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Review

Chemical foundations of hydrogen sulfide biology

Qian Li [a,d,*], Jack R. Lancaster Jr. [a,b,c,d]

[a] Department of Anesthesiology, University of Alabama at Birmingham, United States
[b] Department of Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham, United States
[c] Department of Environmental Health Sciences, University of Alabama at Birmingham, United States
[d] Center for Free Radical Biology, University of Alabama at Birmingham, United States

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ABSTRACT

Following nitric oxide (nitrogen monoxide) and carbon monoxide, hydrogen sulfide (or its newer systematic name sulfane, H_2S) became the third small molecule that can be both toxic and beneficial depending on the concentration. In spite of its impressive therapeutic potential, the underlying mechanisms for its beneficial effects remain unclear. Any novel mechanism has to obey fundamental chemical principles. H_2S chemistry was studied long before its biological relevance was discovered, however, with a few exceptions, these past works have received relatively little attention in the path of exploring the mechanistic conundrum of H_2S biological functions. This review calls attention to the basic physical and chemical properties of H_2S, focuses on the chemistry between H_2S and its three potential biological targets: oxidants, metals and thiol derivatives, discusses the applications of these basics into H_2S biology and methodology, and introduces the standard terminology to this youthful field.

Contents

* Corresponding author. Address: Department of Anesthesiology and Center for Free Radical Biology, University of Alabama at Birmingham, 901 19th St. S., Birmingham, AL 35294, United States. Fax: +1 205 934 7437.
E-mail address: qianli@uab.edu (Q. Li).

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Introduction

Hydrogen sulfide (or its newer systematic name sulfane [1], H_2S) had been conventionally considered as a toxic molecule until 17 years ago when Abe and Kimura first suggested its physiological function in the nervous system [2]. In 2008, Yang et al. developed mice deficient in the H_2S generating enzyme cystathionine γ-lyase (CSE) and discovered the development of hypertension in these CSE knockouts [3]. Their study further confirmed the endogenous generation of H_2S and its physiological relevance. Since then, H_2S has been found to play a variety of roles in mammals ([4–8] and the accompanying review in this issue) and more intriguingly, is considered as the third "gasotransmitter"[1] after nitric oxide (nitrogen monoxide, ·NO) and carbon monoxide [9–14]. In contrast to the tremendous number of reports on its potential therapeutic effects [13,15–17], the underlying mechanisms are poorly understood. H_2S biochemistry has been reviewed, suggesting mechanisms including reducing oxidative stress and protein post-translational modification [18–20]. However, the chemistry defining the interactions between H_2S and its direct targets has been largely overlooked. Here we provide an overview of H_2S chemistry that is biologically relevant but has been studied mostly from other aspects, and discuss applications in H_2S biochemistry and biology. Since there has recently been interest in the similarities and interactions between H_2S and ·NO biology [21–27], we categorize H_2S chemistry based on the three potential targets that H_2S may share with ·NO, oxidants, metals and thiol (RSH) derivatives. The goal is to reemphasize the importance of basic chemistry on the road of biological adventures.

Basic physical and chemical properties

Under ambient temperature and pressure, H_2S is a colorless gas with an odor of rotten eggs. It is flammable and poisonous in high concentrations. Acute exposure to 500 ppm can cause death [28]. In this regard, caution should be used for handling [29]. H_2S is soluble in water, its solubility has been reported to be about 80 mM at 37 °C [19], 100 mM in water at 25 °C [30], 122 mM in water at 20 °C [31] and up to ~117 mM (condition unspecified) [17]. The differences are apparently due to the experimental conditions including pressure, temperature and the composition of the solution. On the other hand, aqueous H_2S is volatile. In other words, H_2S always equilibrates between the gas phase and the aqueous phase (first equilibrium of Eq. (1)). Its properties of gas–aqueous distribution including Henry's Law coefficient have been studied [32]. H_2S is lipophilic [14,31] and can diffuse through membranes without facilitation of membrane channels (lipid bilayer permeability $P_M \geqslant 0.5 \pm 0.4$ cm/s) [33].

$$H_2S_{(g)} \rightleftharpoons H_2S_{(aq)} \rightleftharpoons HS^- + H^+ \rightleftharpoons S^{2-} + 2H^+ \quad (1)$$

H_2S is a weak acid, it equilibrates with its anions HS^- and S^{2-} in aqueous solution (second and third equilibria of Eq. (1)). Its pKa values appear frequently in publications, particularly review articles, however, the original research reports are rarely cited. Here are mentioned a few good sources. A survey of publications prior to 1970 showed that the reported pKa_1 values varied from 6.97 to 7.06 at 25 °C, and pKa_2 from 12.35 to 15 [34]. Based on that survey the pKa_1 value of 7.02 was suggested [35]. Thereafter, a similar range of pKa_2 values (12.20–15.00 at 25 °C) has been reported [36], whereas higher values (17.1 ± 0.2 at room temperature [37], >17.3 ± 0.1 at 25 °C [38], 19 at 25 °C [39] and 19 ± 2 [40]) have also been reported. Assuming a pKa_1 value of 7, it can be calculated that 28% of the total hydrogen sulfide in a pH 7.4 solution exists as H_2S, whereas 72% is in the form of HS^-. The high pKa_2 value indicates that S^{2-} is negligible in the solution. The pKa value of a compound depends on conditions including temperature and the solution composition. Millero and Hershey reviewed both thermodynamics and kinetics studies on aqueous H_2S, and derived equations for the calculation of both pKa and the solubility of H_2S under certain pressure, temperature and composition of the solution [41,42]. Using precise pKa values under the exact experimental conditions is important for the calculation of H_2S concentration. It has been shown that at physiological pH the concentration of H_2S (or $H_2S_{(aq)}$) at 20 °C (pKa_1 6.98) can be twice as much as that at 37 °C (pKa_1 6.76) (Fig. 3 in [29]).

Practically, the three equilibria in Eq. (1) represent the real dynamics of the H_2S solution. One can easily predict that in an open system, according to Le Châtelier's Principle the equilibria will continuously shift to the left, in the direction of forming $H_2S_{(aq)}$ which then escapes from solution. It has been reported that half of H_2S can be lost from solution in five minutes in cell culture wells, three minutes in a bubbled tissue bath and an even shorter time in the Langendorff heart apparatus [43]. This fact should be taken into consideration for the actual H_2S concentration in an experimental system containing headspace, which has been utilized in most of the studies on H_2S. This may also explain to some extent the remarkable variations in the reported H_2S concentrations in tissues and plasma [44–46]. Moreover, one should also be aware that based on Eq. (1), the leftward equilibrium shift could cause not only a tremendous decrease in H_2S concentration, but also a considerable increase of the solution pH. Eq. (1) is also the basis of the application of H_2S gas or inorganic metallic sulfide such as sodium sulfide (Na_2S) and sodium hydrosulfide (NaHS) as H_2S sources in solution. Caution should be taken since an unbuffered stock solution from H_2S gas tends to be acidic, whereas that from metallic sulfide is basic (Eq. (1)). In the following discussion, unless specified we use H_2S to indicate all three species H_2S, HS^- and S^{2-}.

The bond dissociation energy of H_2S is 90 kcal/mol [18], essentially the same as the S–H bond in thiols (92.0 ± 1.0 kcal/mol [47]). The element sulfur can exist in molecules with a broad range of formal oxidation states including −2 as in H_2S, 0 as in elemental sulfur (S_8), +2 as in sulfur monoxide (SO), +4 as in sulfite (SO_3^{2-}) and +6 as in sulfate (SO_4^{2-}). With the lowest oxidation state of −2, the sulfur in H_2S can only be oxidized. Therefore, H_2S is a reductant. The standard reduction potential

[1] A note of terminology, the definition of a "gas" is a substance possessing perfect molecular mobility and the property of indefinite expansion to fill the available space. This is true of each of these substances in the pure state under standard conditions but obviously does not accurately describe the physical properties of these substances (as well as O_2 and CO_2) in virtually all of their biological actions which are more appropriately described as dissolved noneletrolytes.