Materials Science

7C/2004G290

EXAFS Study of Glycoconjugated Bioactive Complex in Aqueous Solution

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Introduction

cis-Dichlorodiammineplatinum, i.e., cisplatin is most promising inorganic pharmaceuticals for anticancer chemotherapy [1]. Several derivatives such as carboplatin, nedaplatin and oxaliplatin, have been developed in order to expand therapeutic spectrum and reduce side effects. We have developed platinum complex having carbohydrate moieties which is well-known bioactive molecules for cellular interaction (Chart 1). The anticancer effect of glycoconjugated platinum complex is significantly depends on the carbohydrate moieties attached [2]. One possibility of the glycoconjugation effect is the difference in the affinities of abundant proteins such as albumin, which is main preserver for platinum pharmaceuticals in the circulation. Here we report the EXAFS study on glycoconjugated platinum complexes **1** and **2** in water and cell culture such as Dulbeco's modified eagle medium (DMEM).

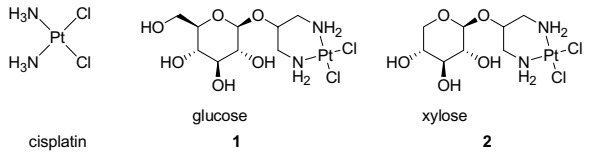


Chart 1

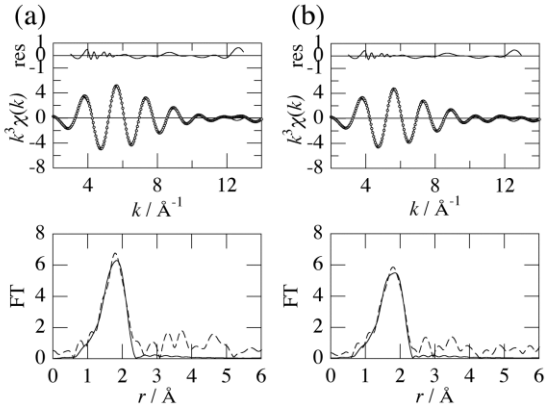
Experimentals

Cisplatin and glycoconjugated platinum complexes **1** and **2** were prepared according to literatures [2]. Fluorescence EXAFS measurements at Pt L_{III} edge (11559 eV) were performed at BL-7C at room temperature, using double crystal Si(111) monochromator and Lytle detector. The ring current was 300-450 mA, and the storage ring was operated with an electron energy of 2.5 GeV. The samples were prepared as water and DMEM solutions of cisplatin, **1** and **2** (1 mM), respectively. The resulting k^3-weighted EXAFS oscillation was analyzed on the basis single scattering and theoretical amplitude and phase functions calculated by means of the FEFF 8.2 program. All calculations were performed with REX2000 ver. 2.0.7 (Rigaku Co.).

Results and Discussion

Figure 1 shows the representative k^3-weighted EXAFS oscillations ($k^3\chi(k)$) and their Fourier transforms of **1** and **2** in water. The $k^3\chi(k)$ oscillations were quite resemble each other, suggesting the similar coordination structure of Pt atom in water and DMEM solution. The $k^3\chi(k)$ oscillations were fitted with sum of two back-scattering contribution, namely, Pt-N ($k^3\chi(k)_N$) and Pt-Cl ($k^3\chi(k)_{Cl}$) to afford coordination number N, interatomic distance r and Debye-Waller factor σ. As previously reported, the theoretical amplitude and phase functions calculated by FEFF 8.2 have enough quality to analyze these EXAFS oscillations. The interatomic distances r_N and r_{Cl} are ca. 2.0 and 2.3 Å for Pt-N and Pt-Cl, respectively, which are in good accordance with those derived from X-ray crystallography. In water, the values of N_N/N_{Cl} were determined to be 3/1 for all platinum complexes examined. This may be caused by the hydrolysis of platinum complexes, i.e., substitution reaction of Cl ligand by water molecules. Hence no significant differences between cisplatin and glycoconjugated platinum complexes was found in the EXAFS structure in aqueous solution. In the DMEM solution, however, the values of N_N/N_{Cl} for cisplatin and **1** were same as those in water, while the value for **2** was ca. 1/1 in DMEM. This suggests platinum complex **2** is in a different situation from cisplatin and **1** in DMEM. Serum albumin, which is a dominant protein in DMEM affords nucleophilic sulfur ligand e.g, their cys-34. Since the Cl and S ligand is not distinguishable in EXAFS, one plausible explanation is that the enhanced affinity of **2** to serum albumin. Further study on these platinum complexes is in progress at our laboratory.

Figure 1 $k^3\chi(k)$ oscillations and their Fourier transforms of **1** (a) and **2** (b) in water.



References

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