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EXAFS Study of Inorganic Pharmaceuticals in Physiological Media

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Introduction

Inorganic pharmaceuticals is a rapidly growing field especially for anti-tumor, anti-rheumatism and anti-diabetes treatments. *cis*-Diamminedichloroplatinum(II), i.e., cisplatin, is one of the most successful inorganic pharmaceuticals. However some malignant cells such as A2480cisR4 and SKOV-35 have detoxification ability owing to their elevated glutathione level. Hence it is important to investigate the reaction between anti-tumor platinum complexes with the endogenous ligand having S-donor. In this study, we studied the reaction between cisplatin and 1,1-cyclobutanedicarboxylatodiammine-platinum(II) (carboplatin) by means of the extended X-ray absorption fine structure (EXAFS) measurement.

Experimental

Cisplatin and carboplatin were purchased from STREM CHEMICALS. Reduced glutathione was purchased from Wako Pure Chemicals Co. Cisplatin and carboplatin were dissolved in phosphate buffered saline (PBS) by heating. The solution was kept at 37 °C with stirring. Reduced glutathione was added to the solutions. 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 and 7C. The EXAFS measurements were carried out at room temperature in transmittance mode. The back-scattering amplitude $F_i(k)$ and the phase shift $\Phi_i(k)$ functions were calculated by FEFF 8.2 program [1]. All calculations were performed with REX2000, version 2.0.7 (Rigaku Co.).

Results and Discussion

Figure 1 shows the Fourier transforms (before phase-shift correction) of the EXAFS at Pt-L_{III} edge of the reactions between cisplatin (a) and carboplatin (b) with reduced glutathione at various reaction times. Before the addition of reduced glutathione (t = 0 min), cisplatin affords two peaks at 1.6 Å and 2.0 Å, while carboplatin gave only one peak at 1.6 Å. These were assigned to back-scattering contribution of nitrogen or oxygen atoms and chlorine atoms, respectively. The concentration of cisplatin and carboplatin were adjusted at 10 and 20 mM, respectively. To the solutions was added 10 equimolar of reduced glutathione to initiate reaction. For cisplatin, the peak at 1.6 Å decreased while the peaks at 2.0 Å increased with the progress of the reaction [2]. In the case of carboplatin, new peak appeared at 2.0 Å as same as the case of cisplatin. However the reaction rate was quite different between cisplatin and carboplatin. The EXAFS oscillations were fitted with the standard EXAFS equation using the theoretically derived $F_i(k)$ and $\Phi_i(k)$ functions. Figure 2 shows the coordination numbers for N/O and Cl/S as a function of the reaction time. The reaction of cisplatin with reduced glutathione substantially completed at 180 min. In the case of carboplatin, on the other hand, the reaction did not complete even at 360 min in spite of the higher concentration of carboplatin and reduced glutathione. This clearly indicated the low sensitivity of carboplatin to GSH plausibly due to the "chelate effect".

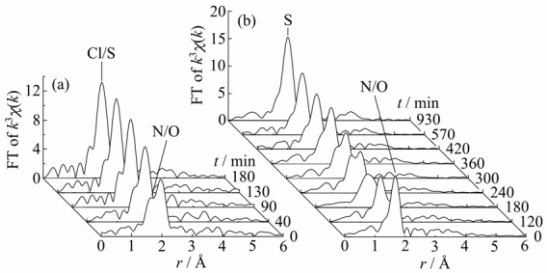

Figure 1 Fourier transforms of k^3-weighted EXAFS oscillations of the reaction of cisplatin (a) and carboplatin (b) with reduced glutathione

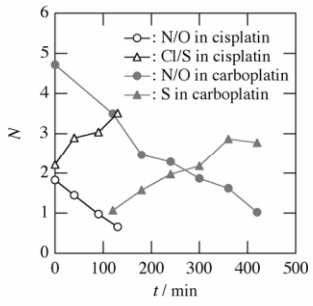

Figure 2 Plots of the coordination numbers $N_{N/O}$ and $N_{Cl/S}$ as a function of the reaction time

References

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