Conversion of Coordinated Sulfur Atom into Sulfoxide Group via Oxidation Reaction of Metal Complexes of Tetradeutates and Sulfur Amino Acids

Sung Sil Lee, Peter P. Fu**, Sung Rack Choi, and Moo-Jin Jun†
Department of Chemistry, Yonsei University, Seoul 120-749, Korea
**N-ional Center for Toxicalogical Research, Jefferson, Arkansas, U.S.A.

ABSTRACT. Reaction between the N₂O₅-type tetradeutate ligand, ethylenediamine-N,N’-di-S-a -isobutylic acid (SS-eniba) and RhCl₃3H₂O has yielded Δ-s-cis- and Δ-uns-cis-[Rh(SS-eniba)Cl₂]. Δ-s-cis-[Rh(SS-eniba)Cl₂] has been utilized to react with S-methyl-L-cysteine (Smc) to give Δ-s-cis-[Rh(SS-eniba)(Smc)]+. The oxidation of Δ-s-cis-[Rh(SS-eniba)(Smc)]+ using H₂O₂ has produced Δ-s-cis-[Rh(SS-eniba)(Smc-o)]+, in which the coordinated sulfur has been converted into the sulfoxide group. In a separate series of experiments the S-methyl-L-cysteine is oxidized by H₂O₂ to give S-methyl-L-cysteine sulfoxide, which is then coordinated to Δ-s-cis-[Rh(SS-eniba)Cl₂] to make the standard comple of Δ-s-cis-[Rh(SS-eniba)(Smc-o)]+ for comparison with the complex obtained from the oxidation of Δ-s-cis-[Rh(SS-eniba)(Smc)]+ by H₂O₂.

INTRODUCTION
Rhodium(III) ion, with its d⁶ electronic con-

*이 논문은 1987년도 동료부 자유공모제에서 연구조성

1. 부여황 한약물의 산화반응에 의한 배위황 원자단으로의 전환*
In a separate series of experiments shown in Fig. 2 the S-methyl-L-cysteine is oxidized to S-methyl-L-cysteine sulfoxide (smc-o), which is then coordinated to the complex 1 to obtain the standard complex of \([\text{Rh}(\text{SS-eniba})\text{smc-o}]^+\) for comparison with the complex 3.

**EXPERIMENTAL**

**Chemical Reagents.** L-Leucine, 1,2-dibromoethane, L-alanine, and rhodium(III) chloride hydrate were used as obtained from Aldrich Chemical Co. S-methyl-L-cysteine was purchased from Nutritional Biochemicals.

**Physical Measurements.** Proton nmr spectra were recorded on a 60 MHz Varian EM-360 L NMR spectrometer or a 8 MHz Varian FT-80A NMR Spectrometer. Electronic absorption spectra were obtained with a Shimadzu UV-240 Spectrophotometer, while infrared spectra were taken with a Shimadzu IR-435 Spectrophotometer. Elemental analyses were performed by Micro-Tech Analytical Laboratories, Skokie, Illinois, U.S.A. Circular dichroism spectra were obtained with a Jasco J-550 C Automatic Recording Spectropolarimeter.

**Preparation of Ethylenediamine-N,N'-di-S-isobutyric Acid (SS-eniba).** 8.0 g of NaOH in 20 ml of water was added to 26.2 g of L-leucine in 100 ml of water. 17.4 g of 1,2-dibromoethane and 10.6 g of Na₂CO₃ were added in portions to this solution while maintaining the system at 70°C. The reaction mixture was stirred for 30 hours at 70°C. The solution was cooled and acidified to pH 6 with conc HCl. The precipitated white product was collected on a filter, washed with water and petroleum ether, and dried in vacuo. Yield: 11.0 g. Anal. Calc'd for C_{14}H_{28}N₄O₂: C, 58.29; H, 9.50; N, 9.71. Found: C, 58.49; H, 9.77; N, 9.60.

**Preparation of s-cis and uns-cis Isomers of Hydrogen Dichloro(ethylenediamine-N,N'-
di-S-isobutylacetato)rhodate(III). *s-cis* and
uns-cis-H[Rh(SS-eniba)Cl2]·H2O. To a solution of 0.20 g of LiOH·H2O dissolved in 20 ml of water was added 1.10 g of SS-eniba. 0.82 g of RhCl3·3H2O was added, and the reaction mixture was refluxed for 2 hours. The pH of the solution was adjusted to 5.0 with dilute LiOH solution and the refluxing was continued for an additional 6 hours. The pH of the solution was adjusted again with LiOH·H2O. The solution was cooled and filtered to remove traces of solids. The filtrate was chromatographed on a column of Dowex 1-X8 anion-exchange resin (100–200 mesh, Cl– form) using a dilute HCl solution (0.01M) as an eluent. The solution was separated into two bands, with the *s-cis* isomer eluting before the uns-cis isomer. Yield. 0.38 g (*s-cis* isomer) and 0.21 g (uns-cis isomer). Anal. Caled for RhC14H22N2O4Cl·H2O: C, 35.09; H, 6.10; N, 5.84; Cl, 14.80. Found: For *s-cis* isomer: C, 34.95; H, 6.14; N, 6.91; Cl, 14.88. For uns-cis isomer: C, 35.14; H, 6.08; N, 5.89; Cl, 14.75.

Preparation of *s-cis*-Ethylenediamine-N,N'–di- S-isobutylacetato(S-methyl-L-cysteine)rhodium (III) Chloride. *s-cis*-Rh(SS-eniba)(smc)Cl·H2O. 0.12 g of *s-cis*-H[Rh(SS-eniba)Cl2]·H2O was dissolved in 15 ml of water and heated on a steam bath. 0.03 g of S-methyl-L-cysteine was slowly added with stirring. The resulting solution was heated for 1 hour. The solution was cooled. Slow evaporation under moving air led to crystallization of the yellowish complex. The product was filtered and washed with ethanol and ether. Yield. 0.04 g. Anal. Caled for RhC14H22N2O4Cl·H2O: C, 37.41; H, 6.45; N, 7.27. Found: C, 37.30; H, 6.39; N, 7.14.

Preparation of *s-cis*-Ethylenediamine-N,N’–di-S-isobutylacetato(S-methyl-L-cysteinesulfoxide) rhodium(III) Chloride. Standard *s-cis*-H[Rh(SS-eniba)(smc–o)]Cl·H2O. 0.12 g of *s-cis*-H[Rh(SS-eniba)Cl2]·H2O was dissolved in 15 ml of water and heated on a steam bath. 0.04 g of S-methyl-L-cysteine sulfoxide was slowly added with stirring and heating was continued for 2 hours. After cooling to room temperature the volume of the solution was reduced to one-half of the original volume upon evaporation under moving air. The solution was chilled in a refrigerator overnight. The product was collected on a Hirsch filter and rinsed with cold water and ether. Yield. 0.07 g. Anal. Caled for Rh
RESULTS AND DISCUSSION

The dichloro rhodium(III) complexes of SS-eniba were prepared by the reaction of the ligand with an aqueous solution of RhCl₃·3H₂O. While the SS-eniba ligand yielded three isomers (Δ-s-cis, -uns-cis and Λ-uns-cis isomers) in the case of the diqua cobalt(III) complexes, only two isomers (Δ-s-cis and Λ-uns-cis) of the possible four isomers depicted in Fig. 3 were formed.

The distinction between the s-cis and uns-cis isomers of [Rh(SS-eniba)Cl₂]⁺ can be made from the electronic absorption and proton nmr spectra shown in Fig. 4–6. The absorption peaks in the uns-cis are at slightly higher energy than the corresponding peaks in the s-cis isomer in the long wavelength region. Such band shifts are consistent with those observed for [Rh(SS-εddp)Cl₂]⁺ [Rh(SS-εddp)en]⁺ and for the isomers of [Co(SS-εddp)en]⁺ and [Co(SS-εdda)L]⁺ series.

The s-cis and uns-cis isomers have been clear-
ly distinguished by their proton nmr spectra: while the $s$-cis isomer has shown a distinct methyl doublet (8 1.0) of the isobutyl arm, two methyl doublets of the same isobutyl arm are shown in the $unscis$ isomer (Fig. 6).

The Cotton effect signs for both $s$-cis and $unscis$ isomer are shown in Fig. 4 and 5, respectively. The $s$-cis isomer shows the negative major CE and is assigned the absolute configuration in agreement with the $\Delta s$-cis-[Co(SS-eddp)en] $^+$ and the $\Delta s$-[Rh(en)$_2$] $^+$ and $\Delta s$-[Rh(en)$_3$] $^+$ complexes. 22-24 The $s$-cis rhodium(III) complex of SS-eniba retains the effective $C_2$ symmetry, 25 and a negative CE is expected for the $s$-cis isomer by analogy to the en complexes. On the other hand, the $unscis$ isomer shows a positive CE and absolute configuration is assigned.

The S-methyl-L-cysteine (smc) has been coordinated to the $s$-cis-[Rh(SS-eniba)Cl] $^-$ to give complex (2) as shown in Fig. 1. The conversion of the coordinated sulfur atom into the sulfoxide group has then been accomplished via the oxidation by $H_2O_2$. The ir spectrum of the complex (2) shows the uncoordinated carbonyl at 1595 cm$^{-1}$ indicating the fact that the S-methyl-L-cysteine has been coordinated via the nitrogen and sulfur donor atoms.

The conversion of the coordinated sulfur atom of the smc ligand into the sulfoxide group is confirmed by the ir spectral data of the ligands and complexes. Fig. 7 shows the ir spectra of smc and smc-o in the 1200-800 cm$^{-1}$ region. While smc-o shows the S-O stretching frequency at 1006 cm$^{-1}$, smc doesn’t have any absorption at near 1000 cm$^{-1}$. In Fig. 8 the S-O stretching frequency of the [Rh(SS-eniba)(smc-o)] $^+$ complex (3) has been shifted to 1140 cm$^{-1}$, which is like those found in [Pt(methioninesulfoxide)Cl$_2$] and complexes of $Mn_2SO$. 26-28

In a separate series of experiments the sulfur atom of smc has been oxidized to the sulfoxide group (smc-o) by $H_2O_2$ and the resultant smc-o ligand has been coordinated to complex (1) to give the standard complex of [Rh(SS-eniba) (smc-o)] $^+$ for comparison with complex (3). Fig. 9 shows the S-methyl group at $\delta 2.8$ for smc-o while the S-methyl group for smc is known to show at $\delta 2.2$. 20

Fig. 7. Infrared spectra of S methylcysteine and S methylcysteine sulfoxide.

Fig. 8. Infrared spectra of $s$ cis [Rh(SS-eniba)(smc)] $^+$ and $uns cis$ [Rh(SS-eniba)(smc-o)] $^+$

Fig. 9. $^1$H nmr spectrum of S methylcysteine sulfoxide.
The standard complex of $[\text{Rh}(\text{SS-eniba})\text{(smc-o)}]^+$ shows the S-O stretching frequency at 1140 cm$^{-1}$ which is coincident as that for complex (3). The methyl group of complex (3) and the standard $[\text{Rh}(\text{SS-eniba})\text{(smc-o)}]^+$ exhibits the chemical shift at $\delta 3.4$. Thus, the conversion of the coordinated sulfur atom into the sulfoxide group is confirmed by comparison of complex (3) with the standard $[\text{Rh}(\text{SS-eniba})\text{(smc-o)}]^+$ complex prepared separately. Upon formation of a sulfoxide group there is localization of one of the electron pairs of the sulfur in the free sulfide ligand into an S-O bond resulting in a greater chemical shift of the methyl group of the sulfoxide ligand. Lying up the second pair of electrons in a Rh–S bond causes a greater methyl chemical shift in the complex.

Upon conversion of the coordinated sulfur atom into the sulfoxide group the sulfur atom itself becomes an asymmetric center. There is possibility that the oxidation reaction can be proceeded stereoselectively. Although the absolute configuration of the asymmetric sulfur atom could not be determined from our current work, further studies such as X-ray crystallographic study on complex (2) should give some insight into any stereoselective nature of the oxidation reaction.

**REFERENCE**