Hydrogen Sulfide: A Reagent for pH-Driven Bioinspired 1,2-Diol Mono-deoxygenation and Carbonyl Reduction in Water

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S *Supporting Information*

ABSTRACT: Hydrogen sulfide (H_2S) was evaluated for its peculiar sulfur radical species generated at different pHs and was used under photolytical conditions in aqueous medium for the reduction of 1,2-diols to alcohols. The conversion steps of 1,2-cyclopentanediol to cyclopentanol via cyclopentanone were analyzed, and it was proven that the reaction proceeds via a dual catalytic/radical chain mechanism. This approach was successfully adapted to the reduction of a variety of carbonyl compounds using H_2S at pH 9 in water. This work opens up the field of environmental friendly synthetic processes using the pH-driven modulation of reactivity of this simple reagent in water.
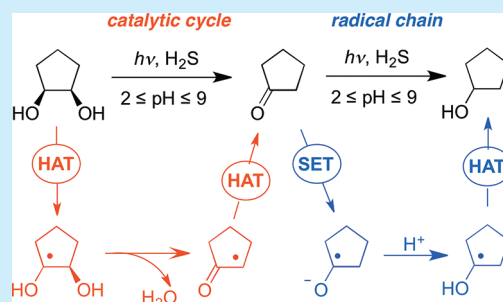
The selective deoxygenation of a 1,2-diol to an alcohol is a difficult chemical conversion that has a myriad of potential synthetic applications and is fundamental to the origin of life. In principle, this conversion can be accomplished by dehydration of a 1,2-diol to an aldehyde or ketone followed by a reduction. The foremost known pathways for the reduction or dehydration of 1,2-diols proceed via intermediate radicals. The Barton—McCombie reaction is, for example, a multistep approach that is applicable to sugar substrates and involves protection and derivatization to an intermediate that undergoes a radical-mediated deoxygenation reaction.[1,2]

The monodeoxygenation of a 1,2-diol is performed in nature by ribonucleotide reductases that employ thiyl radical based chemistry (Figure 1). The ribose unit of ribonucleotide
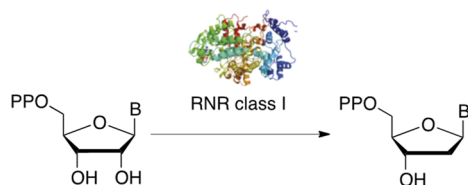
Figure 1. Transformation of ribonucleotides to 2′-deoxy-ribonucleotides.

diphosphates is converted into 2-deoxyribose units required as building blocks for the de novo synthesis of DNA.[3,4] In this mechanism,[5,6] one of the cysteine residues at the active site generates a thiyl radical CyS• which effects H-abstraction from C-3′. There follows elimination of the OH group in C-2′ with translocation of the radical center to C-2′, quenching of the newly formed C-2′ radical and reduction of the C-3′ carbonyl group. Essentially, a (3′,2′)-spin center shift occurs, eliciting a β-C—O scission and elimination of water.[7] A pair of cysteine

residues provide the electrons via a disulfide radical anion to reduce the intermediate ketone to an alcohol.

The dehydration of simple 1,2-diols initiated by HO• radicals with formation of the corresponding aldehyde or ketone has been extensively studied, principally as a model system for carbohydrate substrates,[8] and in connection with the mechanism of diol dehydratase.[9,10] The 1,2-dihydroxyalkyl radicals that are intermediates in this reaction readily undergo either acid- or base-catalyzed elimination of water to afford a carbon-centered radical stabilized by an adjacent carbonyl group.[11] The intermediate carbonyl compound formation has a very large industrial utilization for natural products and polyol conversions, and efforts have been carried out in this field toward environmental friendly approaches in water.[12,13]

The enzymatic mechanisms operating in Figure 1 can be taken as inspiration for using sulfur radical chemistry in the 1,2-diol transformation to monoalcohols and the reduction of carbonyl compounds. Indeed, bioinspired chemical conversions are quite interesting since they open up perspectives for new catalytic processes as well as for green methodologies.[14] The simplest thiol H_2S in the past decade has attracted increasing interest in a multidisciplinary context from chemistry to biology.[15,16] Research has highlighted the strong versatility of this molecule due to a variety of oxidation states[17,18] and the peculiar reactivity of its sulfhydryl and disulfide radical species driven by different pHs in aqueous systems. Some of us previously investigated the pH-sensitive biomimetic cis–trans isomerization process involving unsaturated fatty acids in liposomes with sulfhydryl radical (HS•) derived from protein modifications or H_2S.[19,20] This simple molecule, present among the other gases in primordial

atmosphere,[21] attracts interest in prebiotic reactions in connection with the origin of life.[22,23]

Here, we report the direct conversion of 1,2-cyclopentane diol to cyclopentanol, starting from the photolysis of H_2S at different pH values in aqueous medium with a complete mechanistic picture. In particular, based on the properties of the HS$^{\bullet}$ radical and inspired by the biological mechanism of ribonucleotide reductases, we developed a dual catalytic/ radical chain system capable of unprecedented organic transformations using H_2S radical chemistry.

Thus, Na_2S was used as source of H_2S in aqueous solution for the reduction of cis-1,2-cyclopentanediol (1) under photolytical conditions in the absence of oxygen. Photolysis (low-pressure Hg lamp, 5.5 W) of N_2-saturated aqueous solutions of 1 (8.3 mM) containing $Na_2S \cdot 9H_2O$ (16.6 mM) was monitored for up to 60 min and at various pH values (2, 4.5, 7 and 9). In all experiments, cyclopentanone (2) and cyclopentanol (3) were the only products. The extent of formation of these products under various conditions is summarized in Table 1 (see also Figures S2–S5). Figure 2a

Table 1. Photolysis (low pressure Hg lamp, 5.5 W) of N_2-Saturated Aqueous Solutions of cis-1,2-Cyclopentanediol (1, 8.3 mM) Containing $Na_2S \cdot 9H_2O$ (16.6 mM) with Formation of Cyclopentanone (2) and Cyclopentanol (3) at Different Irradiation Times and pH[a]

pH	time (min)	1 (mM)	2 (mM)	3 (mM)
2	20	6.7	1.5	0.1
	40	5.3	2.7	0.3
	60	4.7	3.1	0.5
4.5	20	6.5	1.3	0.5
	40	5.2	2.1	1.0
	60	4.6	2.4	1.3
7	20	5.9	0.5	1.9
	40	4.6	0.9	2.8
	60	3.9	1.2	3.2
9	30	7.8	c	0.5
	40	7.3	c	1.0
	60[b]	6.2	c	2.1

[a]Reaction temperature was constant at 42 ± 1 °C. [b]pH = 7.5, after 60 min irradiation. [c]Undetectable.

shows the irradiation time profile of the disappearance of 1 (□, ■) and the formation of 2 (○, ●) and 3 (△, ▲) at pH 4.5 (dashed lines) and 7 (full lines), respectively. The percentage of starting material conversion was similar, i.e., after 60 min, a 45% conversion was obtained at pH 4.5 (□) and 52% (■) at pH 7, whereas in the product distribution cyclopentanone predominated at pH 4.5 (○) and cyclo-pentanol at pH 7 (▲). The ratio of the two products was strongly influenced by the pH conditions and also by the reaction time, indicating the intermediacy of 2 in the formation of product 3.

trans-1,2-Cyclopentanediol behaves exactly like the cis-isomer, giving the same conversion and the same trend in the product formation for 2 and 3 (see Figure S6). Further support for the intermediate reduction step 2 → 3 was obtained by observing the direct reduction of cyclopentanone (2) under identical experimental conditions. Figure 2b shows the irradiation time profile for the formation of 3 at various pHs (see Figure S7). Interestingly, reduction efficiency increases with pH, becoming very effective at pH 9.
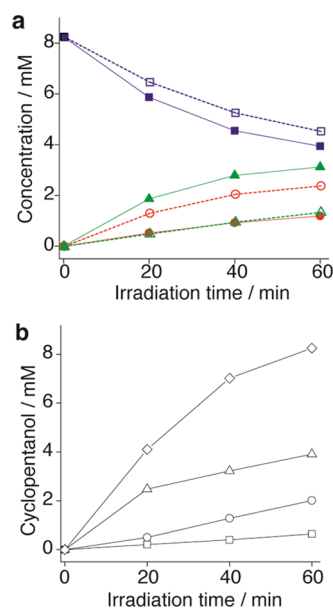
Figure 2. (a) Monodeoxygenation of cis-1,2-cyclopentanediol; concentration of 1 (□, ■), 2 (○, ●), and 3 (△, ▲) vs irradiation time at pH 4.5 (dashed lines) and pH 7 (full lines) for the photolysis of N_2-saturated cis-1,2-cyclopentanediol (1) aqueous solutions (8.3 mM) containing $Na_2S \cdot 9H_2O$ (16.6 mM). (b) Formation of 3 vs irradiation time for the photolysis of N_2-saturated cyclopentanone (2) aqueous solutions (8.3 mM) containing $Na_2S \cdot 9H_2O$ (16.6 mM), different irradiation times, and pH values: □, pH 2; ○, pH 4.5; △ pH 7; ◇, pH 9.

To evaluate the versatile behavior of H_2S, its properties must be considered: its weak acidity (pK_a 6.98 at 25 °C, 6.76 at 37 °C[24]); one-electron reduction and hydrogen abstraction from both H_2S and HS$^-$ under photolytic conditions (Figure 3a). The sulfhydryl radical (HS$^{\bullet}$/S$^{\bullet-}$) has a pK_a value (~4) three units lower than that of H_2S.[20,25] The HS$^{\bullet}$ radical adds reversibly to HS$^-$ to form the dimer radical HSSH$^{\bullet-}$ (pK_a unknown). The S$^{\bullet-}$ adds reversibly to HS$^-$ to give HSS$^{\bullet 2-}$, with forward and reverse rate constants of 4.0×10^9 M^{-1} s^{-1} and 5.1×10^5 s^{-1}, respectively, with the equilibrium constant K_{eq} being 8,000 M^{-1}.[25] The bond dissociation enthalpy of H_2S, DH_{298}(HS–H) is 91.2 ± 0.1 kcal/mol, which is 3.8 kcal/mol stronger than methanethiol [DH_{298}(CH$_3$S–H) = 87.4 ± 0.5]. H_2S reactivity is therefore analogous to that of thiols with respect to H atom donation and H atom abstraction by the HS$^{\bullet}$ radical (Figure 3a).[26] The reduction potential of the dimeric radical, E(HSS$^{\bullet 2-}$, H$^+$/2HS$^-$) was determined to be 0.69 V vs NHE at pH 7,[25] whereas the reduction potential E(HSS$^-$/HSS$^{\bullet 2-}$) is estimated to be −1.13 V.[27] Therefore, the dimeric radical is a good reducing agent for a variety of organic molecules.

These observations suggest the mechanism depicted in Figure 3b: the HS$^{\bullet}$/S$^{\bullet-}$ radical couple generated by photolysis of H_2S/HS$^-$ in aqueous environment abstracts a H atom from 1 to give the radical 4. This species undergoes a β-C−O scission and elimination of H_2O, with the shift of the radical center to give 5, which completes the catalytic cycle by reacting with H_2S/HS$^-$ regenerating HS$^{\bullet}$/S$^{\bullet-}$. The so-formed cyclo-pentanone (2) is reduced to the radical anion 6 by the dimeric radical species HSSH$^{\bullet-}$/HSS$^{\bullet 2-}$. Subsequent protonation (7) and H atom abstraction from H_2S/HS$^-$ affords the product 3 completing the radical chain. The reversible addition of HS$^{\bullet}$/ S$^{\bullet-}$ radical to H_2S/HS$^-$ is the key step that plays a role in the
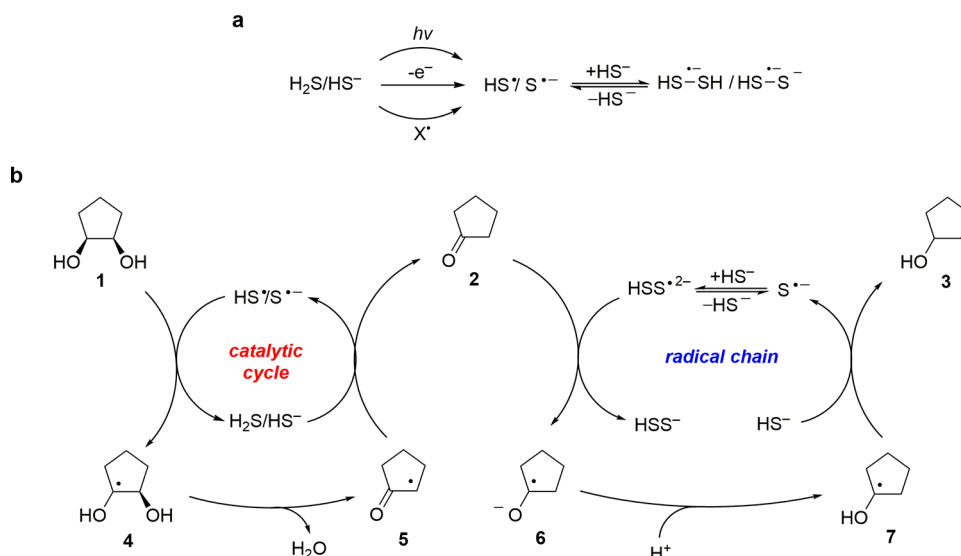
Figure 3. (a) Hydrogen sulfide (H_2S/HS^-) affords the sulfhydryl radical ($HS^•/S^{•-}$) that adds reversibly to the parent compound to form the dimeric radical species. (b) Dual catalytic/radical chain mechanism for the deoxygenation of *cis*-1,2-cyclopentanediol (**1**) to cyclopentanol (**3**) via cyclopentanone (**2**).

efficacy of this conversion. Interplay of the various pK_a values (known and still unknown) ensures that the dimeric radical species is present across the pH range (2–9) used.

The reduction **1** → **2** in aqueous solution has no precedent in the literature. The reaction of $HS^•/S^{•-}$ radical with **1** is endothermic (~3 kcal/mol), although polar effects should stabilize the transition state based on $DH[Me_2(HO)C–H]$.[28] In the reaction of *cis*-1,2-cyclopentanediol, no trace of *trans*-isomer was observed, and vice versa for the reaction with *trans*-1,2-cyclopentanediol, suggesting that the reverse reaction **4** → **1** is much slower than water elimination. On the other hand, the reaction of radical **5** with H_2S/HS^- is thermoneutral based on $DH[MeC(O)CH(–H)Me]$.[26] The water elimination step (**4** → **5**) is a general feature in carbohydrate free-radical chemistry.[8]

Examining the data in Table 1, two features of the experiments at pH 9 are notable: (i) cyclopentanone was undetectable and (ii) there was less conversion of the starting material (25% after 60 min of reaction time) compared to other pHs. These data indicated the low availability of sulfhydryl radicals ($HS^•/S^{•-}$) at alkaline pH, but the fast reduction of carbonyl moiety to **3** as described above. On the other hand, the reduction of the carbonyl moiety at pH 2 is limited due to the very low concentration of the necessary radical species ($HSSH^{•-}/HSS^{•2-}$).

To determine the efficiency of the dimeric radical species ($HSSH^{•-}/HSS^{•2-}$) for one-electron transfer to a carbonyl group, the reduction of 2-hydroxycyclohexanone (**8**) at pH 9 was examined. Photolysis (low-pressure Hg lamp, 5.5 W) of N_2-saturated aqueous solutions of **8** (8.3 mM) containing $Na_2S\cdot9H_2O$ (16.6 mM) was carried out for different times (up to 60 min) at pH 9. In all experiments, cyclohexanone (**9**) and cyclohexanol (**10**) were formed as the only products (eq 1).
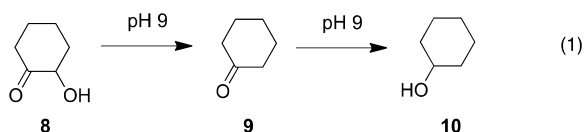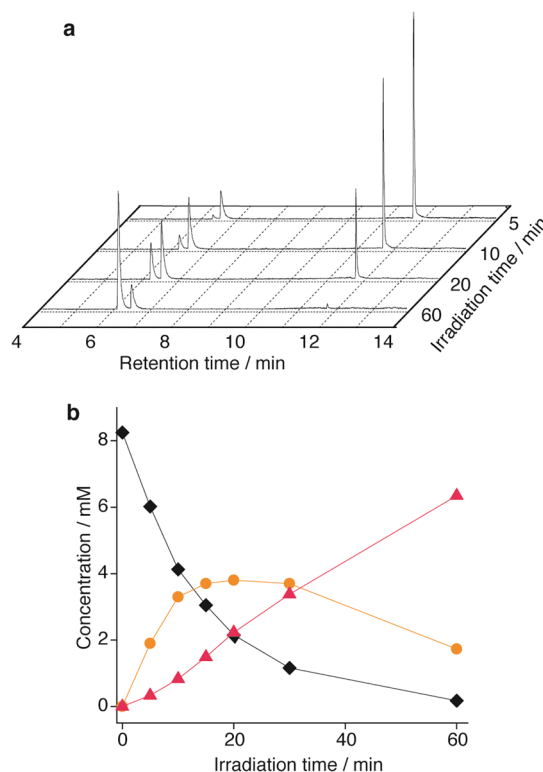

(1)

Figure 4a shows representative GC analyses. Figure 4b displays a graph with the disappearance of **8** (♦) and the formation of **9** (●) and **10** (▲) as a function of the reaction time, showing clearly that the reaction **8** → **10** occurs stepwise. The loss of **8** was matched by the formation of **9** and **10**, with 2%, 21% and 77%, respectively after 60 min. The reaction also occurs at pH

Figure 4. (a) GC analyses after photolysis of N_2-saturated 2-hydroxycyclohexanone (**8**) aqueous solutions (8.3 mM) containing $Na_2S\cdot9H_2O$ (16.6 mM), pH adjusted to 9.0, at 42 ± 1 °C and different irradiation times. (b) Concentration of **8** (♦), **9** (●), and **10** (▲) vs irradiation time at pH 9 and at a constant temperature of 42 °C.

7, in a similar way, but much slower, e.g., after 20 min, the conversion of **8** was 73% at pH 9 and 37% at pH 7 (see Figures S8 and S9). Therefore, the overall reaction 1 proceeds via a dual radical chain mechanism (see also Figure S10).

Considering the efficiencies of the cyclopentanone (**2**) and cyclohexanone (**9**) reductions, the scope of the methodology for the reduction of carbonyl compounds to the corresponding alcohols was further explored. Thus, under identical experimental conditions, aldehydes **11** and **12** as well as ketones **13**, **14**, and **15** all gave exclusively the corresponding alcohols with yield ≥90% (Figure 5a,b, see also Figures S11 and S12). The
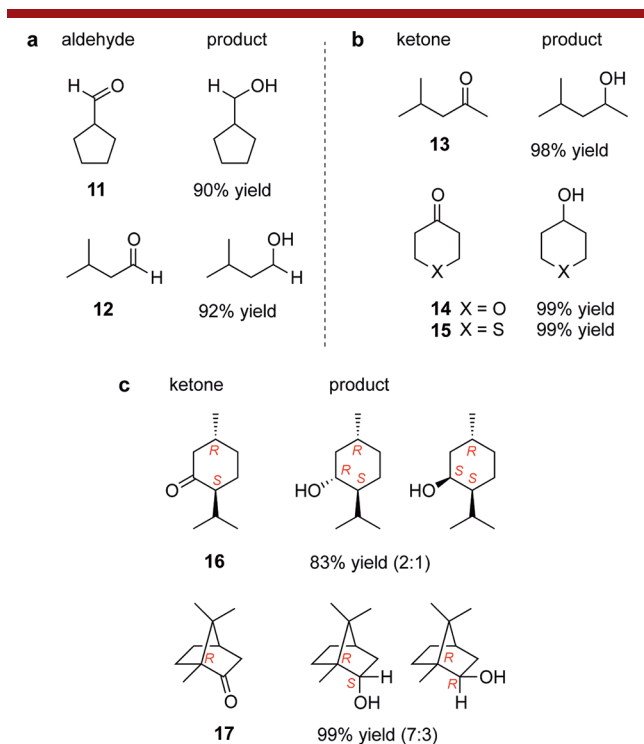
Figure 5. Reduction of aldehydes (a) and ketones (b, c) to the corresponding alcohols. N_2-saturated aqueous solutions of carbonyl compound (8.3 mM) containing $Na_2S\cdot9H_2O$ (16.6 mM), pH adjusted to 9 at 42 ± 1 °C, were irradiated for 60 min. Yields by GC analysis based on products formation (see the SI for details).

stereochemical outcome of the reduction process was studied using (−)-menthone (**16**) and (1R)-(+)-camphor (**17**). The reduction of **16** led to a 2:1 mixture of (1R,2S,5R)-(−)-menthol and (1S,2S,5R)-(+)-neomenthol in 83% yield, while the reduction of **17** gave a 7:3 mixture of (+)-borneol and isoborneol in close to quantitative yield (Figure 5c, see also Figure S13). The method of reduction described is attractive because it occurs under mild conditions and employs inexpensive, easily removed reagents.

In summary, we have described a highly efficient biomimetic method in aqueous environment to reduce 1,2-diols and carbonyl compounds to mono-ols with simple inexpensive reagents inspired by the biological transformation of ribonucleotides to deoxyribonucleotides. The method utilizes radicals ($HS^{\bullet}/S^{\bullet-}$ and $HSSH^{\bullet-}/HSS^{\bullet2-}$) derived from hydrogen sulfide. Application of the methodology reported herein is in progress, and is being appropriately adapted for the reduction of ribose and other carbohydrates. The mechanism shown here can be also helpful for understanding other chemical transformations evoked in prebiotic life,[29,30] involving

this simple molecule present in the mixture of gases on Earth and then substituted by cysteine and its disulfide in the actual biological environment.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01713.

Experimental procedures and GC analyses of all reactions Figures S1−S13 (PDF)

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Notes
The authors declare no competing financial interest.

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