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Chemically Reversible Reactions of Hydrogen Sulfide with Metal Phthalocyanines

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Supporting Information

ABSTRACT: Hydrogen sulfide (H_2S) is an important signaling molecule that exerts action on various bioinorganic targets. Despite this importance, few studies have investigated the differential reactivity of the physiologically relevant H_2S and HS^- protonation states with metal complexes. Here we report the distinct reactivity of H_2S and HS^- with zinc(II) and cobalt(II) phthalocyanine (Pc) complexes and highlight the chemical reversibility and cyclability of each metal. ZnPc reacts with HS^-, but not H_2S, to generate $[ZnPc\text{-}SH]^-$, which can be converted back to ZnPc by protonation. CoPc reacts with HS^-, but not H_2S, to form $[Co^{I}Pc]^-$, which can be reoxidized to CoPc by air. Taken together, these results demonstrate the chemically reversible reaction of HS^- with metal phthalocyanine complexes and highlight the importance of H_2S protonation state in understanding the reactivity profile of H_2S with biologically relevant metal scaffolds.

Hydrogen sulfide (H_2S) is an endogenously produced molecule that plays important and diverse roles in both vasoregulation and neurotransmission, as well as other physiological processes.[1−10] As a gaseous small-molecule signaling agent, endogenous H_2S joins NO and CO as a gasotransmitter, and all three mediate important functions through action on bioinorganic targets.[7−10] Unlike NO and CO, however, H_2S exists in different protonation states at physiological pH, which can facilitate lipid and water solubility in the diprotic (H_2S) and monoanionic (HS^-) forms, respectively. Furthermore, the redox potential, nucleophilicity, and tendency to form insoluble metal salts also vary with the H_2S protonation state, thus complicating reactivity with transition-metal centers.[3] Despite its widespread importance, the coordination chemistry of H_2S with bioinspired transition-metal scaffolds remains underexplored by comparison to CO and NO.[11] Although H_2S binding to ruthenium- and iron-based complexes have been reported,[11−16] investigations of isolated porphyrinoid scaffolds remain limited.[17−20] Motivated by the growing interest in the biochemical functions of H_2S and the lack of information on the differential reactivity of H_2S and HS^- in bioinorganic contexts, we report here the differential reactivity of H_2S and HS^- toward metal phthalocyanine (Pc) complexes and highlight the chemically reversible reactions of HS^- with these platforms.

Phthalocyanines are planar, aromatic porphyrin derivatives that have been used previously as models of bioinorganic reactivity including the reversible binding of NO, CO, and O_2 to heme mimics[21] and the reduction of CO.[22] Metal phthalocyanine complexes have characteristic UV−vis spectroscopic signatures[23] including the Q band (600−700 nm), which provides information on the oxidation state and binding modes of the central metal ion, as well as the B band (300−400 nm) and window region (400−550 nm), which provide information about bound ligands and the metal oxidation state.[24] On the basis of these characteristics, as well as the solubility[23] and redox properties,[24] we viewed ZnPc and CoPc as promising initial platforms on which to investigate the differential reactivity of H_2S and HS^- with redox-inactive and -active metal complexes.

Because of its redox inactivity, we reasoned that the treatment of ZnPc with H_2S or HS^- would result in metal ligation rather than metal-based redox chemistry. To probe such reactivity, we titrated ZnPc in tetrahydrofuran (THF) with H_2S gas (up to 100 equiv or by bubbling for 15 min) but failed to observe any reaction by UV−vis spectroscopy. By contrast, titration of ZnPc in THF with NaSH dissolved in dimethyl sulfoxide (DMSO) resulted in clean conversion to a new species, as evidenced by a 5 nm bathochromic shift of the Q band, the appearance of a broad absorbance centered at 410 nm, and well-anchored isosbestic points at 329, 381, and 667 nm (Figure 1a). Control experiments titrating ZnPc in THF with DMSO, H_2O, KOH in DMSO, H_2S

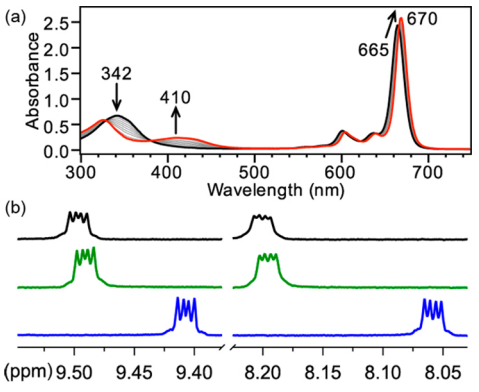

Figure 1. (a) UV−vis titration of ZnPc (6.3 μM in THF, black) with NaSH (0.25 equiv increments of 8 mM NaSH in DMSO up to 5 equiv). (b) ^{1}H NMR (600 MHz, THF-d_8) spectra of 600 μM ZnPc (top, black), 600 μM ZnPc with 2 equiv of KOH in DMSO-d_6 (middle, green), and 600 μM ZnPc with 2 equiv of NaSH in DMSO-d_6 (bottom, blue).

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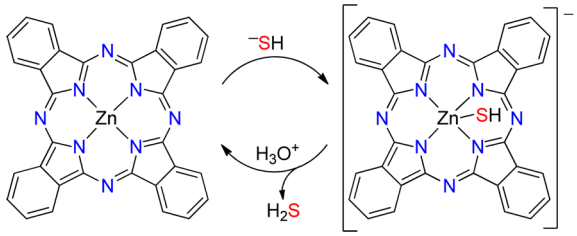
in DMSO, or S_8 failed to change the ZnPc UV−vis spectrum. The addition of aqueous NaSH to ZnPc in THF resulted in reactivity identical with that of the DMSO experiments, suggesting that the availability of weakly acidic protons does not influence the reactivity. Similarly, the addition of $[NBu_4][BH_4]$, a stronger reductant than H_2S or HS^-,[25] failed to change the UV−vis spectrum of ZnPc, suggesting that HS^--mediated reduction of the metal or ligand was not occurring. To probe the binding stoichiometry, we constructed a Job plot by monitoring changes in absorbance as a function of the ZnPc and NaSH molar ratios, which resulted in data consistent with 1:1 binding (Figure S2 in the Supporting Information, SI). Taken together with the above experiments, these studies suggest the formation of a $[ZnPc\text{-}SH]^-$ adduct upon treatment of ZnPc with HS^-.

To confirm that HS^- was binding to the zinc(II) center and not reacting with the Pc ring directly, we used ^1H NMR spectroscopy to investigate changes in the Pc resonances upon reaction with NaSH. Treatment of ZnPc in THF-d_8 with 2 equiv of NaSH in DMSO-d_6 resulted in an upfield shift in the Pc ^1H NMR resonances from 9.59 and 8.20 ppm to 9.41 and 8.06 ppm, respectively (Figure 1b). Furthermore, the dd splitting pattern of the Pc ring is maintained upon treatment with NaSH, indicating that C_4 rotational symmetry is preserved. This symmetry preservation precludes the possibility of HS^- nucleophilic addition or $HS^\bullet$ radical addition into the Pc ring because such an addition would lower the overall symmetry of the complex and subsequently increase the complexity of the coupling. Treatment of ZnPc in THF-d_8 with 2 equiv of KOH in DMSO-d_6 failed to change the ^1H NMR spectrum of ZnPc significantly, indicating that the changes in the chemical shift upon treatment of ZnPc with HS^- were not simply derived from acid−base chemistry (Figure 1b).

Because ZnPc binds HS^- but not H_2S, we reasoned that bound HS^- should be acid-labile, thus allowing for chemically reversible coordination of HS^- by the addition of a suitable proton source (Scheme 1). To test this hypothesis and to demonstrate the

Scheme 1



chemically reversible binding of HS^- to ZnPc, we first generated $[ZnPc\text{-}SH]^-$ in situ by treating ZnPc in THF with 10 equiv of NaSH in DMSO and then added an equimolar amount of AcOH. As predicted, the characteristic spectral features of $[ZnPc\text{-}SH]^-$ at 410 and 670 nm reverted to the 342 and 665 nm absorbances corresponding to the parent ZnPc (Figure 2). A further addition of NaSH in DMSO regenerated the 410 and 670 nm $[ZnPc\text{-}SH]^-$ spectral features.[26]

Having established that redox-inactive ZnPc binds HS^- but not H_2S, we next investigated the reactions of HS^- and H_2S with redox-active CoPc. We chose CoPc because of its well-defined and readily monitored redox states of blue $Co^{II}Pc$ and green $[Co^{I}Pc]^-$.[27,28] Paralleling the chemistry observed for ZnPc, CoPc does not react with H_2S gas (up to 100 equiv or by bubbling for 15 min). Titration of CoPc in THF with NaSH in DMSO,

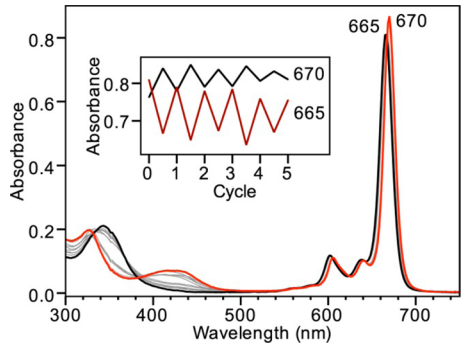


Figure 2. UV−vis spectra of ZnPc (2 μM in THF, black) treated with 10 equiv of NaSH in DMSO (red). Treatment with 10 equiv of AcOH regenerates the original ZnPc spectrum. This system can be cycled numerous times (inset).[26]

however, resulted in a significant bathochromic shift of the Q band from 656 to 697 nm, the emergence of a broad absorbance at 467 nm centered in the window region, and well-anchored isosbestic points at 316, 370, 555, and 676 nm (Figure 3). These

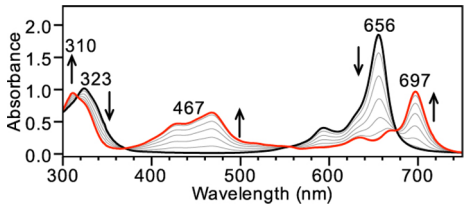
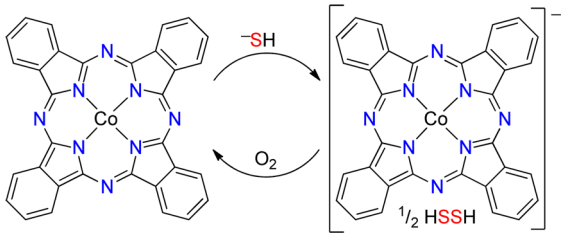


Figure 3. UV−vis titration showing the reduction of CoPc (7 μM in THF, black) to $[Co^{I}Pc]^-$ (red) by NaSH (1 equiv increments of 21.7 mM NaSH in DMSO up to 10 equiv).

new absorbances match the reported spectrum of $[Co^{I}Pc]^-$[27] and also match the spectrum of $[Co^{I}Pc]^-$ generated from CoPc and $[NBu_4][BH_4]$ (Figure S1 in the SI). A Job plot constructed by monitoring the absorbance at 467 nm as a function of the CoPc and HS^- molar ratio is consistent with a 1:1 reaction of CoPc with HS^- (Figure S3 in the SI). This reaction stoichiometry, as well as previous work using CoPc to oxidize thiolates to disulfides, is consistent with the initial oxidation of HS^- to HSSH with potential conversion to further oxidation products (Scheme 2).[29−33]

Scheme 2



On the basis of the observed HS^--mediated reduction of CoPc, we reasoned that the observed reactivity could be reversed by oxidation with atmospheric O_2 to generate a chemically reversible and cycleable system. To demonstrate this redox cycling, we first treated a THF solution of CoPc with 10 equiv of NaSH under N_2 to generate $[Co^{I}Pc]^-$ and then exposed the solution to air, which resulted in rapid oxidation back to the

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parent CoPc (Figure 4). The subsequent addition of NaSH regenerates $[Co^{I}Pc]^{-}$. If protected from O_2 under a N_2

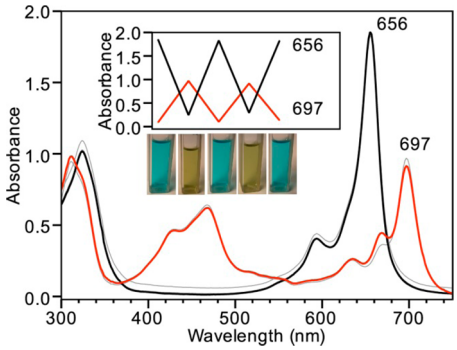

Figure 4. UV−vis spectra of CoPc (7 μM in THF, black trace, blue cuvette) after treatment with 10 equiv of NaSH in DMSO (red trace, green cuvette). Subsequent exposure to atmospheric O_2 regenerates CoPc. The inset shows changes in the Q band, corresponding to three cycles of treatment with HS^{-} followed by exposure to air.

atmosphere, the $[Co^{I}Pc]^{-}$ product is stable and does not spontaneously revert to CoPc. Unlike ZnPc, this chemically reversible reaction with HS^{-} results in a color change that can be easily detected by the naked eye (Figure 4, inset), highlighting the potential for future use in chemically reversible colorimetric HS^{-} detection.

Taken together, these studies with ZnPc and CoPc demonstrate the differential reactivity of HS^{-} and H_2S toward metal centers and highlight how these changes in a protonation state can be used to generate chemically reversible HS^{-} ligation, in the case of ZnPc. Additionally, these examples of chemical reversibility clarify the fundamental reaction chemistry of porphyrin-derived scaffolds with H_2S and expand the fundamental understanding of how H_2S interacts with biologically relevant metal scaffolds. To further expand on this chemistry, we are currently pursuing water-soluble derivatives for chemically reversible anaerobic H_2S detection, which will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, UV−vis data, Job plots, and ^{1}H NMR data for ZnPc and CoPc after reaction with NaSH. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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