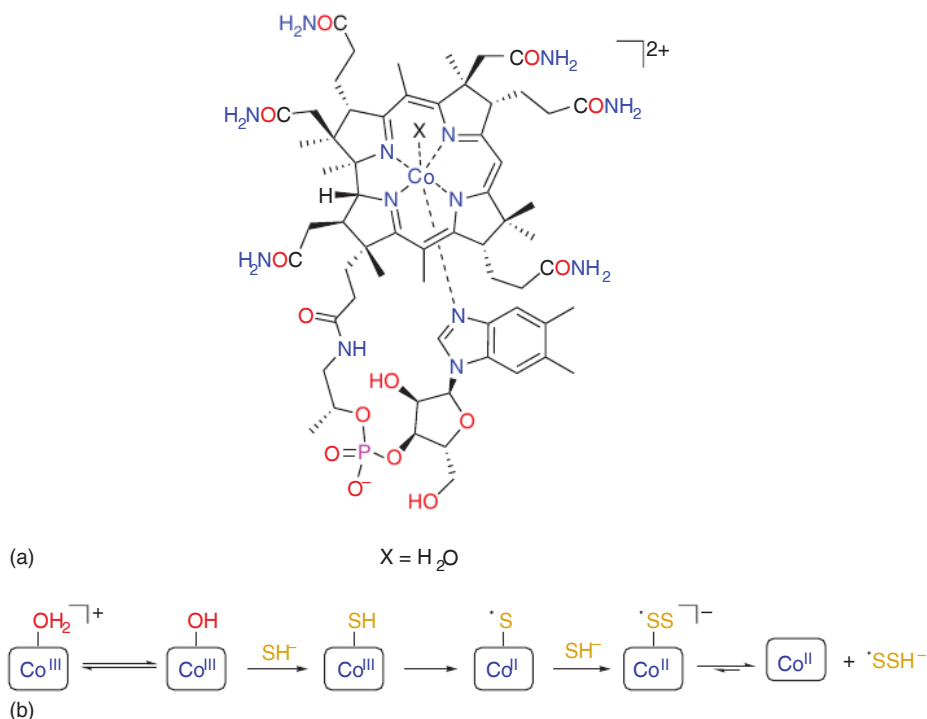


Figure 7 (a) Chemical structure of aquacobalamin. (b) Proposed reaction pathway between cobalamin and H₂S under anaerobic conditions. For more details, see Ref. 164 [Based on Salnikov, D. S., Kucherenko, P. N., Dereven'kov, I. A., Makarov, S. V., & van Eldik, R. (2014). Kinetics and Mechanism of the Reaction of Hydrogen Sulfide with Cobalamin in Aqueous Solution. *European Journal of Inorganic Chemistry*, 2014(5), 852–862]

these challenges.¹⁷⁶ Despite its widespread use, the MB method is relatively insensitive with a limit of detection (LOD) of approximately 2 μ M, thus making it insufficient for detecting low concentrations of H₂S that may be physiologically relevant in biological systems.¹⁷⁷ Another H₂S detection method, called the monobromobimane (mBB) method, is generally more accurate and is significantly more sensitive (LOD \sim 2 nM) than MB. This technique relies on the reaction of mBB with H₂S to furnish sulfide dibimane, which can be detected either spectrophotometrically or by fluorescence spectroscopy.^{178,179} The mBB method requires basic conditions and low oxygen concentrations in order to obtain the highest sensitivity for H₂S. Coupling this technique to high-performance liquid chromatography (HPLC) analysis provides information on the speciation of H₂S and H₂S_n because mBB also reacts with biological thiols and poly- and persulfide species.¹⁸⁰ However, this additional reactivity can be problematic when trying to use the mBB method to measure H₂S under normoxic, physiological conditions.

Amperometric electrodes have also been developed to complement spectrophotometric techniques for H₂S detection.^{181,182} In general, these sensors consist of an ion-selective membrane and a polarizing voltage, which allows

H₂S permeation into the electrode. The interior of the electrode contains a strongly basic solution of Fe(CN)₆³⁻, which is reduced selectively by H₂S to Fe(CN)₆⁴⁻. The generated ferrocyanide is re-oxidized by a platinum electrode, which generates a current relative to the amount of H₂S present.^{183,184} This technique is advantageous over other methods in that it can be used in unadulterated biological samples, such as tissue homogenates, cultured cells, and even circulating blood of living animals,¹⁸⁵ allowing for time-resolved measurement of H₂S dynamics. Sulfide electrodes are limited in that they cannot provide information at sub-cellular resolution and are known to be highly pressure and temperature sensitive, requiring frequent recalibration.²¹

The past decade has seen rapid development and implementation of fluorescent and colorimetric reaction-based H₂S probes for use in biological applications. These systems generally consist of a chromophore appended with a sulfide-sensitive protecting group. Attack by H₂S releases the active species, resulting in a colorimetric or fluorescence response. Several recent reviews provide a comprehensive background on advances in the development of such sensors.^{186–191} Compared to the methods discussed above, these probes allow for spatiotemporal monitoring of H₂S levels in cells and tissues that is minimally invasive.

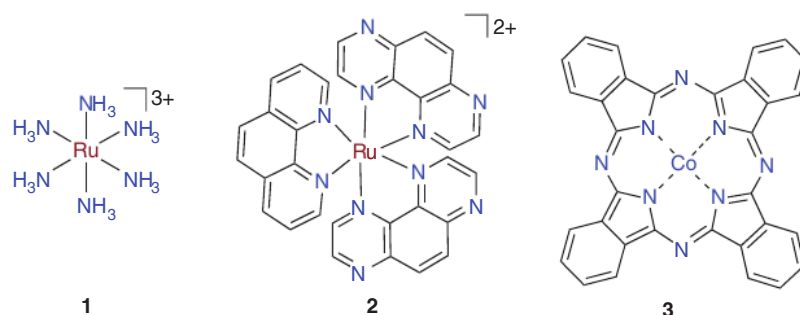


Figure 8 Metal complexes that detect H_2S through reduction

This section will focus on the use of inorganic complexes for H_2S detection. Compared to sensors based on organic dyes, metal-based lumiphores generally have the advantage of high photostability, large Stokes shifts, which reduces self-quenching, and long-lived luminescence lifetimes (see *Luminescence Behavior & Photochemistry of Organotransition Metal Compounds*), which permits time-gated luminescence imaging and minimizes interference from biological autofluorescence.^{192–194}

4.2 Metal-Based H_2S Sensors

Although we note that metal–organic framework (MOF)-based sensing platforms have recently been explored for the detection of H_2S ,^{195,196} this section will focus solely on small-molecule probes. In a general sense, metal-based sensors take advantage of the strong reducing power and nucleophilicity of H_2S and HS^- .¹⁸⁶ For example, the reduction of the $[\text{Ru}(\text{NH}_3)_6]^{3+}$ (**1**, Figure 8) by sulfide in pH 7.4 aqueous solution was employed to develop a microchip-based system for continuous monitoring of H_2S levels in the central nervous system of guinea pigs.¹⁹⁷ Similarly, electron transfer between H_2S and a Ru^{II} polypyridyl complex (**2**, Figure 8) induces a phase shift in the luminescence of the complex, which was leveraged to develop reversible sensors capable of monitoring H_2S dynamics over extended periods of time.¹⁹⁸ In complex **3** (Figure 8), the Co^{II} center is reduced by H_2S to Co^{I} , resulting in a shift in the electronic absorbance spectrum. The metal center can be cleanly oxidized back to Co^{II} upon exposure to air, thereby conferring a degree of reversibility to this system.¹⁹⁹ In a different study which highlights the use of metalloproteins for this application, reduction of the Cu^{II} center of a fluorescently tagged azurin protein isolated from *Pseudomonas aeruginosa* by H_2S resulted in an increase in fluorescence.²⁰⁰ This response could be reversed back to the quenched state upon treatment with $\text{K}_3\text{Fe}(\text{CN})_6$.

Luminescent Zn^{II} (**4**),²⁰¹ Co^{II} (**5**),²⁰² Ru^{II} (**6**),^{198,203} and Ir^{III} (**7–11**)^{204–208} complexes have been reported as H_2S sensors (Figure 9). With the exception of **5**, which appears to sense H_2S through noncovalent interactions,²⁰² these scaffolds include H_2S -reactive masking groups, such as an azides, nitros, dinitrophenyl sulfonyl, or dinitrophenyl ethers. These functional groups can quench the photoexcited metal-to-ligand charge transfer state (MLCT) via photoinduced electron transfer (PET), thereby preventing photoluminescent emissive decay pathways. Nucleophilic attack of H_2S on these groups modifies them such that PET to the excited state is no longer energetically viable, resulting in an increase in metal-based photoluminescence intensity. Of these compounds, only **6** and **7** have been used in biological contexts. The high sensitivity of **6** toward H_2S ($\text{LOD} = 45 \text{ nM}$) enabled the monitoring of lysosomal H_2S levels in live cells, as well as endogenous H_2S levels in living zebrafish and mice.²⁰³ Despite the significantly lower sensitivity of **7** ($\text{LOD} = 4.35 \mu\text{M}$) compared to **6**, this compound was similarly able to detect H_2S in vitro and in vivo.²⁰⁸ Complex **6** was also activated by hypoxic environments, suggesting that its H_2S -detection capabilities under these conditions is limited. Although compounds **8–11** have not been studied in biological settings, they offer interesting opportunities for the development of electrochemiluminescent (ECL) sensors, which rely on the generation of luminescent excited states by redox chemistry rather than photon absorption.²⁰⁹

The narrow emission energies, long-lived luminescence lifetimes, and large Stokes shifts of the photoexcited LaPorte forbidden f–f states of the lanthanides Eu^{III} and Tb^{III} (see *Lanthanides: Luminescence Applications; Lanthanides: Luminescence*)^{210,211} have also been leveraged in the development of luminescent H_2S -responsive probes (**12–16**; Figure 10).^{212–217} These complexes contain an H_2S -reactive functional group such as an azide or dinitrophenyl ether, which quenches the complex photoexcited state in a similar manner to the transition metal complexes discussed above. The reaction of these groups with H_2S restores luminescence by converting these groups to forms

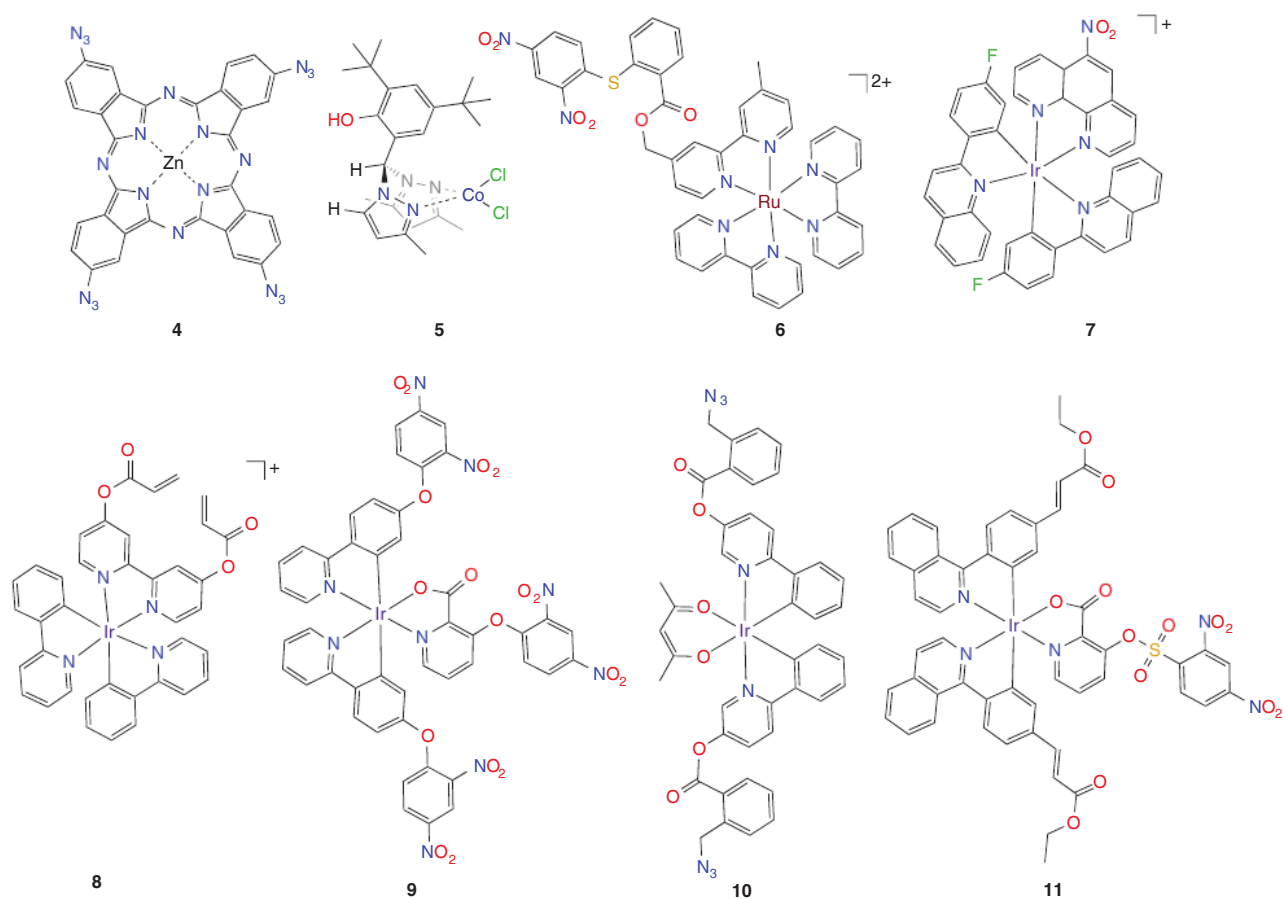


Figure 9 Luminescent metal complexes for H_2S detection

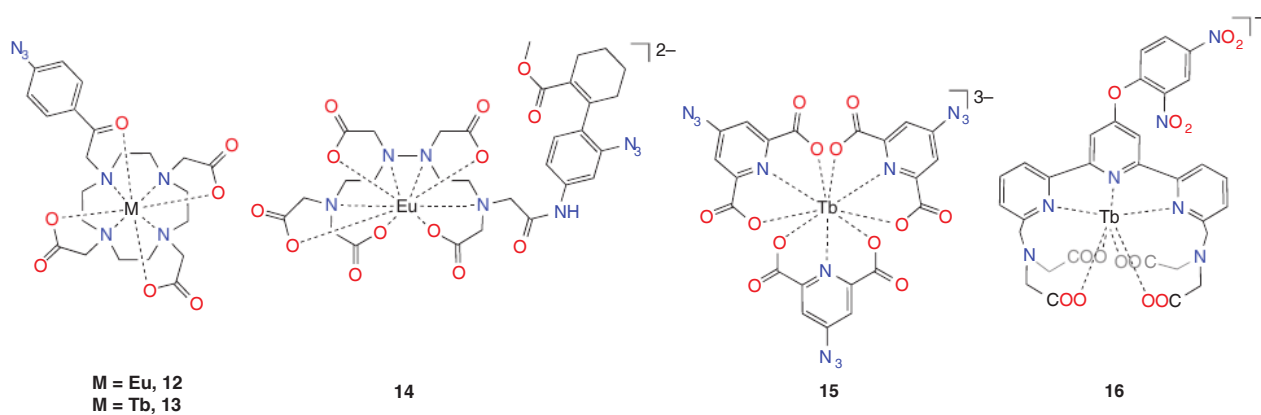


Figure 10 Luminescent lanthanide-based H_2S -sensing complexes

that cannot engage in PET. Compound **12** was the first example of a kinetically stable Eu^{III} complex that could be used for detection of H_2S . The biological compatibility of **12** was demonstrated by using it to detect this

gasotransmitter in human serum.²¹² More recently, a Eu^{III} probe bearing a functionalized aminopolycarboxylate ligand (**14**) was reported. This probe can detect H_2S produced by CSE in aqueous solution and was used in

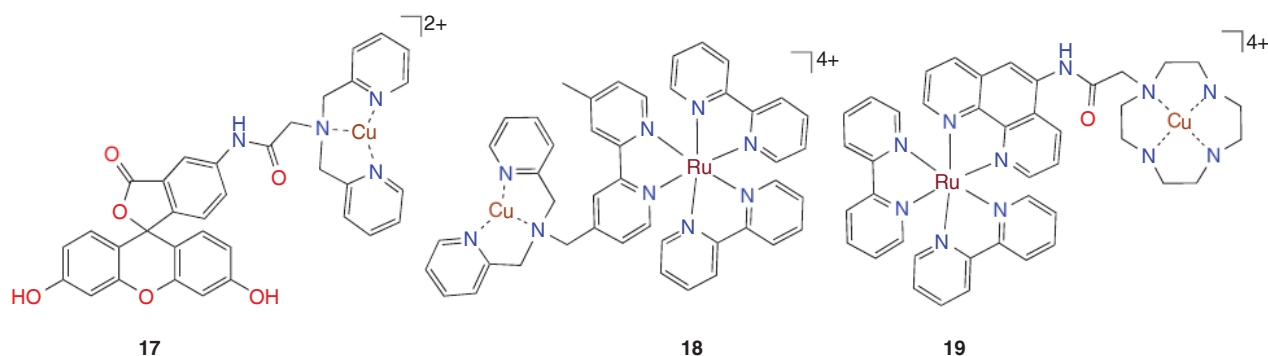


Figure 11 Luminescent H_2S sensors that detect H_2S through metal displacement

a high-throughput screening assay to identify potential inhibitors of this enzyme.²¹⁵ Another lanthanide-based H_2S sensor, a Tb^{III} complex bearing azide-substituted pyridine carboxylate ligands (**15**), was able to detect H_2S at concentrations as low as 10 nM in aqueous solution. This compound was used in a paper-based assay to detect trace H_2S exhaled by mice.²¹³ Lastly, a Tb^{III} complex containing a 2,6-dinitrophenol functionalized terpyridine type ligand (**16**) was used to detect H_2S in living cells.²¹⁶

4.3 Metal Displacement Sensors

The characteristic low solubility of metal sulfide salts offers a possible strategy for the detection of H_2S through metal displacement reactions. Since 1685,^{218,219} H_2S has been used to precipitate small concentrations of Cu^{II} , Sn^{II} , Pd^{II} , and Hg^{II} as a means of diagnosing their presence. As such, compounds containing these metal ions, in addition to Zn^{II} , Cd^{II} , Pb^{II} , and Ag^{I} , have all been utilized for detection of this gas.^{220–227} Generally, this strategy relies on compounds that contain both a photoluminescent dye and a metal ion bound by a chelator, such as 1,4,7,10-tetraazacyclododecane (cyclen) or di-(2-picoly) amine (DPA).^{188,194} One of the first sensors employing this approach combined the fluorescent dye fluorescein with the DPA ligand bound to Cu^{II} (**17**, Figure 11).²²⁸ The emission of fluorescein is quenched by the paramagnetic Cu^{II} center,²²⁹ but is restored upon exposure to H_2S , which removes the Cu^{II} in the form of insoluble CuS .²²⁰ Following this example, sensors containing organic fluorescent dyes such as rhodamine, anthracene, and 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) that act through metal ion displacement have been reported.^{187,230,231} The following discussion focuses specifically on inorganic lumiphores that detect H_2S through metal displacement reactions.

The heterobimetallic $\text{Ru}^{\text{II}}\text{-Cu}^{\text{II}}$ complex $[\text{Ru}(\text{bpy})_2(\text{bpy-DPA})]^{4+}$ (**18**; bpy-DPA = 4-methyl-4'-[*N,N*-bis(2-picoly) amino-methylene]-2,2'-bipyridine; Figure 11) was reported to be a sensitive (LOD = 20 nM) turn-on luminescent H_2S

sensor that is activated by precipitation of CuS .²³² This complex was also used as an ECL sensor to measure sulfide concentration in the cortex of adult male rats.²³³ A similar ruthenium complex containing phenanthroline appended with a cyclen chelator was also shown to sense H_2S in the presence of Cu^{II} (**19**, Figure 11). This complex is capable of detecting H_2S over a broad pH range and can detect H_2S in vitro with a rapid turn-on response time.²³⁴

A number of Cu^{II} displacement sensors have been reported that capitalize on the long-lived luminescence of the lanthanides Eu^{III} and Tb^{III} (**20–27**, Figure 12).^{235–242} Although some of these compounds, such as **20**, were used to monitor H_2S in petroleum plant waste streams,²³⁷ a few of these probes have found applications in biological settings. Heterobimetallic $\text{Eu}^{\text{III}}\text{-Cu}^{\text{II}}$ compounds **21** and **22** bearing β -diketonate ligands and DPA Cu^{II} -chelating moieties were found to be relatively nontoxic and capable of selectively detecting intracellular H_2S in vitro.^{241,242} More recently, **23** was reported as a luminescent probe with a rapid turn-on response, high sensitivity, and good selectivity for H_2S . Furthermore, this compound could be used to measure H_2S production from both the slow-releasing H_2S donor morpholin-4-ium 4-methoxyphenyl(morpholino)phosphinodithioate (GYY4137) and CSE, as well as to determine intracellular H_2S levels in Na_2S -stimulated cells.²³⁵

4.4 H_2S Detection via Metal Coordination

Researchers have developed probes that can detect H_2S via changes in fluorescence or absorbance upon direct coordination of this gasotransmitter to the metal center. The Zn^{II} tris(pyrazoyl)borate complex **28** containing 7-mercapto-4-methylcoumarin was the earliest coordination-based H_2S sensor with a LOD of 1 μM .²⁴³ Binding of H_2S to the Zn center results in the release of the coumarin ligand and a concomitant color change, making **28** a colorimetric sensor. Pyridoxal (**29**),^{244,245} porphyrin (**30–35**),^{246–248} phthalocyanine (**36**),¹⁹⁹ and salen (**37**)²⁴⁹

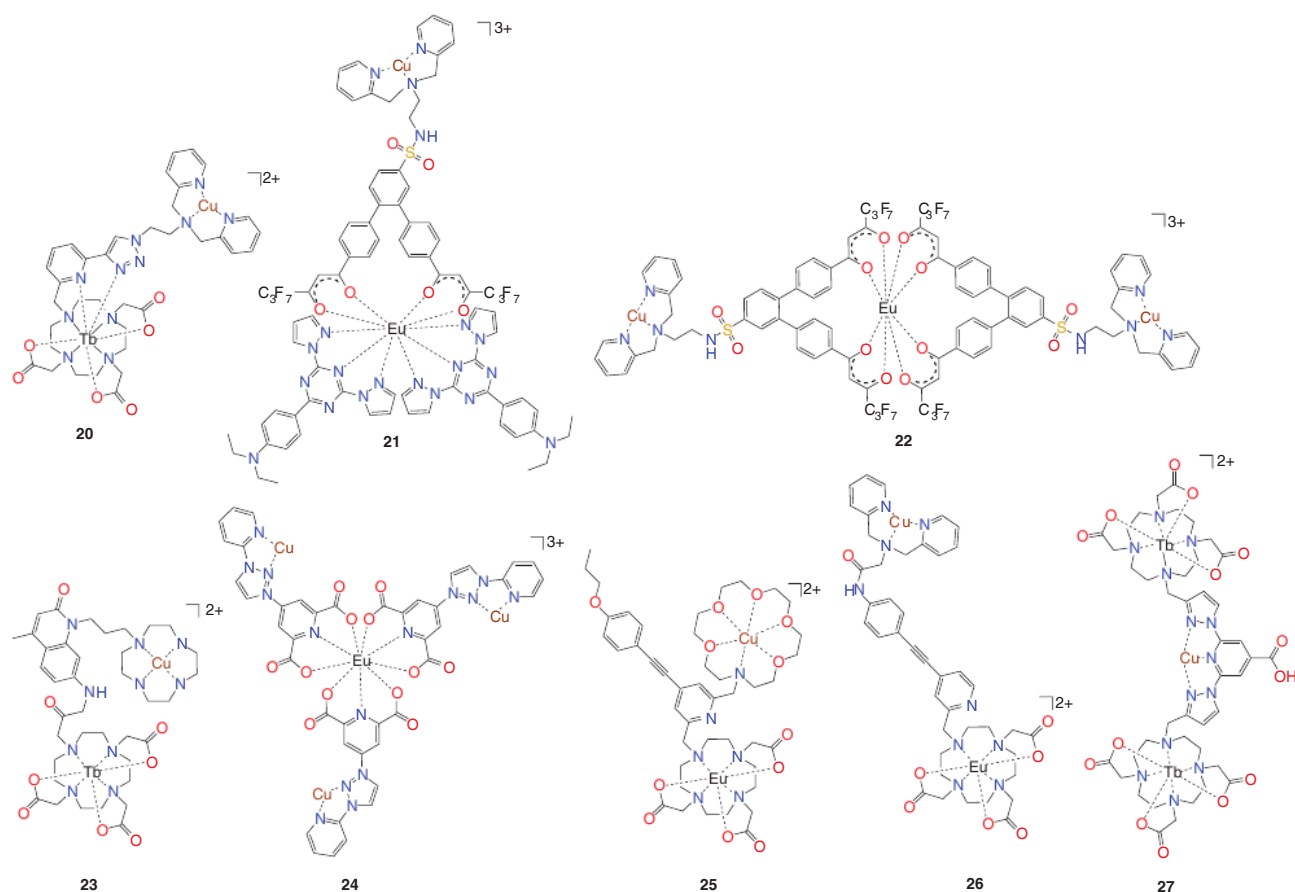


Figure 12 Luminescent lanthanide-based H_2S probes that rely on metal displacement for detection

complexes have also been shown to sense H_2S via direct metal coordination (Figure 13). Compound **31** displays decent selectivity for H_2S over a range of biologically relevant anions, thiols, and oxidants.²⁴⁷ A second study found that **31** failed to bind sulfide in organic solution, a result that reveals the importance of solvent effects and proton availability for this class of sensors.²⁴⁸ The absorption spectra of porphyrin compounds **34** and **35** undergo significant changes in the presence of excess HS^- . The metal center, however, undergoes subsequent reduction to give unresolved reaction products,²⁴⁸ which might hinder their use as colorimetric H_2S sensors.

Researchers have also leveraged the ability of metalloproteins and enzymes to bind H_2S for the development of coordination-based sensors. The general approach combines an H_2S -binding metalloprotein with a fluorescent tag. The metalloprotein chromophores of these systems exhibit significant shifts in their absorbance wavelengths upon binding to H_2S . The change in absorbance of the metalloprotein chromophore can modulate the emission intensity of fluorescent tag by attenuating or enhancing the availability of photons from the excitation

source. This strategy relies on the use of fluorescent tags with excitation wavelengths near absorbance maxima of the protein or enzyme in the absence of H_2S , which prevents fluorescence of the tag. Coordination of $\text{H}_2\text{S}/\text{HS}^-$ to the metal center causes the protein absorbance to shift, unmasking the fluorophore, which results in an increase in fluorescence intensity. Fluorophore-tagged analogs of Horse skeletal muscle myoglobin isolated from horse skeletal muscle,²⁵⁰ cobalt peptide deformylase (PDF) from *Escherichia coli*,²⁵¹ and HbI from *L. pectinatus*²⁵² have all been used as H_2S sensors of this type with good selectivity over other biological thiols and sensitivity in the nanomolar range. The metal-sulfide interaction in PDF was supported by X-ray crystallography, which demonstrated that both the Co and Ni-containing forms of this enzyme coordinate H_2S (Figure 14).²⁵¹

The coordination-based approach for H_2S detection is intriguing given the low stability and high reactivity of many metal H_2S and hydrosulfido complexes,^{26,27,253–256} In contrast to the reaction-based and metal displacement sensors, these systems can potentially give rise to reversible H_2S probes, an important property that could be used to

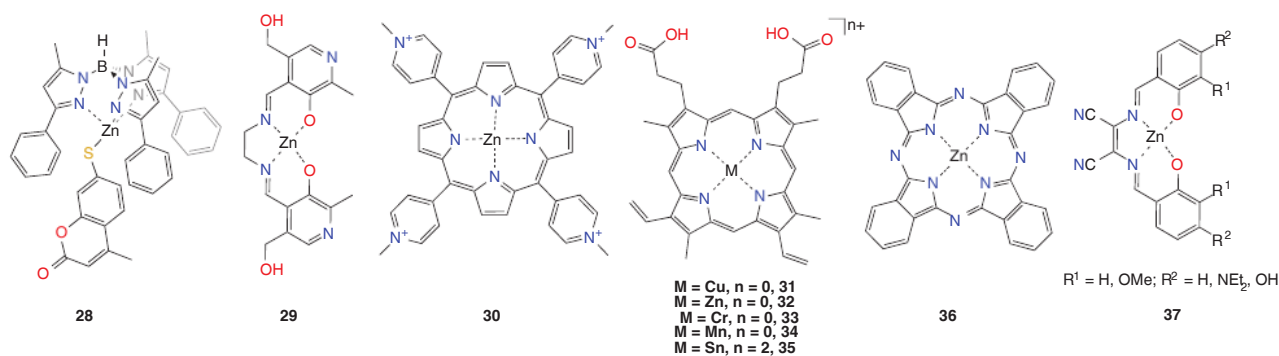


Figure 13 Inorganic complexes that detect H₂S upon metal coordination

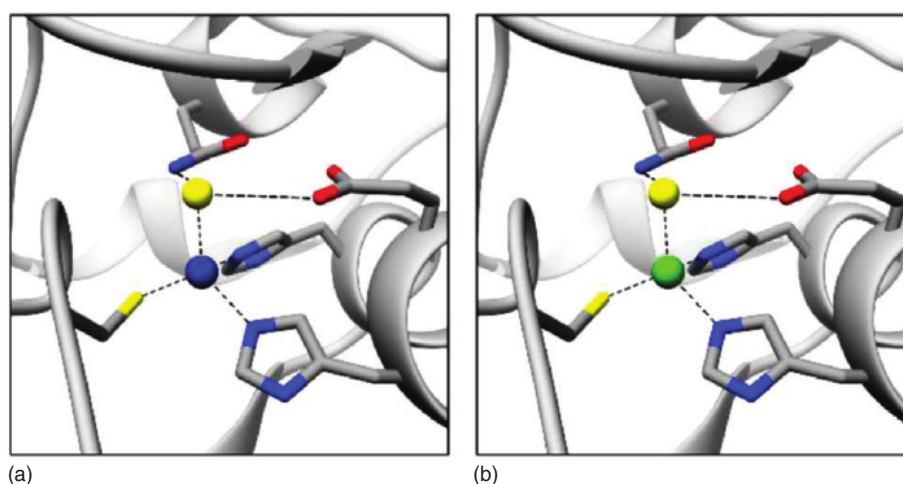


Figure 14 X-ray structures of the sulfide-bound adducts of (a) Co-PDF and (b) Ni-PDF (PDB: 4AZ4, 4AL2). [Based on PDB: 4AZ4, 4AL2, RCSB Protein Data Bank]

monitor H₂S dynamics in biological or industrial settings. For example, treatment of the hydrosulfide adduct of **33** or **36** with acetic acid or oxygen regenerates the parent complexes.¹⁹⁹ Similarly, purging solutions of H₂S-treated HbI with argon produces the free protein, which can then detect additional sulfide.²⁵² Together these studies highlight the utility of the coordination-based approach for development of reversible sensors.

5 METAL COMPLEXES AS AGENTS FOR H₂S DELIVERY

5.1 Simple Inorganic Salts

Despite the numerous advances in understanding the biological activity of H₂S, it remains a challenge to deliver this gas to biological systems. The use of H₂S in

its gaseous state is challenged by its toxicity, flammability, and volatility.^{257,258} Simple metal sulfide salts such as Na₂S and NaSH are the most commonly employed sources of H₂S in biological studies.²⁵⁸ Although these salts are generally easier to handle than gaseous H₂S, they are typically obtained commercially with very low purity levels,²⁵⁹ a limitation that makes it challenging to discern the precise amount of H₂S delivered by these salts. Furthermore, a 10 μM aqueous solution of NaSH has a half-life of only 0.5 min due to volatilization of H₂S,²⁶⁰ and the H₂S generated from intravenously injected Na₂S is rapidly exhaled.²⁶¹ In addition, toxic side effects from these salts may arise from their rapid release rate of H₂S in aqueous solution, which fails to mimic endogenous H₂S dynamics. Motivated by these limitations, researchers have developed slow-release H₂S donors that produce this gas on biologically relevant time scales. A number of different small-molecule sulfide donors have been recently reported.^{257,258,262–264} These include simple molecules that

undergo uncontrolled hydrolysis,^{174,175,265–267} in addition to organic H₂S-releasing compounds that are selectively activated by light,^{268–272} enzymatic activity,^{273–276} thiols,^{277–284} and ROS.^{285–288} In contrast to the prevalence of inorganic CO- and NO-releasing molecules,^{289–294} an overwhelming majority of H₂S donors are organic molecules. Herein, recent efforts towards the development of metal-based small-molecule H₂S donors are described.

5.2 Tetrathiomolybdate

Tetrathiomolybdate ([MoS₄]²⁻; TM) is a widely available reagent that is used in organic chemistry for sulfur transfer and reduction reactions.^{295,296} This ion is prepared by the reaction of the oxymolybdate anion ([MoO₄]²⁻) and H₂S in basic aqueous solution.²⁹⁷ Historically, TM has received significant attention for its ability to inhibit Cu^I-trafficking proteins through the formation of sulfur-bridged Cu–Mo clusters.²⁹⁸ This orally available complex has been widely used to treat disorders associated with improper copper metabolism, such as Wilson's disease.

Although TM has been long known to release H₂S under acidic²⁹⁹ or high-temperature^{300,301} conditions, recent work has demonstrated that this compound, and to a lesser extent tetrathiotungstate ([WS₄]²⁻, TT), produce this gas via hydrolysis under biological conditions.^{302–305} TM generates H₂S via hydrolysis over a period of hours in buffered aqueous solution³⁰² and interacts with biological thiols, such as glutathione, to produce other reactive persulfide and polysulfide species.³⁰³ The H₂S generated through TM hydrolysis was shown to prevent H₂O₂-induced oxidative stress and preserve cellular function in vitro.³⁰² When administered intravenously, TM significantly reduces infarct size in mice subjected to either myocardial or cerebral ischemia³⁰⁴ and prevents oxidative damage and loss of functional activity in preclinical stroke models.³⁰⁵ A recent report suggested that H₂S produced by TM hinders its anticancer activity in A549 adenocarcinoma cells by enhancing cell growth at low concentrations and upregulating H₂S producing enzymes.³⁰⁶

Mechanistic studies suggest that the protective effects of TM arise from its ability to decrease mitochondrial ROS levels³⁰⁴ and improve antioxidant enzyme activity,³⁰⁵ which are consistent with the therapeutic effects reported for H₂S.³⁰⁷ Further mechanistic studies have suggested that TM and TT are transported into cells by anion exchange protein-1 (AE-1).³⁰³ Despite the promise of TM as a biologically relevant H₂S donor, it was reported that TM obtained from different commercial sources produced variable amounts H₂S,³⁰⁴ highlighting the difficulty of obtaining these simple compounds in analytically pure forms. In addition, the H₂S release from TM is uncontrollable; once the complex is placed in aqueous solution, H₂S is spontaneously generated and the release cannot be targeted to a specific location in vivo. It would be advantageous to

develop agents that produce H₂S selectively in response to specific stimuli, allowing for selective and controlled H₂S production in complex biological systems.

5.3 Light-Activated Donors

Light-activated H₂S-releasing agents have been recognized as promising tools for studying the biological and therapeutic properties of this gas.^{262,263} Photoactivatable donors allow for localized and noninvasive delivery of H₂S in vitro and offer exciting possibilities for delivery in vivo. Upon irradiation with a specific wavelength of light, the donor undergoes photoinduced decomposition to cleave a photoactivated protecting group and release an H₂S-producing moiety. The first example of a photocaged H₂S donor consisted of a *bis*-orthonitrobenzyl protected geminal-dithiol (*gem*-dithiol).²⁶⁸ The nitrobenzyl protecting groups are removed upon reaction with 365 nm light to produce an unstable *gem*-dithiol, which undergoes rapid hydrolysis in aqueous solution to produce H₂S. Other photoactivated H₂S donors containing *gem*-dithiol, thiobenzaldehyde, and ketoprofenate moieties have also been reported.^{257,268–270}

The vast majority of these photoactivated compounds require ultraviolet (UV) light ($\lambda \leq 400$ nm) for activation. This requirement limits the applicability of these donors in vivo given that these wavelengths ineffectively penetrate biological tissue and can give rise to phototoxicity.³⁰⁸ As such, researchers have sought to develop light-activated donors that function at lower energy wavelengths.

By virtue of their favorable photophysical properties (see *Photochemistry of Transition Metal Complexes*)^{309,310} metal compounds have been widely used for light-activated delivery of CO and NO.^{310–314} By contrast, photoactivated H₂S donors based on inorganic systems have not been reported until recently. An early example of a metal-based H₂S release platform used polyethylene glycol functionalized LiYF₄:Yb/Tm upconverting nanoparticles (UPNCs) conjugated to a caged *gem*-dithiol compound. Under near-infrared (NIR) irradiation, the UPNCs emit UV light, which then unmask the protected *gem*-dithiol to produce H₂S. This strategy was shown to deliver H₂S both in living cells and ex vivo in a pork skin model.³¹⁵ A complementary nanoparticle-based system consisting of a singlet oxygen (¹O₂) photosensitizer and 1,3-diphenylisobenzothiophene (DPBT) encapsulated in artificial polymersomes has also been reported. The photosensitizer, a Pt^{II} porphyrin complex or biscyclometalated Ir^{III} compound, generates ¹O₂ upon irradiation with visible light, which subsequently reacts with DPBT to produce H₂S.³¹⁶ These early studies have demonstrated how the photochemical properties of metal complexes can be leveraged to develop selective H₂S donors that can be activated by light irradiation.

The characterization and biological activity of a red light-activated H₂S-releasing Ru^{II} complex were recently

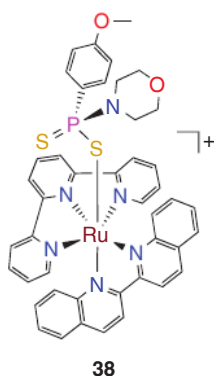


Figure 15 Chemical structure of compound **38**

reported.³¹⁷ In this study, coordination of GYY4137^{173,174} to a ruthenium photocage (**38**, Figure 15) suppresses the spontaneous hydrolysis-driven H₂S release from this compound. Compound **38** produces H₂S in living cells upon irradiation with red (631 nm) light and protects H9c2 cardiomyoblast cells against an in vitro model of ischemic reperfusion injury. Compound **38** is the first example of an inorganic small-molecule H₂S donor that is activated by irradiation with red light; a BODIPY-based thiocarbamate compound was reported as the first NIR light-activated organic H₂S donor in the same year.²⁷² This work highlights how transition metal complexes may serve as viable light-activated H₂S donors that can operate in biologically relevant settings.

5.4 Reduction-Activated Donors

The redox chemistry of transition metal ions offers unique opportunities for redox-responsive delivery of biologically relevant molecules. The redox environment of biological tissue or cells can vary dramatically depending on the specific cell type, organelle, or conditions. In the presence of low O₂ levels, a state known as hypoxia, the cellular environment becomes highly reducing as cells and tissue lose the ability to maintain redox balance.³¹⁸ In this context, several inorganic complexes containing metals such as Ru, Os, Pt, Cu, and Co have been developed as redox-activated prodrugs,^{319–323} which release cytotoxic anticancer agents upon reduction that occurs in hypoxic cells. A recent report has shown that a dinuclear persulfide (μ -S₂²⁻) bridged ruthenium compound (**39**, Figure 16) produces H₂S selectively upon reduction.³²⁴ The ability of this complex to produce H₂S upon reduction was leveraged to deliver this gasotransmitter to hypoxic cells, making **39** the first example of a hypoxia-activated H₂S donor. Notably, mechanistic studies revealed that the reduction process does not proceed through production of H₂S₂ like many organic persulfide compounds,^{280,325–329} but

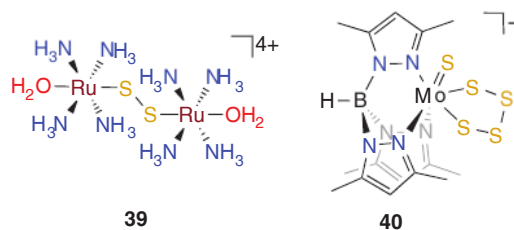


Figure 16 Redox-active metal complexes that produce RSS upon reduction

rather directly produces H₂S. Lastly, this complex was shown to preserve cell viability in H9c2 cardiomyoblast cells subjected to an in vitro model of ischemic reperfusion injury. Given that the redox chemistry of transition metal ions is highly dependent on the nature of the supporting ligands, persulfide-bridged metal complexes offer exciting opportunities for the development of tunable H₂S donors that can deliver this gas under a wide span of biologically relevant redox potentials.

Recently, a Mo^{IV} tetrasulfido complex (**40**, Figure 16) was reported to undergo a two-electron reduction to produce HS₂⁻ and a Mo^{VI} trisulfide species.³³⁰ The reductive release of HS₂⁻ by compound **40** was only demonstrated in organic solvent or aqueous organic mixtures, but this study demonstrates the potential of this class of compounds for the development of inorganic complexes for delivery of H₂S and other RSS to biological systems.

6 OUTLOOK AND CONCLUSIONS

Studies on the biological activity of H₂S and related RSS have highlighted diverse reactivity of these species with metal-containing biomolecules. This immense diversity and the complex nature of these reactions have made it difficult to obtain intimate mechanistic understanding of these processes. In some cases, such as CcO, model compounds that mimic the active site of the enzyme or proteins have greatly increased understanding of the reactivity between H₂S and these biomolecules. The biological targets of H₂S and its derived RSS have only just begun to be elucidated and a number of biologically relevant metal-containing biomolecules, such as ZF proteins, are still not well studied. Investigation of the biological activity of H₂S is further complicated by its propensity to form reactive polysulfides and persulfides, which possess biological activity distinct from that of H₂S.^{331,332}

The utility of inorganic complexes for H₂S detection and delivery in biological environments has only recently been realized. Inorganic complexes display favorable photophysical properties compared to organic fluorophores

and offer exciting opportunities for ECL-based H₂S sensors. Furthermore, reduction-activated and coordination-activated sensors have shown promise for the development of reversible H₂S sensors that could potentially be used to monitor biological H₂S dynamics over extended periods of time.

Inorganic complexes have only recently begun to be investigated for their use as H₂S donors for delivery of biologically relevant concentrations of this gas in vitro. The rich photochemical and redox properties of coordination compounds offer exciting opportunities for the development of novel H₂S donors for use as tools for studying the role of H₂S and related RSS in biological processes and disease.

7 ACKNOWLEDGMENTS

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8 RELATED ARTICLES

Sulfur: Organic Polysulfanes; Nitrogen Monoxide (Nitric Oxide): Bioinorganic Chemistry; Photochemistry of Transition Metal Complexes; Cytochrome Oxidase; Iron: Heme Proteins & Dioxygen Transport & Storage; Iron: Heme Proteins, Mono- & Dioxygenases; Iron: Heme Proteins, Peroxidases, Catalases & Catalase-Peroxidases; Luminescence Behavior & Photochemistry of Organotransition Metal Compounds; Lanthanides: Luminescence Applications; Lanthanides: Luminescence; Cobalamin Biosynthesis and Insertion; Sulfur: Inorganic Chemistry

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