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Platinum(II) Complexes with D-Glucosamine and its Derivatives

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Abstract

Neutral and (or) ionic platinum(II) complexes of D-glucosamine, 1,3,4,6-tetra-*O*-acetyl-D-glucosamine and *p*-metoxybenzylidene-*N*-1,3,4,6-tetra-*O*-acetyl-D-glucosimine were prepared and characterized by chemical analyses, conductance measurements, and vibrational spectroscopy (IR and far-IR). The reactions of $PtCl_4^{2-}$ with monodentate Schiff base yield complexes of the related aminosugar, indicating the hydrolysis of the primary ligand.

Introduction

Searching for new PDD analogs with better water solubility, we reported in a preliminary communication the new group of neutral platinum complexes: *cis*-Pt(aminosugar)$_2Cl_2$ [1]. We now present the details of the preparation and characterization of *cis*-Pt(D-glucosamine)$_2Cl_2$ and other neutral or ionic platinum complexes containing 1,3,4,6-tetra-*O*-acetyl-D-glucosamine or its Schiff base as a ligand. The *cis*-complexes are interesting because of their potential cytostatic activity; the others are of interest because they are 'non-normal' products of the reaction between $PtCl_4^{2-}$ and a N-donor ligand. Until now, only a few platinum complexes with aminosugar derivatives have been found [2]. However, the interactions between some other metals and aminosugars [3–5], especially in solution [3], and between metals and the multidentate Schiff base of aminosugars [6, 7] have been examined. In the latter cases, very stable chelate complexes have been formed. To our knowledge, the analogous reactions of the monodentate Schiff base have not been described. These reactions seemed interesting because of the possibility of forming the K[Pt(L)Cl_3] type complexes which would be stabilized by the bulky size of the ligand. Simultaneously, this ligand (Schiff base) can undergo destruction by hydrolysis, leading finally to the ionic complex with a small ligand. Such complexes are rather difficult to prepare; however, they are considered to be very desirable intermediate products in the synthesis of PDD analogs with two different amine ligands: *cis*-Pt(L'L)X_2 [8, 9].

Experimental

Starting Materials and Experimental Details

Commercially available D-glucosamine hydrochloride (Polfa) was used without further purification. K_2PtCl_4 was prepared from metallic platinum by known procedures [10]. DMF (Reachim) was distilled onto a molecular sieve under reduced pressure. The ligands 1,3,4,6-tetra-*O*-acetyl-D-glucosamine (ac. glu), its hydrochloride, and p-metoxybenzylidene-*N*-1,3,4,6-tetra-*O*-acetyl-D-glucosamine (benz.ac. gli) were prepared according to published methods [11]. TLC was undertaken using Merck silica gel on glass plates in systems: **A** = CH_3OH–$CHCl_3$ (5:95), **B** = CH_3OH–CH_3COCH_3 (1:1), **C** = C_3H_7OH–HCOOH–H_2O (20:1:5). IR spectra over the 4000–400 cm^{-1} region (KBr pellets) were measured in a Specord spectrophotometer, over the 450–100 cm^{-1} region (nujol mulls) in a Perkin–Elmer 180 spectrophotometer. Conductivities were measured in a Radelkis OK-102/1 conductometer.

Synthesis and Description of New Compounds

cis-Pt-(D-glucosamine)$_2Cl_2$, **1**

To a solution containing 0.83 g (2 mmol) of K_2PtCl_4 in *ca.* 20 cm^3 of water the D-glucosamine hydrochloride (0.86 g, 4 mmol) was added. The resulting solution was stirred at room temperature and 0.34 g (4 mmol) of $NaHCO_3$ in 30 cm^3 of water was added dropwise. The mixture was allowed to stand in a refrigerator for 6 days. Water was evaporated *in vacuo* over P_4O_{10}. The substance obtained (yield 35–60%) is hygroscopic, poorly soluble in ether, alcohols and CH_2Cl_2, but easily soluble in DMF and H_2O. Melting point 155–160 °C (dec). TLC: $R_f = 0$ (**A**). Electric conductivity: $\lambda_M = 24$ ohm^{-1} cm^2 mol^{-1} (DMF, $c = 10^{-4}$ M). *Anal.* Calc. for $Pt(C_6H_{11}O_5NH_2)_2Cl_2$: C, 23.0; H, 4.19; N, 4.49; Cl, 11.3. Found: C, 22.7; H, 4.38; N, 4.90; Cl, 11.0%. IR–far IR: see Table I.

Products of Reaction Between K_2PtCl_4 and 'Benz. ac.gli' in 1:1 Ratio

K[Pt(ac. glu)Cl_3], **2**

'Benz.ac.gli' (0.46 g, 1 mmol) was dissolved in methanol and then added to a water solution of

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TABLE I. Some Frequencies in IR–far IR Spectra of Compound **1** and Free Ligand [cm^{-1}]

Compound	ν_{N-H} ν_{O-H}	ν_{C-H}	δ_{N-H}	δ_{C-H} δ_{O-H} ν_{C-O}	ν_{C-O} ν_{C-N}	ν_{Pt-Cl}
$C_6H_{10}O_5NH_2$	3320vs,b	2900s,b	1640m,b	1400s,b 1340m 1280m,b 1200m,b	1080s 1030s	
$C_6H_{10}O_5NH_2 \cdot HCl$	3270vs 3080w 3020w	2920m	1600m 1570m 1520m	1410m 1380m 1335w 1310w 1240m	1175m 1110m 1090m 1060m 1030m	
$Pt(C_6H_{10}O_5NH_2)_2Cl_2$ **1**	3380s,b 3250s,b	2920m	1640m 1570m	1400m,b 1300m,b 1250m,b	1180m 1080m 1035m	326m 334m

K_2PtCl_4 (0.41 g, 1 mmol). The mixture was stirred for 15 h and left to stand for 6 days in darkness. Methanol was removed and the residue was extracted with CH_2Cl_2. The water phase was lyophilized and the resulting substance was treated with acetone and then filtered. The crude product (0.51 g, 74% yield) was crystallized from acetone–ether giving a yellow compound, melting point 170 °C (dec.). TLC: R_f = 0.02 (**A**), 0.88 (**B**), 0.86 (**C**). Electric conductivity: λ_M = 96 ohm^{-1} cm^2 mol^{-1} (acetone, $c = 10^{-4}$ M). *Anal.* Calc. for $K[Pt(C_{14}H_{21}O_9N)Cl_3]$: C, 24.4; H, 3.08; N, 2.03; Cl, 15.4. Found: C, 24.8; H, 3.06; N, 2.22; Cl, 15.1%. IR–far IR: see Table II.

cis- and trans-Pt(ac.glu)$_2$Cl$_2$, 3 and 4

After drying of the CH_2Cl_2 solution (see above) with molecular sieves and evaporation of the solvent, 0.2 g of crude product was obtained. Several crystallizations from acetone–ether and acetone–CH_2Cl_2 yielded two substances: (a) **3**, colourless, TLC: R_f = 0.82 (**A**), 0.96 (**B**), 0.89 (**C**). Electric conductivity: λ_M = 15 ohm^{-1} cm^2 mol^{-1} (DMF, $c = 10^{-4}$ M). *Anal.* Calc. for $Pt(C_{14}H_{21}O_9N)_2Cl_2$: C, 35.00; H, 4.41; N, 2.91; Cl, 7.39. Found: C, 34.54; H, 4.40; N, 2.77; Cl, 7.54%. IR–far IR spectra: see Table II.

(b) **4**, yellow, TLC: R_f = 0.79 (**A**), 0.97 (**B**), 0.91 (**C**). Electric conductivity: λ_M = 19 ohm^{-1} cm^2 mol^{-1} (acetone, $c = 10^{-4}$ M). *Anal.* Found: C, 34.68; H, 3.99; N, 2.68; Cl, 7.90%. IR–far IR: see Table II. Compound **3** is poorly soluble in acetone, while **4** is readily soluble. Both compounds are soluble in CH_2Cl_2 and DMF.

Products of Reaction between K_2PtCl_4 and 'Benz. ac.gli' in 1:2 Ratio

Ionic complexes **2**

A solution of 0.93 (2 mmol) of 'benz.ac.gli' in acetone was added to K_2PtCl_4 (0.41 g, 1 mmol) in water. The procedure was followed as described above for the reagents in the 1:1 ratio. The ionic complex identical to **2** was obtained from the water phase in 50% yield. Melting point 170 °C (dec.). TLC: R_f = 0.02 (**A**), 0.88 (**B**), 0.87 (**C**). Electric conductivity: λ_M = 100 ohm^{-1} cm^2 mol^{-1} (acetone, $c = 10^{-4}$ M). *Anal.* Found: C, 23.90; H, 2.72; N, 2.20; Cl, 14.9%. IR–far IR spectra are identical to those for $K[Pt(ac.glu)Cl_3]$.

Neutral complexes **3**, **4** *and Pt(benz.ac.gli)$_2$Cl$_2$,* **5**

After evaporation of the CH_2Cl_2 extract (see above), a chromatographically heterogenous residue (0.6 g) was obtained from which three individual compounds were isolated:

(a) Identical to **3**, TLC: R_f = 0.82 (**A**), 0.96 (**B**), 0.89 (**C**). Electric conductivity: λ_M = 17 ohm^{-1} cm^2 mol^{-1} (DMF, $c = 10^{-4}$ M). *Anal.* Found: C, 35.55; H, 4.80; N, 2.46; Cl, 7.55%. IR–far IR spectra are identical with those of **3**.

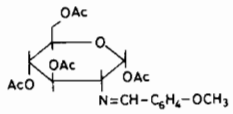
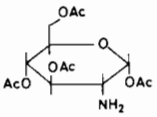
(b) Identical to **4**, TLC: R_f = 0.80 (**A**), 0.96 (**B**), 0.90 (**C**). Electric conductivity: λ_M = 17 ohm^{-1} cm^2 mol^{-1} (acetone, $c = 10^{-4}$ M). *Anal.* Found: C, 35.43; H, 4.66; N, 3.03; Cl, 7.67%. IR–far IR spectra are identical to those of **4**.

(c) **5**, TLC: R_f = 0.89 (**A**). Electric conductivity: λ_M = 12 ohm^{-1} cm^2 mol^{-1} (acetone, $c = 10^{-5}$ M). *Anal.* Calc. for $Pt(C_{22}H_{27}O_{10}N)_2Cl_2$: C, 44.13; H, 4.51; N, 2.34; Cl, 5.93. Found: C, 43.50; H, 4.17; N, 2.60; Cl, 5.81%. IR–far IR: see Table II.

Results and Discussion

One could expect that the direct reaction between $PtCl_4^{2-}$ and an aminosugar possessing a free 1-OH group would provide metallic platinum as the main product. Actually, when the reaction was carried out at room temperature, most of the platinum(II) was reduced, but at low temperature (*ca.* 5 °C) the

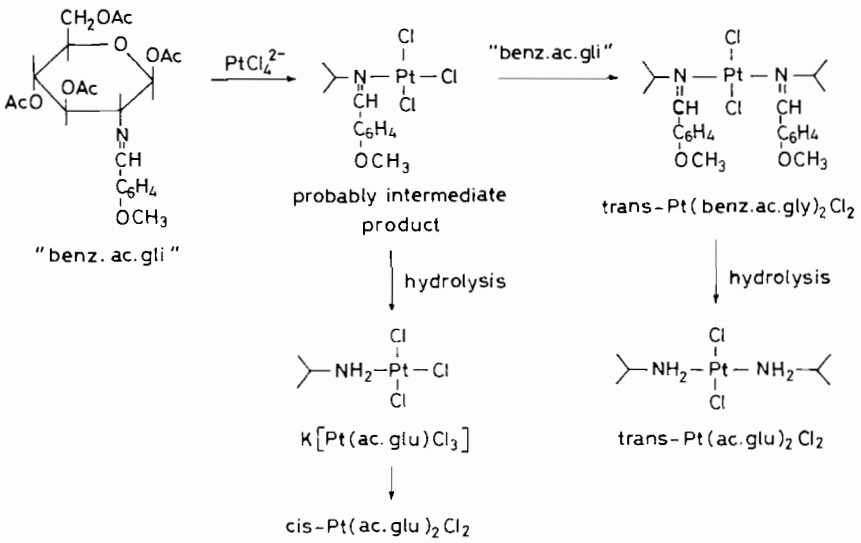
TABLE II. Some Frequencies in IR–far IR Spectra of Compounds **2**–**5** and Free Ligands (cm^{-1})

Compound	ν_{N-H}	ν_{C-H}	$\nu_{C=O}$	δ_{N-H}	$\nu_{C=C}$ $\nu_{C=N}$	δ_{C-H} of the aromatic ring	ν_{Pt-Cl}
 " benz. ac. gli "		3050m 2950w 2920w 2850w	1755s 1750s		1660s 1640s 1610m 1560m 1510m	830m	
 " ac. glu "	3360m 3250w	2970w 2950w 2900w	1755s 1740s	1605m			
K[Pt(ac.glu)Cl_3], **2**	3220w,b 3200w,b	2930w	1750s 1740s 1730s	1620w,st 1570m			328b
cis-Pt(ac.glu)$_2$, 3	3220w 3200w,b 3120w	2930w,b	1755s 1740s	1620w,b			338m 348m
trans-Pt(ac.glu)$_2Cl_2$, **4**	3220w 3200w 3120w	2930w,st	1750s	1605m 1580w			336m
trans-Pt(benz.ac.gli)$_2Cl_2$, **5**		2960w 2930w 2920w 2850w	1750s		1655w 1640m 1610m 1560w 1515m	830m	336m

'normal' product, *cis*-dichlorobis(D-glucosamine)platinum(II) **1**, was obtained. The low electric conductivity and the elemental analysis are in good agreement with the suggested formula. The IR–far IR spectra of **1** indicate the presence of a coordinated NH_2 group because of shifting in ν_{N-H} and δ_{N-H} absorption compared with the parent ligand (ν_{N-H}, ν_{O-H} of free base ~3320), its hydrochloride – 3270, 3080, 3020 cm^{-1}, and of complex – 3380, 3250 cm^{-1}; δ_{N-H} of free ligand – 1640 cm^{-1}, of its hydrochloride – 1600, 1570, 1520 cm^{-1} and of complex – 1640, 1570 cm^{-1} (Table I). The presence of two Pt–Cl stretching vibrations (334, 326 cm^{-1}) indicates the *cis*-configuration of **1**.

The other reaction presented here between $PtCl_4^{2-}$ and the monodentate Schiff base of tetra-*O*-acetyl-D-glucosamine runs according to Scheme 1. The main product proved to be a monosubstituted ionic complex **2** not only when the substrates were in 1:1 ratio but also when they were in 1:2 ratio, probably because of the bulky size of the neutral ligand. The proposed structure of potassium trichloro(1,3,4,6-tetra-*O*-acetyl-D-glucosamine) platinate(II) results from analytical data, electric conductivity (this value is characteristic for ionic complexes of 1:1 type [12]) and IR–far IR spectra. In the IR spectrum of **2**, compared with that of the Schiff base, the bands at 2920, 2850 cm^{-1} (ν_{C-H} of CH_3–O–aryl group), 1660, 1640, 1610, 1510 cm^{-1} ($\nu_{C=N}$, $\nu_{C=C}$), 830 cm^{-1} (δ_{C-H} of aromatic ring) disappeared (characteristic for the *p*-metoxybenzylidene fragment). The IR spectrum of the complex shows absorption bands due to the vibrations of the tetra-*O*-acetyl-D-glucosamine ligand coordinated by the $-NH_2$ group (ν_{N-H} at 3200 cm^{-1}, δ_{N-H} at 1620, 1570 cm^{-1}). The presence of Pt–Cl bonds is confirmed by a broad band at 328 cm^{-1}.

The neutral complexes (yield 20% at the 1:1 reagents ratio and 50% at the 1:2 ratio) were formed as a mixture of isomers: *cis*-dichlorobis(1,3,4,6-tetra-*O*-acetyl-D-glucosamine)platinum(II), **3**, *trans*-dichlorobis(1,3,4,6-tetra-*O*-acetyl-D-glucosamine)-platinum(II), **4**, and a small quantity of *trans*-dichlorobis (*p*-metoxybenzylidene-*N*-1,3,4,6-tetra-*O*-acetyl-D-glucosamine)platinum(II), **5**. Their structures result from analytical data, low electric conductivities and IR–far IR spectra. Only compound **5** shows an absorption characteristic for the *p*-metoxybenzylidene fragment: 2960, 2920, 2850, 1655, 1640, 1515, 830 cm^{-1}. In the far IR spectrum, a singlet at 336 cm^{-1} has been found which seems to be responsible for *trans* configuration of Cl–Pt–Cl bonds (Table II).



Scheme 1.

Two other complexes **3** and **4**, which can be separated by their different solubility in organic solvents, show the same characteristic frequencies in the spectra of the IR region (Table II), indicative of the presence of acetyl–amino sugar coordinated to Pt by the $-NH_2$ group (~3200, 1580–70 cm^{-1}). However, they differ in the Pt–Cl stretching region. Compound **3** is characterized by the presence of two bands (348 and 338 cm^{-1}), as is expected for *cis* configuration, while *trans*-compound **4** has only one at 336 cm^{-1}.

The mixture obtained of ionic and neutral complexes indicates that the presented reactions run non-stereospecifically. Moreover, during this reaction (or isolation of products), cleavage of the Schiff base occurs and almost all isolated complexes contain only the tetra-*O*-acetyl-D-glucosamine as a ligand. The hydrolysis of the Schiff base must be the step following its substitution to Pt. This conclusion results from comparison of the products of the reaction presented above in substrates ratio 1:2 to an analogous one described earlier by Thiel and Beck [2] where 1,3,4,6-tetra-*O*-acetyl-D-glucosamine was used as a ligand. The products of both these reactions should be identical if the Schiff bases were hydrolyzed before coordination to Pt. The main product of the reaction described by Thiel and Beck is a *cis*-neutral complex (identical with our **3**) which is a 'normal' product, whereas we obtained the monosubstituted ionic complex K[Pt(ac.glu)Cl_3], **2**. These results indicate that the bulky-sized Schiff base ligand exchanges one Cl^- substituent leading to the first Pt(benz.ac.gli)-Cl_3^- ion. The second 'benz.ac.gli' molecule has difficulties in entering the coordinating sphere of the metal, so small quantities of the by-product, *i.e.*, Pt(benz.ac.gli)$_2Cl_2$ which has *trans*-configuration, could be formed. The neutral ligands of primary products easily undergo hydrolysis, so we can isolate complexes with acetyl–aminosugar (**2** and **4**) and only a minor amount of the complex with Schiff base **5**. The *cis*-Pt(ac.glu)$_2Cl_2$ **3** seems to be the result of the indirect reaction where K[Pt-(ac.glu)Cl_3] and 'benz.ac.gli' or 'ac.glu' have been engaged.

In conclusion, the reactions between $PtCl_4^{2-}$ and the monodentate Schiff base of aminosugars can provide some interesting products: ionic complexes of the K[PtLCl_3] type (where L is a fairly small amino–sugar molecule) and *trans* neutral complexes which are unlikely to be available in other ways.

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