A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: A Dinuclear Persulfide-Bridged Ruthenium Compound is a Hypoxia-Selective Hydrogen Sulfide (H2S) Donor.

Authors: Joshua J. Woods and Justin J. Wilson

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202012620

Link to VoR: https://doi.org/10.1002/anie.202012620

WILEY-VCH

10.1002/anie.202012620

WILEY-VCH

COMMUNICATION

A Dinuclear Persulfide-Bridged Ruthenium Compound is a Hypoxia-Selective Hydrogen Sulfide (H_2S) Donor.

Joshua J. Woods,[a,b] and Justin J. Wilson*[a]

[a] J. J. Woods, Prof. J. J. Wilson
Department of Chemistry and Chemical Biology
Cornell University
Ithaca, NY 14853
E-mail: jjw275@cornell.edu
[b] J. J. Woods
Robert F. Smith School for Chemical and Biomolecular Engineering
Cornell University
Ithaca, NY 14853

Supporting information and the ORCID identification number(s) for the authors of this article can be found under:

Abstract: Hydrogen sulfide (H_2S) is a gaseous molecule that has received attention for its role in biological processes and therapeutic potential in diseases such as ischemic reperfusion injury. Despite its clinical relevance, delivery of H_2S to biological systems is hampered by its toxicity at high concentrations. Herein, we report the first metal based H_2S donor that delivers this gas selectively to hypoxic cells. We further show that H_2S release from this compound protects H9c2 rat cardiomyoblasts from an in vitro model of ischemic reperfusion injury. These results validate the utility of redox-activated metal complexes as hypoxia-selective H_2S-releasing agents for use as tools to study the role of this gaseous molecule in complex biological systems.

Hydrogen sulfide (H_2S) has long been known to be a highly toxic gas with a noxious odor. In 1996, this perception was changed by the discovery that this gas is produced endogenously in mammals and functions as a modulator for neurological activity.[1] Since this discovery, further work has revealed that H_2S is an important signaling molecule involved in angiogenesis and the prevention of oxidative stress.[2] Furthermore, H_2S has promising therapeutic potential for the treatment of Alzheimer's disease, Parkinson's disease, ischemic reperfusion injury (IRI), stroke, and cancer.[3] The implementation of H_2S in medicine, however, is limited by its gaseous nature, flammability, and toxicity at high concentrations. As such, significant research efforts have focused on developing easily handled prodrugs for this gaseous molecule.[4–12] Simple sulfide salts such as Na_2S or NaSH rapidly release H_2S upon dissolution in aqueous solution. Although these complexes are more practical for the delivery of H_2S than its direct administration as a gas, their rapid release profiles do not mimic endogenous H_2S production and often elicit toxic side effects.[13] To circumvent these challenges, several groups have developed synthetic compounds that release H_2S upon activation by external stimuli such as light,[14–21] pH,[22,23] and reactive oxygen species.[24,25] These compounds allow localized and controllable delivery of H_2S in complex biological systems, making them promising therapeutic candidates.

In this study, we sought to develop H_2S donors that could be selectively activated for therapeutic intervention in conditions such as cancer, IRI, or stroke. Under these pathological conditions, cells and tissue exist in a state of hypoxia, causing them to lose the ability to maintain redox balance and the cellular environment becomes reducing.[26] In this context, the redox chemistry of Cu, Pt, Co, Fe, Ru, Os and Ir has been used to develop prodrugs that are specifically activated in hypoxic cells to produce reactive anticancer compounds.[27–31] Our strategy to develop a redox-activated H_2S donor invoked the dinuclear ruthenium persulfide (μ-S_2^{2-}) core [$Ru^{III}SSRu^{III}$]. This moiety is labile towards reduction in protic solvents, producing H_2S and the related Ru^{II} species.[32–34] In this report, we describe our initial evaluation of a ruthenium persulfide complex as a platform for hypoxia-activated delivery of H_2S in cultured cells and demonstrate the ability of this complex to protect against an in vitro model of ischemic reperfusion injury. These results highlight the value of metal-based H_2S donors as tools for understanding the therapeutic utility of this gasotransmitter.

The compound $[(H_2O)Ru(NH_3)_4(\mu\text{-}S_2)Ru(NH_3)_4(OH_2)]^{4+}$ ([**1**]$^{4+}$, Figure 1) was obtained as the chloride salt ([**1**]Cl_4) by treatment of *trans*-$[Ru(NH_3)_4(SO_2)Cl]^+$ with amalgamated zinc in 0.1 M HCl followed by purification with cation-exchange chromatography.[32] This complex was characterized by NMR, UV/vis, and resonance Raman spectroscopies in addition to reverse-phase high-performance liquid chromatography (HPLC), elemental analysis, and x-ray crystallography (Figures 1 and S1-S5, Supporting Information, SI).

X-ray diffraction-quality crystals of [**1**]$(SiF_6)_2$ were obtained by vapor diffusion of acetone into a solution of [**1**]$(SbF_6)_4$ in 0.1 M DCl (Figure 1). Relevant details are included in the SI (Tables S2 and S3). The complex crystallizes such that the asymmetric unit consists of one half of the molecule, with a center of inversion located in the middle of the persulfide bond. Overall, the Ru–S and S–S interatomic distances agree well with previously explored Ru persulfide complexes (Table S1, SI). The S–S interatomic distance is the longest reported for a persulfide-bridged diruthenium complex (Table S1, SI) and falls between the value expected for a sulfur-sulfur single (2.03 Å for Me_2S_2)[35] and double bond (1.887 Å for S_2).[36–38] This intermediate bond order has been observed in other persulfide-bridged diruthenium

10.1002/anie.202012620

complexes and is attributed to highly delocalized π-bonding within the persulfide core.[34]

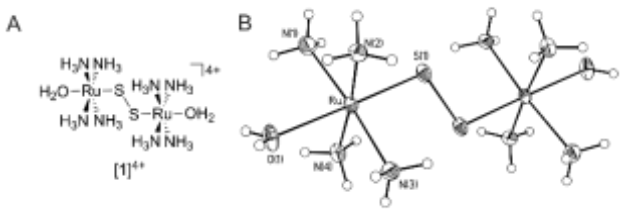


Figure 1. (A) Chemical and (B) X-ray crystal structure of [**1**]$(SiF_6)_2$. The SiF_6^{2-} counterions have been omitted for clarity. Thermal ellipsoids are depicted at the 50% probability level. Selected geometric parameters (Å,°): S(1)–S(#1) 2.0186(13), Ru–S(1) 2.1659(7), Ru–O(1) 2.177(2), Ru–S(1)–S(#1) 111.63(5).

To assess the suitability of [**1**]Cl_4 for hypoxia activation, we analyzed the redox activity of this compound using cyclic voltammetry (CV; Figure 2). In pH 7.4 PBS, the CV of [**1**]Cl_4 displays an irreversible reduction peak with an onset potential of –716 mV vs. SCE (feature II, Figure 2). The irreversibility of this feature may arise from dissociation of the complex upon reduction. Importantly, the onset of the irreversible reduction for [**1**]Cl_4 lies within the required range (–0.75 to –0.35 V vs. SCE)[39,40] for hypoxia selectivity. Another feature, an irreversible oxidation, occurs with an onset potential of 490 mV, a potential that is unlikely to be accessible under biological conditions (feature IV, Figure 2). Following oxidation, a weak feature at 150 mV vs. SCE (features III/V, Figure 2) appears, which possibly corresponds to oxidation products of [**1**]$^{4+}$ obtained after sweeping these higher potentials.

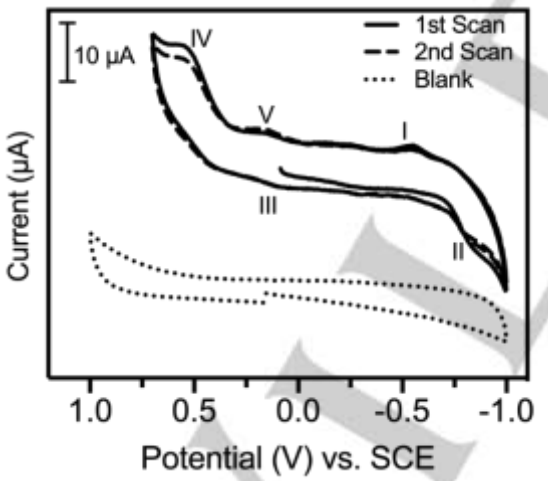


Figure 2. Top: Cyclic voltammogram of [**1**]Cl_4 in PBS (pH 7.4, 23 °C). Bottom: Cyclic voltammogram of PBS. Conditions: glassy carbon working electrode, Pt wire counter electrode, Ag/AgCl quasi-reference electrode, and 0.1 V s^{-1} scan rate.

For [**1**]Cl_4 to be useful as a biological delivery vehicle for H_2S that does not give rise to acute toxicity, the release of this gas molecule should be gradual rather than instantaneous. We examined the potential of [**1**]Cl_4 to release H_2S upon treatment with a panel of biologically relevant reducing agents. We found that the presence of Ru(III) in solution interferes with the commonly used methylene blue assay for H_2S detection (Figure S6-S9, SI). As such, the turn-on fluorescent probe SF4 was used to monitor release of H_2S from [**1**]Cl_4 (Figures 3 and S10-S11, SI). No increase in emission intensity was detected when [**1**]Cl_4 was incubated at 37 °C, indicating that the complex does not release H_2S under these conditions (Figure 3). This result is consistent with UV/vis spectroscopic studies that show this compound to remain >95% intact after incubation in pH 7.4 PBS at 37 °C for 24 h and >75% intact after 72 h (Figure S12, SI). When [**1**]Cl_4 is treated with a 10-fold excess of the reducing agents HSO_3^-, cysteine, glutathione (GSH), and ascorbate, the emission of the H_2S sensor SF4 increases gradually over the course of 190 min, confirming that reductive activation of [**1**]Cl_4 triggers H_2S release. Notably the H_2S yield scales directly with the reducing power of the species and incubation with other biologically relevant species, such as anionic nucleophiles (OH^-, Cl^-, aspartate) and oxidants (GSSG, H_2O_2, $NaNO_2$, NaHClO, ^{t}BuOOH) does not trigger H_2S release (Figure S11, SI). These results suggest that this compound will be a useful agent for hypoxia-activated delivery of this gas.

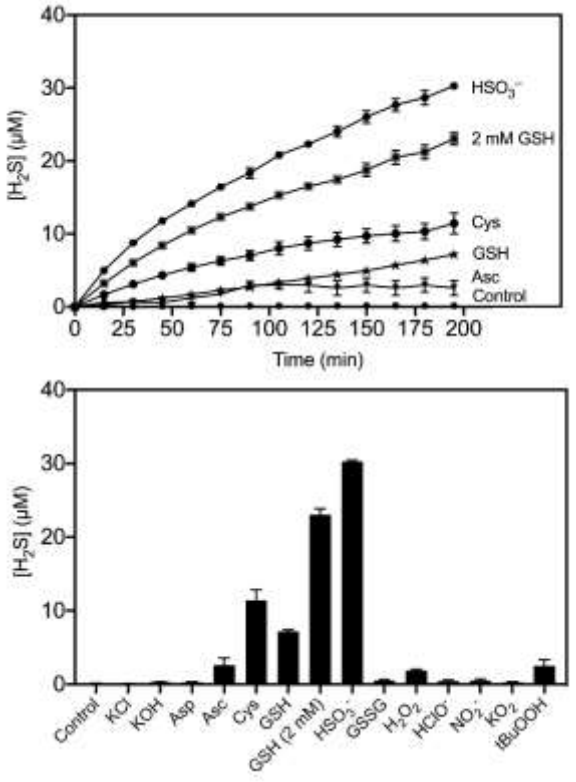


Figure 3. Top: H_2S-release profile from [**1**]Cl_4 (20 μM) in pH 7.4 PBS at 37 °C in the presence of biologically relevant reducing agents (200 μM unless indicated). Bottom: Quantification of [H_2S] produced by [**1**]Cl_4 after incubation in pH 7.4 PBS with relevant biological species (200 μM) [**1**]Cl_4 for 190 min at 37 °C. Results are reported as mean ± SD (*ns* = not significant; *n* = 3–4).

Following these initial studies, we sought to further elucidate the pathway of H_2S release from [**1**]Cl_4. Two possible mechanisms were considered (Figure S13). The first mechanism (Type I) progresses via reduction of the Ru^{3+} centers. The labile Ru^{2+} would undergo aquation to release H_2S_2, which would then disproportionate to form H_2S and higher order polysulfides. The

10.1002/anie.202012620

second mechanism (Type 2) considered involves initial reduction of the persulfide bond to yield Ru^{III}-SH type complexes, which undergo further reduction and ligand substitution to produce H_2S and a Ru^{II} species.

To probe these mechanisms, we first treated [**1**]Cl_4 with 40-fold excess GSH or 10-fold excess ascorbate in the presence of the polysulfide-selective fluorescent probe DSP-3 (Figure S14-S15, SI).[41] No change in DSP-3 fluorescence after 40 min of treatment was observed, suggesting that polysulfide species are not produced during the reduction of [**1**]Cl_4 To further confirm these results, we monitored the reaction between [**1**]Cl_4 and 10-fold excess GSH by UV/vis spectroscopy in the presence of 0.5 M isonicotinamide (isn), a technique previously employed to study the reduction reaction between GSH and Ru^{III} ammine complexes (Figure S16, SI).[42] Upon addition of GSH to a solution containing [**1**]Cl_4 and 0.5 M isonicotinamide (isn), a peak rapidly appears at 427 nm, which is characteristic of *trans*-$[isn(NH_3)_4Ru(SH)]^{2+}$.[43] Taken together, these results suggest that decomposition of [**1**]Cl_4 upon reduction proceeds through a mechanism similar to Type 2 (Figure S13, SI) to selectively release H_2S without initial production of polysulfide species. This reactivity pattern contrasts that of many organic H_2S donors that contain polysulfide bonds produce reactive polysulfide species as intermediate products.[44–49]

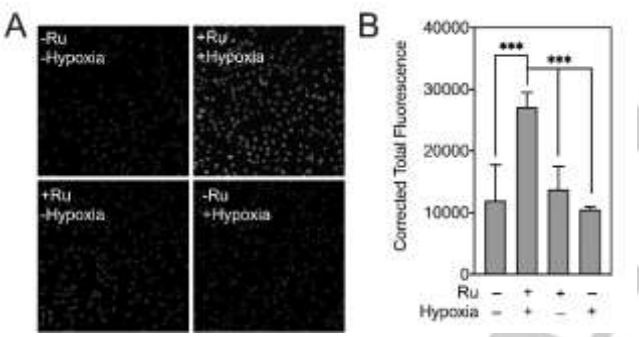


Figure 4. (A) Representative images of H_2S-release from [**1**]Cl_4 in vitro. HeLa cells were loaded with 5 μM SF7-AM for 30 min, washed, and loaded with 0 or 50 μM [**1**]Cl_4 for 1 h. Cells were then incubated in GBSS under either hypoxic (95:5 N_2/CO_2) or normoxic (95:5 Air/CO_2) conditions for 3 h. (B) Corrected total fluorescence of HeLa cells incubated in the conditions described (see SI for details). Results are reported as mean ± SD (***p<0.001, *n* = 3-4).

Given the promising H_2S-release profile and selectivity of [**1**]Cl_4, we investigated the biological activity of this complex. The complex is effectively nontoxic at concentrations up to 200 μM in cervical cancer (HeLa) and rat cardiomyoblast (H9c2) cells (Figure S17, SI). Additionally, [**1**]Cl_4 is taken up by cells effectively (Figure S18, SI), as determined by graphite furnace atomic absorption spectroscopy. Based on its cell permeability and low toxicity, we next investigated the ability of [**1**]Cl_4 to selectively release H_2S in hypoxic cells using the cell-trappable, H_2S-responsive fluorescent probe, SF7-AM.[50] Cells that were only treated with [**1**]Cl_4 or subjected to hypoxic conditions in the absence of the complex showed no significant increase in fluorescence intensity compared to control cells. In contrast, we observe a significant increase in fluorescence intensity in cells treated with both [**1**]Cl_4 and hypoxic conditions, indicating that both components are required for intracellular release of H_2S (Figure 4). Additionally, when HeLa cells were treated with a spent solution of the complex (See SI for details, Figure S19-S20, SI), we observed no increase in fluorescence intensity with incubation under normoxic or hypoxic conditions (Figure S20, SI). This result confirms that the fluorescence enhancement observed for cells treated with [**1**]Cl_4 under hypoxic conditions arises from H_2S produced by the complex.

H_2S has therapeutic properties for preventing the damaging effects of IRI in heart disease and stroke.[51–55] We therefore investigated the ability of [**1**]Cl_4 to protect H9c2 rat cardiomyoblast cells from this condition using an in vitro model for IRI. hen cells were pretreated with [**1**]Cl_4 prior to hypoxia, a dose-dependent increase in cell viability relative to the untreated cells was observed, indicating that this compound gives rise to cytoprotective effects (Figure 5). One the major mechanisms of the therapeutic effect of H_2S for the treatment of IRI is the activation of the mitochondrial K_{ATP} channel,[56–59] an energy-dependent transporter of mitochondrial K^+ ions. H_2S will activate this channel, causing the mitochondria to expunge K^+ ions to decrease the mitochondrial membrane potential (MMP). The decreased MMP will lead to diminished uptake of Ca^{2+} ions, preventing mitochondrial calcium overload, the primary cause of the cytotoxicity of IRI. To confirm that H_2S mediates the protective effects of [**1**]Cl_4, the H9c2 cells were incubated with the K_{ATP} channel inhibitor glibenclamide[60] (10 μM) prior to subjecting them to IRI. In the presence of glibenclamide, [**1**]Cl_4 fails to protect the cells from death due to IRI (Figure 5). This result indicates that the cytoprotective effects of [**1**]Cl_4 arise from its ability to release H_2S, which acts directly on the mitochondrial K_{ATP} channel. Furthermore, treatment with the spent solution described above did not give rise to any of the observed protective effects, confirming that the cytoprotective effects of [**1**]Cl_4 arise from its ability to produce H_2S in hypoxic cells (Figure S21, SI).

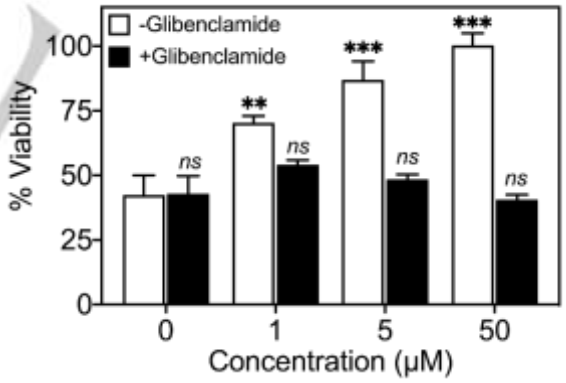


Figure 5. Protective effects of [**1**]Cl_4 at various concentrations in H9c2 cells exposed to hypoxia-reoxygenation injury after preincubation with 0 or 10 μM glibenclamide. Results are reported as mean ± SD (*ns* = not significant; **p<0.01; ***p<0.001; n = 3).

In summary, by applying the "activation by reduction" principle that has been leveraged for the design of metal-based anticancer agents, we have been able to use [**1**]Cl_4 as the first H_2S donor that is activated selectively by reduction in hypoxic cells. This work demonstrates that Ru persulfide complexes are viable platforms for H_2S delivery. Furthermore, it highlights how transition metal compounds, in general, may serve as viable candidates for releasing H_2S and other reactive-sulfur species,

adding to their prior roles as delivery agents for the more well-known gasotransmitters CO and NO.[61–67]

Acknowledgements

This work was supported by the National Science Foundation (NSF-GRFP for J. J. Woods DGE-1650441 and NSF CAREER for J. J. Wilson CHE-1750295) and the American Heart Association (predoctoral fellowship for J. J. Woods, 20PRE35120390). This work made use of the Cornell University NMR facility, which is supported in part by the NSF (CHE-1531632), and the Cornell Institute of Biotechnology Imaging Facility, which is supported in part by the NIH (NIH S10RR025502). Dr. Weiwei An and Professor Alexander R. Lippert (Southern Methodist University) are thanked for supplying SF4. Ida DiMucci and Professor Kyle Lancaster (Cornell University) are thanked for assistance with Resonance Raman spectroscopy. Professor Jeremey Baskin is thanked for use of his confocal fluorescence microscope.

Conflict of Interest

None reported.

Keywords: ruthenium complexes • hydrogen sulfide • hypoxia • persulfide complex • reduction-activated

[1] K. Abe, H. Kimura, *J. Neurosci.* **1996**, *16*, 1066–1071.

[2] H. Liu, M. N. Radford, C. Yang, W. Chen, M. Xian, *Br. J. Pharmacol.* **2019**, *176*, 616–627.

[3] J. L. Wallace, R. Wang, *Nat. Rev. Drug Discov.* **2015**, *14*, 329–345.

[4] J. C. Foster, S. C. Radzinski, X. Zou, C. V Finkielstein, J. B. Matson, *Mol. Pharm.* **2017**, *14*, 1300–1306.

[5] M. Whiteman, A. Perry, Z. Zhou, M. Bucci, A. Papapetropoulos, G. Cirino, M. E. Wood, in *Handb. Exp. Pharmacol.*, **2015**, pp. 337–363.

[6] C. R. Powell, K. M. Dillon, J. B. Matson, *Biochem. Pharmacol.* **2018**, *149*, 110–123.

[7] P. Rose, B. W. Dymock, P. K. Moore, *Methods Enzymol.* **2015**, *554*, 143–167.

[8] Y. Zhao, A. K. Steiger, M. D. Pluth, *J. Am. Chem. Soc.* **2019**, *141*, 13610–13618.

[9] M. M. Cerda, Y. Zhao, M. D. Pluth, *J. Am. Chem. Soc.* **2018**, *140*, 12574–12579.

[10] C.-M. Park, Y. Zhao, Z. Zhu, A. Pacheco, B. Peng, N. O. Devarie-Baez, P. Bagdon, H. Zhang, M. Xian, *Mol. Biosyst.* **2013**, *9*, 2430.

[11] Y. Zhao, S. Bhushan, C. Yang, H. Otsuka, J. D. Stein, A. Pacheco, B. Peng, N. O. Devarie-Baez, H. C. Aguilar, D. J. Lefer, et al., *ACS Chem. Biol.* **2013**, *8*, 1283–1290.

[12] K. M. Dillon, R. J. Carrazzone, Y. Wang, C. R. Powell, J. B. Matson, *ACS Macro Lett.* **2020**, *9*, 606–612.

[13] Y. Zheng, X. Ji, K. Ji, B. Wang, *Acta Pharm. Sin. B* **2016**, *5*, 367–377.

[14] J. J. Woods, J. Cao, A. R. Lippert, J. J. Wilson, *J. Am. Chem. Soc.* **2018**, *140*, 12383–12387.

[15] N. O. Devarie-Baez, P. E. Bagdon, B. Peng, Y. Zhao, C.-M. Park, M. Xian, *Org. Lett.* **2013**, *15*, 2786–2789.

[16] W. Chen, M. Chen, Q. Zang, L. Wang, F. Tang, Y. Han, C. Yang, L. Deng, Y.-N. Liu, *Chem. Commun.* **2015**, *51*, 9193–9196.

[17] N. Fukushima, N. Ieda, K. Sasakura, T. Nagano, K. Hanaoka, T. Suzuki, N. Miyata, H. Nakagawa, *Chem. Commun.* **2014**, *50*, 587–589.

[18] A. K. Sharma, M. Nair, P. Chauhan, K. Gupta, D. K. Saini, H. Chakrapani, *Org. Lett.* **2017**, *19*, 4822–4825.

[19] S. Y. Yi, Y. K. Moon, S. Kim, S. Kim, G. Park, J. J. Kim, Y. You, *Chem. Commun.* **2017**, *53*, 11830–11833.

[20] Z. Xiao, T. Bonnard, A. Shakouri-Motlagh, R. A. L. Wylie, J. Collins, J. White, D. E. Heath, C. E. Hagemeyer, L. A. Connal, *Chem. Eur. J.* **2017**, *23*, 11294–11300.

[21] Y. Zhao, S. G. Bolton, M. D. Pluth, *Org. Lett.* **2017**, *19*, 2278–2281.

[22] J. Kang, Z. Li, C. L. Organ, C.-M. Park, C. Yang, A. Pacheco, D. Wang, D. J. Lefer, M. Xian, *J. Am. Chem. Soc.* **2016**, *138*, 6336–6339.

[23] A. K. Gilbert, Y. Zhao, C. E. Otteson, M. D. Pluth, *J. Org. Chem.* **2019**, *84*, 14469–14475.

[24] Y. Zhao, M. D. Pluth, *Angew. Chem. Int. Ed.* **2016**, *55*, 14638–14642.

[25] C. R. Powell, K. M. Dillon, Y. Wang, R. J. Carrazzone, J. B. Matson, *Angew. Chemie* **2018**, *130*, 6432–6436.

[26] W. R. Wilson, M. P. Hay, *Nat. Rev. Cancer* **2011**, *11*, 393–410.

[27] I. Romero-Canelón, P. J. Sadler, *Inorg. Chem.* **2013**, *52*, 12276–12291.

[28] U. Jungwirth, C. R. Kowol, B. K. Keppler, C. G. Hartinger, W. Berger, P. Heffeter, *Antioxidants Redox Signal.* **2011**, *15*, 1085–1127.

[29] A. Sharma, J. F. Arambula, S. Koo, R. Kumar, H. Singh, J. L. Sessler, J. S. Kim, *Chem. Soc. Rev.* **2019**, *48*, 771–813.

[30] E. Reisner, V. B. Arion, B. K. Keppler, A. J. L. Pombeiro, *Inorg. Chim. Acta.* **2008**, *361*, 1569–1583.

[31] N. Graf, S. J. Lippard, *Adv. Drug Deliv. Rev.* **2012**, *64*, 993–1004.

[32] C. R. Brulet, S. S. Isied, H. Taube, *J. Am. Chem. Soc.* **1973**, *95*, 4758–4759.

[33] J. Amarasekera, T. B. Rauchfuss, *Inorg. Chem.* **1989**, *28*, 3875–3883.

[34] J. Amarasekera, T. B. Rauchfuss, S. R. Wilson, *Inorg. Chem.* **1987**, *26*, 3328–3332.

[35] R. Steudel, *Angew. Chem. Int. Ed.* **1975**, *14*, 655–664.

[36] B. Meyer, *Chem. Rev.* **1976**, *76*, 367–388.

[37] L. R. Maxwell, V. M. Mosley, S. B. Hendricks, *Phys. Rev.* **1936**, *50*, 41–45.

[38] A. Mueller, W. Jaegermann, *Inorg. Chem.* **1979**, *18*, 2631–2633.

[39] W. R. Wilson, R. F. Anderson, W. A. Denny, *J. Med. Chem.* **1989**, *32*, 23–30.

[40] A. P. King, H. A. Gellineau, J. E. Ahn, S. N. MacMillan, J. J. Wilson, *Inorg. Chem.* **2017**, *56*, 6609–6623.

[41] C. Liu, W. Chen, W. Shi, B. Peng, Y. Zhao, H. Ma, M. Xian, *J. Am. Chem. Soc.* **2014**, *136*, 7257–7260.

[42] D. R. Frasca, M. J. Clarke, *J. Am. Chem. Soc.* **1999**, *121*, 8523–8532.

[43] C. G. Kuehn, H. Taube, *J. Am. Chem. Soc.* **1976**, *98*, 689–702.

[44] S. Xu, Y. Wang, Z. Parent, M. Xian, *Bioorg. Med. Chem. Lett.* **2020**, *30*, 126903.

[45] D. Liang, H. Wu, M. W. Wong, D. Huang, *Org. Lett.* **2015**, *17*, 4196–4199.

[46] M. M. Cerda, M. D. Hammers, M. S. Earp, L. N. Zakharov, M. D.

Pluth, *Org. Lett.* **2017**, *19*, 2314–2317.

[47] S. G. Bolton, M. M. Cerda, A. K. Gilbert, M. D. Pluth, *Free Radic. Biol. Med.* **2019**, *131*, 393–398.

[48] B. Yu, Y. Zheng, Z. Yuan, S. Li, H. Zhu, L. K. De La Cruz, J. Zhang, K. Ji, S. Wang, B. Wang, *J. Am. Chem. Soc.* **2018**, *140*, 30–33.

[49] A. Chaudhuri, Y. Venkatesh, B. C. Jena, K. K. Behara, M. Mandal, N. D. P. Singh, *Org. Biomol. Chem.* **2019**, *17*, 8800–8805.

[50] V. S. Lin, A. R. Lippert, C. J. Chang, *PNAS* **2013**, *110*, 7131–7135.

[51] C. Szabó, *Nat. Rev. Drug Discov.* **2007**, *6*, 917–935.

[52] Y. Zhao, C. Yang, C. Organ, Z. Li, S. Bhushan, H. Otsuka, A. Pacheco, J. Kang, H. C. Aguilar, D. J. Lefer, et al., *J. Med. Chem.* **2015**, *58*, 7501–7511.

[53] Z. Zhang, H. Huang, P. Liu, C. Tang, J. Wang, *Can. J. Physiol. Pharmacol.* **2007**, *85*, 1248–1253.

[54] J. W. Elrod, J. W. Calvert, J. Morrison, J. E. Doeller, D. W. Kraus, L. Tao, X. Jiao, R. Scalia, L. Kiss, C. Szabo, et al., *PNAS* **2007**, *104*, 15560–15565.

[55] J. W. Calvert, S. Jha, S. Gundewar, J. W. Elrod, A. Ramachandran, C. B. Pattillo, C. G. Kevil, D. J. Lefer, *Circ. Res.* **2009**, *105*, 365–374.

[56] W. Liang, J. Chen, L. Mo, X. Ke, W. Zhang, D. Zheng, W. Pan, S. Wu, J. Feng, M. Song, et al., *Int. J. Mol. Med.* **2016**, *37*, 763–772.

[57] D. Johansen, K. Ytrehus, G. F. Baxter, *Basic Res. Cardiol.* **2006**, *101*, 53–60.

[58] G. Tang, L. Wu, W. Liang, R. Wang, *Mol. Pharmacol.* **2005**, *68*, 1757–1764.

[59] B. Jiang, G. Tang, K. Cao, L. Wu, R. Wang, *Antiox. Redox Signal.* **2010**, *12*, 1167–1178.

[60] C. Ripoll, W. J. Lederer, C. G. Nichols, *J Cardiovasc. Electrophysiol.* **1993**, *4*, 38–47.

[61] H. J. Xiang, M. Guo, J. G. Liu, *Eur. J. Inorg. Chem.* **2017**, 1586–1595.

[62] R. Alberto, R. Motterlini, *Dalton Trans.* **2007**, 1651–1660.

[63] R. D. Rimmer, A. E. Pierri, P. C. Ford, *Coord. Chem. Rev.* **2012**, *256*, 1509–1519.

[64] N. L. Fry, P. K. Mascharak, *Acc. Chem. Res.* **2011**, *44*, 289–298.

[65] P. C. Ford, *Coord. Chem. Rev.* **2018**, *376*, 548–564.

[66] M. J. Rose, P. K. Mascharak, *Coord. Chem. Rev.* **2008**, *252*, 2093–2114.

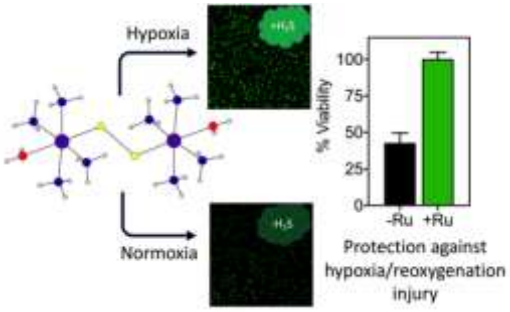
[67] F. Zobi, *Future Med. Chem.* **2013**, *5*, 175–188.

10.1002/anie.202012620

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents



Targeting hypoxia with H_2S Donors: Exploration of the biological activity of a dinuclear persulfide-bridged ruthenium persulfide complex identifies an exciting class of compounds for delivery of H_2S to hypoxic cells.

Institute and/or researcher Twitter usernames: @CornellChem @JWilsonLab