Chemistry

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EXAFS Analysis of Coordination Structure of Glycoconjugated Bioactive Complex

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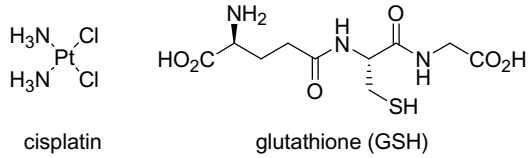
Introduction

Inorganic pharmaceuticals have been developed in the field such as anti-cancer, anti-rheumatism and anti-diabetes treatments. Medicinal inorganic chemist improves the efficacy of these drugs by changing ligands. *cis*-Diamminedichloroplatinum(II), namely cisplatin, is a most successful drug in the field of inorganic anti-cancer drug. The mechanism of cisplatin in the tumor necrosis has been investigated *in vitro*. Nuclear magnetic resonance (NMR) of ^{15}N and ^{195}Pt is a powerful tool to study a coordination structure in the aqueous medium. However, this technique sometimes requires ^{15}N or ^{195}Pt-enriched sample, which is quite difficult to prepare especially for sophisticated inorganic pharmaceuticals. As an alternative way, we have investigated the EXAFS approach to study cisplatin derivatives in aqueous environment. In this report, we demonstrate the EXAFS analysis of the decomposition of cisplatin with glutathione which is an abundant tripeptide in biological system (Chart 1).



cisplatin glutathione (GSH)

Chart 1

Experimentals

Cisplatin and potassium tetrakis(thiocyanato)-platinate(II) ($K_2[Pt(SCN)_4]$) was prepared according to literatures [1,2]. Glutathione was purchased from Wako Pure Chemicals Co. Cisplatin (150 mg) was dissolved in (50 mL) by heating. The solution was kept at 37 °C with stirring. To the solution was added glutathione (1.56 g) to initiate decomposition of cisplatin. After appropriate time, a portion of the solution was poured into a cell (path length was 1.0 cm). Pt-L_{III} edge EXAFS spectra were collected at BL-10B. The EXAFS measurements were carried out at room temperature in transmittance mode. The back-scattering amplitude $F_S(\boldsymbol{k})$ and the phase shift $\Phi_S(\boldsymbol{k})$ functions between Pt and S atoms were derived from the Pt-L_{III} edge EXAFS and X-ray crystallography of $K_2[Pt(SCN)_4]$. All calculations were performed with REX2000, version 2.0.7 (Rigaku Co.).

Results and Discussions

Fig. 1 shows the Pt-L_{III} edge EXAFS Fourier transforms of the reaction between cisplatin and glutathione at the various reaction times. Before the addition of glutathione (t = 0 min), two peaks were found at 1.6 Å and 2.0 Å (before phase-shift correction). And these were assigned to back-scattering contribution of nitrogen and chlorine atoms coordination to platinum, respectively. While the peak at 1.6 Å decreased, the peak at 2.0 Å increased monotonically with the progress of the reaction. After 6 hours, the Fourier transforms of Pt-L_{III} edge EXAFS shows essentially one peak at 2.0 Å. The EXAFS oscillation can be fitted using the back-scattering amplitude $F_S(\boldsymbol{k})$ and the phase shift $\Phi_S(\boldsymbol{k})$ functions between Pt and S atoms derived from $K_2[Pt(SCN)_4]$. The fittings were converged with the coordination number n = 4.2, the atomic distance r = 2.32 Å and Debye-Waller factor σ = 0.065. These observations were fairly agreed with the earlier work reported by Berners-Price and Kuchel by means of NMR technique [3]. This encourages us to apply the EXAFS technique to tailor-made inorganic pharmaceuticals. The investigation for glycoconjugated bioacive complex is in progress.

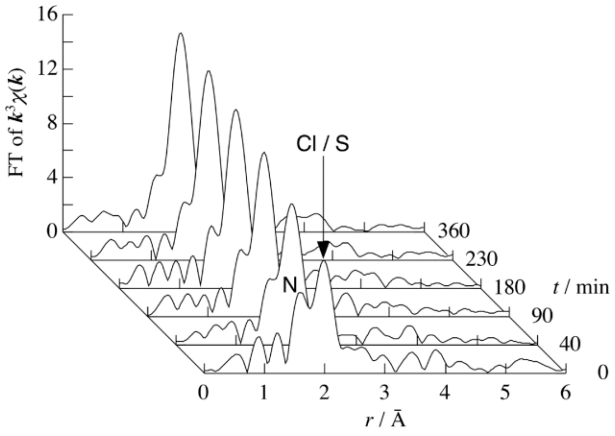


Fig. 1 Fourier transforms of Pt-L_{III} edge for the mixture of cisplatin and glutathione in water.

References

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[3] S. J. Berners-Price, P. W. Kuchel, *J. Inorg. Biochem.*, **38**, 305 (1990).

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