

Oxidation/reduction interconversion of thiols and disulfides using hydrogen and oxygen catalyzed by a rhodium complex

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Received 20 May 2005; accepted 30 June 2005

Available online 21 July 2005

Abstract—RhH(PPh₃)₄ catalyzes reduction of disulfides to thiols by hydrogen and RhH(PPh₃)₄/1,4-bis(diphenylphosphino)butane (dppb) catalyzes oxidation of thiols to disulfides by oxygen.

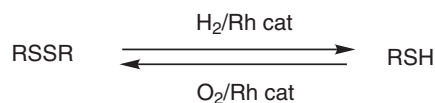
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The interconversion of disulfides and thiols is a fundamental transformation in organosulfur chemistry and such switching plays important roles in biological system. Of various reductants and oxidants, hydrogen and oxygen are apparently the most convenient. They are inexpensive, easy to remove, and produce water as the only byproduct. Since these reagents themselves are inert to the sulfur compounds, metal catalysts are employed.

Hydrogen reduction of disulfide to thiol catalyzed by metal complex was not known, which is contrasted to many examples of hydrogenolysis of organosulfur compounds. An exception is the reaction of a cyclic disulfide reported by Kessler in the presence of 10 equiv of Pd black.¹ The lack of such study may be partly due to the catalyst deactivation and the difficulty in the selective reduction of S–S bond without affecting C–S bond.

What is called autoxidation of thiols to disulfides in the presence of a metal complex, typically copper phthalocyanine under alkaline conditions, is well known.^{2,3} Although the mechanism is not fully clear, the reaction is considered to involve coupling reaction of sulfur radicals, which are formed from thiolate anions by one-electron oxidation with the metal complex. Several thiol oxidation reactions with oxygen under neutral conditions were reported.⁴ However, they often required long reaction time even at relatively high temperatures.

These indicate that the development of a catalyst for the interconversion of disulfides and thiols is still a subject not fully solved. It would also be interesting if a single catalyst can be used both for the oxidation and reduction by switching hydrogen and oxygen atmosphere. In this regard, an oxidation reaction of thiols to disulfides recently reported by Tanaka and Ajiki is interesting, which proceeded rapidly at 0 °C using a rhodium cation complex.⁵ It was considered to be a dehydration reaction and reversible. Relatively high catalyst loading (5 mol %), however, was employed for the oxidation reaction and the reduction reaction was not examined.⁶



Scheme 1.

During our investigations on the development of organosulfur transformations utilizing transition metal catalysis, rhodium complexes were found effectively to activate S–S bonds: disulfide exchange reaction,⁷ addition to unsaturated compounds,⁸ alkylthiolation of C–H bond,⁹ and alkylthio exchange reaction with C–S bond⁹ were reported. Mechanistically, the reactions were considered to involve oxidative addition of S–S bond with low valent rhodium complexes to form S–Rh–S intermediates. It is a logical extension of this methodology to examine hydrogenolysis of the Rh–S bond to form S–H bond under hydrogen. We also found that a rhodium complex activated a thiol and underwent alkylthio exchange and reduction reaction with a

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Table 1. RhH(PPh₃)₄ catalyzed disulfide reduction with hydrogen

$\text{RSSR} + \text{H}_2 \xrightarrow[\text{toluene, refl. 0.5 h}]{\text{RhH(PPh}_3)_4} \text{RSH}$			
Entry	R	Cat./mol %	Yield (%)
1	<i>n</i> -C ₈ H ₁₇	0.5	93
2	<i>n</i> -C ₁₂ H ₂₅	0.5	86
3	<i>p</i> -(<i>t</i> -Bu)C ₆ H ₄	0.25	98
4	<i>p</i> -(<i>t</i> -BuMe ₂ SiO)C ₆ H ₄	0.25	91
5	<i>p</i> -ClC ₆ H ₄	0.25	95
6	MeO ₂ CCH(NHBoc)CH ₂	1.0	90
7	<i>t</i> -BuCOO(CH ₂) ₂	0.25	92
8	<i>t</i> -BuOCONH(CH ₂) ₂	0.5	96

thioacetylene.⁹ Since, in this reaction, Rh–S compounds should be formed from thiol S–H, it was conceivable that the oxidation of the intermediate would generate S–S bond. In accordance, we observed during our studies oxidation of thiols to disulfides by trace amounts of oxygen. Described here is disulfide reduction reaction to thiol under hydrogen and thiol oxidation reaction to disulfide under oxygen, which are catalyzed generally by 0.1–0.5 mol % of RhH(PPh₃)₄ (Scheme 1).

Treatment of dioctyl disulfide with atmospheric hydrogen at toluene reflux in the presence of RhH(PPh₃)₄ (0.5 mol %) gave 1-octanethiol in 93% yield (Table 1, entry 1). Addition of phosphine invariably inhibited the reaction, which is contrasted to the thiol oxidation reaction (vide infra). The reduction proceeded in high yields even at 80 °C in toluene or in THF, when 5 mol % of the catalyst was employed. Several alkyl and aryl disulfides were converted to thiols under the same conditions employing 0.25–1 mol % of the catalyst. Aromatic disulfides possessing either electron-withdrawing or donating groups effectively reacted (entries 3, 4, and 5). This is an unprecedented metal-catalyzed reduction of disulfides to thiols with hydrogen, and a rhodium catalyst turned out to be effective for this transformation.¹⁰

The same rhodium complex is capable to catalyze the oxidation reaction of thiols to disulfides in the presence of oxygen. When 1-octanethiol was reacted in methanol at 0 °C for 1 h under an oxygen atmosphere in the presence of RhH(PPh₃)₄ (0.1 mol %) and 1,4-bis(diphenylphosphino)butane (dppb) (0.2 mol %), dioctyl disulfide was obtained in 93% yield (Table 2, entry 1).¹¹ Although the phosphine itself was not soluble in methanol, the addition of the thiol formed a homogeneous orange solution under an argon atmosphere. Then, the balloon was changed to oxygen, which rapidly turned the solution green. At the end of the reaction, the orange color was regenerated. Essentially no reaction took place in the absence of RhH(PPh₃)₄ or under an argon atmosphere with rigorous removal of oxygen. Phosphine was important in the oxidation reaction, and only 4% of the disulfide was formed in the absence of dppb. Effect of other phosphines are as follows: dppe, 8%; dppe, 6%; dppp, 62%; dpppentane, 32%; dppf, 44%; PPh₃, 4%; (*p*-ClC₆H₄)₃P, 3%; (*p*-MeOC₆H₄)₃P, 4%. The reactions using dppp, dpppen-

Table 2. RhH(PPh₃)₄/dppb catalyzed thiol oxidation with oxygen

$\text{RSH} + \text{O}_2 \xrightarrow[\text{MeOH, 40 } ^\circ\text{C}]{\text{RhH(PPh}_3)_4\text{-dppb}} \text{RSSR}$				
Entry	R	Cat./mol %	Time (h)	Yield (%)
1	<i>n</i> -C ₈ H ₁₇	0.1	1	93
2 ^a	<i>n</i> -C ₁₂ H ₂₅	0.5	2.5	99
3	<i>s</i> -C ₄ H ₉	0.1	1	95
4	<i>cyclo</i> -C ₆ H ₁₁	0.1	1	100
5	1-Adamantyl	2.5	2	91
6	Me ₂ CH(CH ₂) ₃ CMeEt	5.0	6	89
7	<i>p</i> -(<i>t</i> -Bu)C ₆ H ₄	0.1	3	95
8	<i>p</i> -(MeO)C ₆ H ₄	0.1	3	96
9	<i>p</i> -ClC ₆ H ₄	0.1	1.5	94
10	MeO ₂ CCH(NHBoc)CH ₂	0.5	1.5	95
11	HO(CH ₂) ₃	0.5	2	87
12	MeO ₂ C(CH ₂) ₂	0.5	1	95

^a Reaction in ethanol.

tane, and dppf gave considerable amounts of the disulfide, and the solution turned green.

Several thiols were oxidized to disulfides under the same conditions. Primary and secondary thiols gave the products in quantitative yields using 0.1 mol % of catalyst in methanol (entries 1–4). 1-Dodecanethiol was reacted in ethanol because of low solubility of the substrate (entry 2). Reactions of tertiary thiols required higher catalysts loading (entries 5 and 6). Aromatic substituents again did not affect the reaction (entries 7, 8, and 9). Functional groups such as carbamate, alcohol, and ester were not affected.¹¹

In summary, a rhodium complex RhH(PPh₃)₄ catalyzes disulfide reduction to thiol with hydrogen and thiol oxidation to disulfide with oxygen. Search for the reaction system, under which thiols and disulfides are effectively interconverted by simply switching hydrogen and oxygen atmosphere, is an interesting subject in future.

Acknowledgements

This work was supported by Grants from the Japan Society of Promotion of Science (Nos. 16109001 and 17689001). M.A. thanks for the support from NEDO of Japan (No. 02A44003d) and the Takeda Science Foundation.

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10. *Reduction of disulfide*: In a two-necked flask equipped with a reflux condenser were placed RhH(PPh₃)₄ (0.25 mol %, 5.76 mg) and di(2-pivaloyloxyethyl)disulfide (2 mmol, 644 mg) in toluene (4.0 mL) under a hydrogen atmosphere, and the solution was heated at reflux for 0.5 h. Then, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving 2-(pivaloyloxy)ethanethiol (593.8 mg, 92%).
11. *Oxidation of thiol*: A solution of RhH(PPh₃)₄ (17.3 mg, 0.1 mol %) and 1,4-diphenylphosphinobutane (dppb, 12.8 mg, 0.2 mol %) in methanol (30 mL) was freeze-evacuated, and was warmed to 40 °C under an argon atmosphere. Then, 1-octanethiol (2.6 mL, 15 mmol) was added, and the argon balloon was exchanged to oxygen. The mixture was stirred for 1 h at the temperature, and passed through a short pad of silica gel to remove the rhodium complex. The solvent was removed under reduced pressure, and Kugel-Rhor distillation gave dioctyl disulfide (2.02 g, 93%).