nts for the low-lying excited state of Ga atoms and alkali metals are ascribed to the strongly repulsive potential arising from the ground state electron configuration.

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Diaminoplatinum(II) Complexes of Glutamic Acid: Obvious Chelating Isomerization

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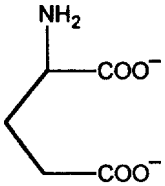
Coordination isomers of *cis*-(N-N)Pt(Glu) prepared by reaction of *cis*-(N-N)Pt(SO_4) (N-N = $2NH_3$, ethylenediamine(en), (R,R)-1,2-diaminocyclohexane (DACH), N,N,N',N'-tetramethylethylenediamine (TMEDA)) with barium glutamate in water have been monitored and characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectra. The reaction at room temperature affords the mixture of O,O'- and N,αO-chelated platinum(II) complexes. The O,O'-chelate initially formed isomerized to N,αO-chelate on standing for a long time or increasing temperature. The ratio of the two isomers at room temperature depends on the nature of the nitrogen donor coligand (N-N).

Introduction

In order to overcome the drawbacks of *cis*-platin such as nephrotoxicity, nausea/vomiting, and myelosuppression along with development of resistance in the tumor cell,[1-5] new type of platinum complexes have been synthesized and

screened for better anticancer agents.[6-9] The platinum complexes of essential amino acids and their homologues are of significant current interest because they reveal both versatile bonding mode and significant antitumor activity.[10-18] In particular, glutamate (I) ligand of the essential amino acids belongs to an unusual and noninnocent class of ligand which is capable of binding to metal in three different bonding modes, *viz.* O,O'-, N,αO-, or N,γO-chelate. Suspiciously, a recent publication reported that the reaction of *cis*-$(NH_3)_2Pt(NO_3)_2$ with glutamic acid under pH control does not afford O,O'-chelated and N,γO-chelated species even at room temperature because of chelate ring size effect.[19]



(I)

In an effort to clearly understand the bonding mode and isomerization process for the platinum complexes of the glutamate ligand, the reaction of several *cis*-(N-N)Pt(SO_4) with glutamate ligand for temperature or time variation are monitored based on various spectral data together with physicochemical properties.

Experimental

Materials and Instrumentation. Potassium tetrachloroplatinate(II) was purchased from Kojima, and glutamic acid (Glu) and amines from Aldrich. *cis*-(N-N)Pt(SO_4) and barium glutamate were prepared according to the standard procedures.[13,20] Elemental analyses were performed by the Advanced Analysis Center at KIST. The infrared spectra were measured as KBr pellets on a MIDAC model 101025 FT-IR spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Gemini-300 NMR spectrometer relative to $SiMe_4$ as an external standard or dioxane as an internal standard. The NMR samples were freshly prepared in 5% D_2O solution. The mass analyses were performed by a Platform (Fisons Inst., Manchester, U.K.) equipped with an electro-spray source at 10 L/min using Havard infusion pump. For the mass analysis, appropriate amount of samples were dissolved in MeOH-water (50 : 50, V/V) containing 1% acetic acid.

Preparation of *cis*-(DACH)Pt(Glu). *cis*-(DACH)Pt(SO_4) (0.81 g, 2 mmol) in 30 mL of water was combined with barium glutamate (0.60 g, 2 mmol) in 30 mL of water. The mixture was stirred for 2 h at room temperature. The white precipitate of $BaSO_4$ was filtered off, and the filtrate was concentrated to about 5 mL under reduced pressure. Addition of excess ethanol to the solution yielded white solids of two isomers of *cis*-(DACH)Pt(N,αO-Glu) and *cis*-(DACH)Pt(O,O'-Glu) in 72%.

The reaction was attempted at elevated temperature of reflux condition, and only *cis*-(DACH)Pt(N,αO-Glu) isomer was obtained in 76% yield. mp. 141℃ (dec.). Anal. found (Calcd. for $C_{11}H_{21}N_3O_4Pt \cdot H_2O$): C, 27.80 (28.00); H, 4.69 (4.90); N, 8.73 (8.90). IR (KBr, cm^{-1}): ν_a (C-O), 1651; δ (N-H), 1557; ν_s (C-O), 1391. ^{1}H-NMR (D_2O, ppm): 3.67 (dd, 1H), 2.54-2.28 (m, 3H), 2.23-1.95 (br, 5H), 1.68-1.46 (br, 2H), 1.40-1.06 (br, 4H). ^{13}C-NMR (D_2O, ppm for C-O): 188.8, 181.3.

Similar procedures were used to prepare NH_3, TMEDA, and en analogues, which gave satisfactory analytical assays.

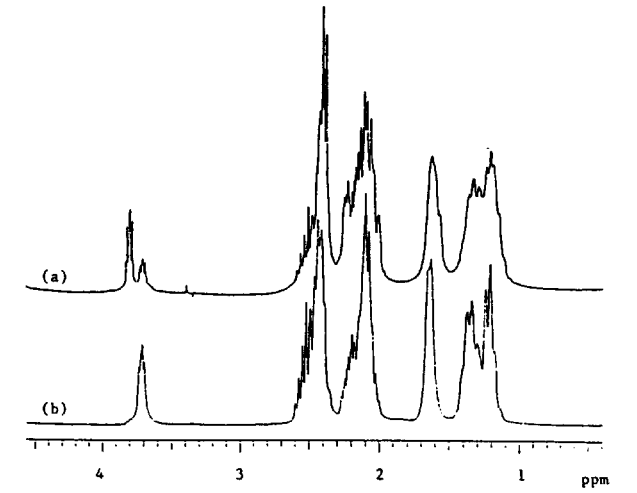


Figure 1. ^{1}H-NMR spectra of the mixture of O,O'-: N,αO-isomer (62 : 38) (a) and N,αO-isomer (b) for (DACH)Pt(Glu).

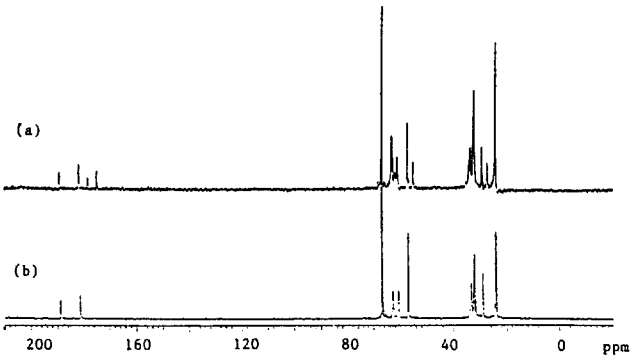


Figure 2. ^{13}C-NMR spectra of the mixture of O,O'-: N,αO-isomer (62 : 38) (a) and N,αO-isomer (b) for (DACH)Pt(Glu).

Results and Discussion

The ^{1}H-NMR spectrum of α-protons of glutamate for the fresh solution of *cis*-(DACH)Pt(Glu) at room temperature showed two resonances located at 3.76 and 3.67 ppm (Figure 1). In ^{13}C-NMR, four distinct carbonyl resonances at 188.9, 181.3, 177.9, and 174.5 ppm were observed (Figure 2). The characteristic resonances indicate the coexistence of two isomers of possible three isomers mentioned above. When the same reaction was allowed to proceed for 2 h at 100℃, ^{1}H peak at 3.76 ppm disappeared and only one doublet of doublet at 3.67 ppm remained (Figure 1). In the ^{13}C spectrum, only two carbonyl resonances at 188.9 ppm and 181.3 ppm were observed (Figure 2). The ^{1}H and ^{13}C-NMR spectra disclose that the reaction at 100℃ affords only N,αO-isomer. The chemical shift at 188.9 ppm indicates a dangling carboxylate whereas that of 181.3 ppm indicates a coordinated carboxyl group. The ^{13}C chemical shifts are consistent with

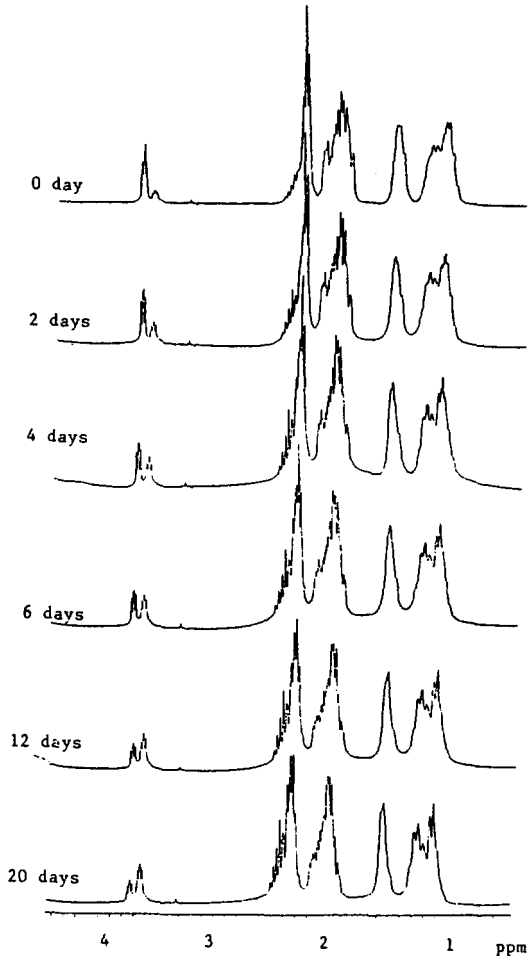


Figure 3. Time-dependent ^{1}H-NMR spectra of (DACH)Pt(Glu).

those of aminomalonate complexes identified by Gibson *et al.*[14] Thus, the other two peaks at 177.9 and 174.5 ppm belongs to the carboxyl of O,O'-chelate complex.[21] Only formation of thermodynamically stable five-membered N,αO-chelate at high temperature seems to be the dominating influence of chelate ring size on the chemistry of platinum complexes of amino acid.[22] Once formed, the N,αO-complex is quite stable even in solution. This, in conjuction with the NMR spectra of isomeric mixture, indicates that the reaction at room temperature affords a mixture of two isomers whereas the reaction at 100℃ forms only N,αO-isomer.

The two isomeric mixture of (DACH)Pt(Glu) was monitored as a function of time in D_2O solvent *via* ^{1}H-NMR (Figure 3). Two isomeric products prepared at 10℃ were examined by ^{1}H-NMR over 20 days, and the sample was maintained at 10℃ during data accumulation. The initial ^{1}H-NMR spectrum for a freshly prepared aqueous solution of (DACH)Pt (Glu) isomers shows two chemical shifts in the region of α-protons of glutamate ligand with the ratio of 4 : 1. When a solution of two isomeric mixture continues to stand at the temperature, the peaks assigned to the N,αO-isomer slowly increase whereas peaks to the O,O'-isomer slowly decrease. The NMR change suggests that reaction of *cis*-(DACH)Pt (SO_4) with barium glutamate initially gives *cis*-(DACH)Pt (O,O'-Glu), and then slowly isomerises to *cis*-(DACH)Pt(N,α O-Glu).

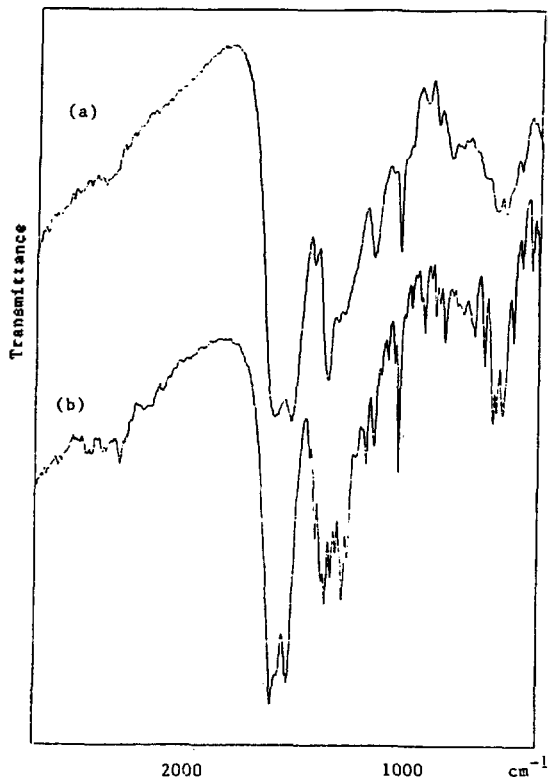


Figure 4. IR spectra of the mixture of O,O'-: N,αO-isomer (34 : 66) (a) and N,αO-isomer (b) for (en)Pt(Glu).

Figure 4 presents each IR spectrum (2800-400 cm^{-1}) for the two isomeric mixture and the N,αO-isomer of *cis*-(en)Pt (Glu) in the solid state. The IR spectrum of N,αO-isomer shows features observed in the spectrum of the isomeric mixture. Comparison between the two spectra shows significant differences that may be related to differences in structure. In particular, the bands of only N,αO-isomer are relatively clear and keen whereas those of the mixture are broad and blunt. Infrared spectrum of N,αO-isomer shows characteristic bands of 1645 and 1624 cm^{-1} assigned to asymetric stretching frequencies of carboxyl group.[21,23,24] It, unfortunately, is not easy to discern the bonding mode of carboxylate group by the carboxyl stretching frequencies. The strong sharp band at 1572 cm^{-1} seems to be N-H bending vibration of coligand amine.[11] The symmetric C-O stretching frequencies of the product appear around 1393 cm^{-1}.

The mass spectra of the two isomeric mixture and N,α O-isomer for (en)Pt(Glu) were depicted in Figure 5. The mass spectra were scanned from 0 upto 1000 amu. Both spectra show the intense molecular ion peak of $[(en)Pt(Glu)+H]^+$ at m/e=401 along with appreciable peaks. Comparison of the two isomer mixture with the N,αO-isomer shows important differences in relative intensities of the peaks. A striking difference is appearance of some additional peaks at m/e=250-350 only in the spectrum of isomer mixture. The characteristic peak at m/e=148 seems to stem from the dissociated glutamic acid $[C_5H_9NO_4+H]^+$. The peak at m/e=148 of the mixture is much more intense than that of N,αO-isomer, presumably due to abundant metastable O,O'-isomers in the isomeric mixture. In the mass spectrum of N,αO-isomer, molecular ion emerged as a base peak.

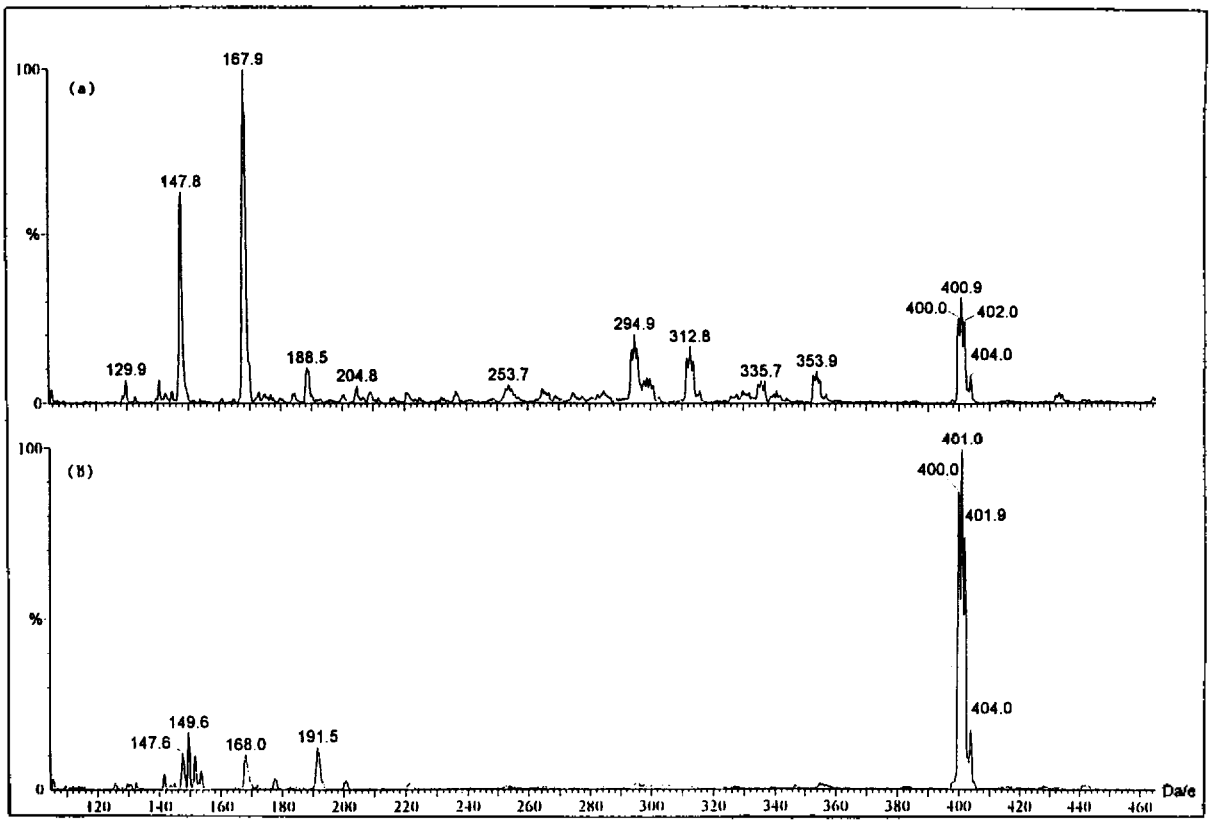
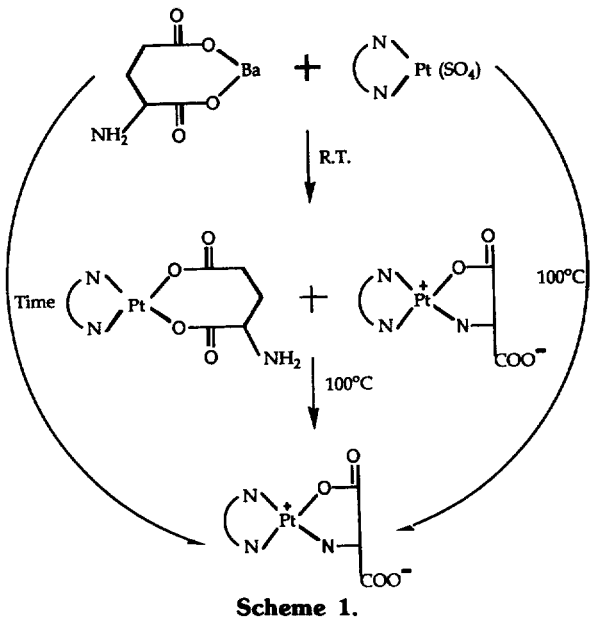


Figure 5. Mass spectra of the mixture of O,O'-: N,αO-isomer (34 : 66) (a) and N,αO-isomer (b) for (en)Pt(Glu).

Table 1. The Ratio of O,O'-/N,αO-Isomer for (N-N)Pt(Glu) at Room Temperature

N-N	O,O'-Isomer (%)	N,αO-Isomer (%)
$2NH_3$	63	37
DACH	62	38
TMEDA	35	65
en	34	66



Scheme 1.

The molecular ion base peak implies that the molecular ion of N,αO-isomer is very stable, which is consistent with above mentioned spectroscopic data.

Analogous reactions of *cis*-(N-N)Pt(SO_4) (N-N = DACH, en, $2NH_3$, TMEDA) with barium glutamate show the similar results except the isomeric ratio of the products. Table 1 discloses that the isomeric ratio of products at room temperature strongly depends upon the diamine coligands. In particular, comparison of the spectrum at 10℃ (Figure 3) with the spectrum at room temperature (Table 1) for (DACH)Pt(Glu) implies that the ratio of the isomeric mixture is also very sensitive to temperature.

In summary, diaminoplatinum (II) complexes of glutamic acid exist in two forms of chelates in solution at room temperature. However, on standing for a long time or increasing temperature, the platinum complexes isomerize to thermally stable form of N,αO-isomer as presented in Scheme 1. Moreover, the isomerization is sensitive to various factors such as temperature, time, and coligand.

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^1H NMR Study of Imidazole, L-Histidine, and Their Derivatives Coordinated to the Paramagnetic Undecatungstocobalto(II)silicate and -nickelo(II)silicate Anions

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^1H NMR spectra of imidazole, 2- and 4(5)-methylimidazole, histamine, L-histidine, L-histidine methyl ester, N_α-acetyl-L-histidine, and L-carnosine coordinated to the paramagnetic undecatungstocobalto(II)silicate ($SiW_{11}Co$) and undecatungstonickelo(II)silicate ($SiW_{11}Ni$) anions are reported. For these complexes the ligand exchange is slow on the NMR time scale and the pure resonance lines of the free ligand and the complexes have been observed separately at room temperature. Two different complexes are formed, depending upon which nitrogen atom of the imidazole ring is coordinated to the cobalt or nickel ion of $SiW_{11}M$. Thus the NMR spectrum of a D_2O solution containing a ligand and $SiW_{11}M$ consists of three sets of lines originating from the free ligand and two complexes. All NMR lines of the $SiW_{11}Co$ complexes have been assigned unequivocally using the saturation transfer technique. The temperature dependence of some spectra are also reported. The NMR spectra of some complexes show that the internal rotation of the substituent on the imidazole ring is hampered by the heteropolyanion moiety even at room temperature.

Introduction

Recently we have reported the ^1H and ^{13}C NMR spectra of some pyridine-type ligands coordinated to paramagnetic heteropolyanions, $[SiW_{11}O_{39}Co^{II}]^{6-}$ and $[SiW_{11}O_{39}Ni^{II}]^{6-}$.[1] The Co^{2+} or Ni^{2+} ion in the heteropolyanion carries a water molecule which can be replaced by various ligands; see Figure 1. Pyridine-type ligands coordinated to $[SiW_{11}MO_{39}]^{6-}$ ($M=Co^{II}$ or Ni^{II}; denoted as $SiW_{11}M$ hereafter) undergo slow exchange on the NMR time scale, exhibiting NMR lines separated from those of free ligands. The slow exchange allowed us to measure the absolute isotropic NMR shifts directly, and to identify the species formed when bidentate ligands such as pyrazine and 4,4'-bipyridyl reacted with $SiW_{11}Co$.

The isotropic NMR shifts ($=\delta_{complex}-\delta_{free\ ligand}$) in paramagnetic system contain contact and pseudocontact contributions. Contact shifts occur when unpaired electron density is transferred from the metal to the ligand nucleus in question, whereas pseudocontact shifts arise from a through-space dipolar interaction between the electronic and nuclear magnetic moments.[2] The pseudocontact shift is proportional to the geometrical factor, $(3\cos^2\theta-1)/r^3$. Therefore, useful information on the conformation of the ligand may be obtained, if the pseudocontact shifts can be determined from the NMR data.

We have extended this study to imidazole, histidine, and