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Cis- and *Trans*-Platinum Complexes of Anilines. A Study of Isomerization Reactions

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Cis- and trans-*[PtL$_2$Cl$_2$] (where L = aniline, 2,5-dimethylaniline and* p*-toluidine) have been synthesized. The* cis*-compounds can be isolated isomerically pure from the reaction of K[PtLCl$_3$] and L in a mixture of water and ethanol. The* trans*-isomers are obtained from the isomerization of the* cis*-compounds. The isomers can be identified from their infrared spectra. The isomer pair, [Pt(2,5-dimethylaniline)$_2$Cl$_2$] respond to Kurnakov's test in acetone solution at room temperature.* Trans*-[Pt(2,5-dimethylaniline)$_2$(thiourea)$_2$]Cl$_2$ has been characterized.*

Introduction

We have recently reported some isomerization reactions of platinum and palladium complexes [PtA$_2$Cl$_2$] where A = pyridine and pyrimidine derivatives [1–3]. We have now studied complexes with anilines. The *cis*-platinum compound of unsubstituted aniline, prepared according to Dhara's method [4] has been reported to have some marginal antitumor activity [5]. We have found that *cis*-[PtL$_2$Cl$_2$] (L = aniline) prepared by this method, contains an impurity. When purified with dimethylformamide, the infrared spectrum of the compound changed. Lock and Zvagulis have also noted that several published procedures for preparing *cis*-complexes lead to the preparation of the *trans*-isomers [6]. This is very important since many of these procedures have been used to prepare samples of *cis*diamine complexes used in animal tests where it was shown that *cis*-complexes were active against some cancers, whereas *trans*-complexes were not.

Since the platinum complexes of substituted aniline had not yet been reported, we have extended our study to other aniline derivatives. We have developed a new reliable method to prepare pure *cis*-aniline compounds and this method is reported here.

Experimental

K[Pt(2,5-dimethylaniline)Cl$_3$]

0.415 (1 mm) of K$_2$PtCl$_4$, 0.121 g (1 mm) of 2,5-dimethylaniline and 2.5 g of KCl were mixed together in 30 ml of water at pH = 2 (adjusted with acetic acid). After 5 hours of stirring, the mixture was filtered. The filtrate was evaporated to dryness and washed with ether. The product was dissolved in acetone and filtered. The acetone filtrate was evaporated to dryness. The product was redissolved in water and filtered. The filtrate was evaporated to dryness. The product was washed with ether and collected by filtration. Yield: 35%.

The aniline and *p*-toluidine compounds were prepared by the same method.

Cis-*[Pt(2,5-dimethylaniline)$_2$Cl$_2$]*

Solution A was prepared by dissolving 0.242 g (2 mm) of 2,5-dimethylaniline in a mixture of 20 ml H$_2$O and 7 ml ethanol. Solution B was prepared by dissolving 0.461 g (1 mm) of K[Pt(2,5-dimethylaniline)Cl$_3$] in 10 ml of water. Solution B was slowly added to solution A and stirred for 4 hours. The yellow product was collected by filtration and washed with water and ether. Yield: 64%.

The aniline and *p*-toluidine platinum compounds were prepared in the same way. ν_{Pt-Cl} = 314,326 (aniline); 316,333 cm^{-1} (*p*-toluidine).

Trans-*[Pt(2,5-dimethylaniline)$_2$Cl$_2$]*

1.25 g (3 mm) of K$_2$PtCl$_4$ was dissolved in 100 ml of water and 1.1 g (9 mm) of 2,5-dimethylaniline was dissolved in 15 ml of ethanol. The two solutions were mixed at room temperature and stirred overnight. The yellow precipitate was filtered off and washed with water, acetone and ether. Yield: 65%.

Trans-*[Pt(aniline)$_2$Cl$_2$]* *and* trans-*[Pt(*p*-toluidine)$_2$Cl$_2$]*

0.415 g (1 mm) of K$_2$PtCl$_4$ and 0.5 g (5.4 mm) of aniline were mixed together in 30 ml of water

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TABLE I. Elemental Analysis of the Platinum Complexes.*

Compounds	%C	%H	%Cl	%S
K[Pt(aniline)Cl_3]	16.62	1.63	24.52	
	16.69	1.75	24.91	
cis-[Pt(aniline)$_2Cl_2$]	31.87	3.12	15.68	
	31.85	3.22	15.75	
trans-[Pt(aniline)$_2Cl_2$]	31.87	3.12	15.68	
	32.03	3.19	15.53	
K[Pt(*p*-toluidine)Cl_3]	18.77	2.03	23.76	
	18.86	2.06	23.96	
K[Pt(2,5-dimethylaniline)Cl_3]	20.77	2.40	22.99	
	20.19	2.46	23.63	
cis-[Pt(2,5-dimethylaniline)$_2Cl_2$]	37.80	4.36	13.94	
	37.28	4.33	13.71	
trans-[Pt(2,5-dimethylaniline)$_2Cl_2$]	37.80	4.36	13.94	
	36.90	4.15	13.24	
trans-[Pt(2,5-dimethylaniline)$_2$(thiourea)$_2$]Cl_2	32.73	4.59	10.73	9.71
	31.08	4.49	10.60	9.90

*Calculated values in first row.

and stirred for 5 hours. The yellow precipitate, which was a mixture of the *cis*- and *trans*-isomers as shown by infrared spectroscopy, was filtered off and washed with water and ether. When dried, the compound was dissolved in a small amount of dimethylformamide (or aniline for the aniline complex). After a short while, a precipitate appeared. Ether was then added to the DMF solution and the mixture was stirred for 30 minutes. The compound was filtered and washed with ether. The infrared spectrum shows only one narrow Pt–Cl stretching band at 336 (aniline) and 323 cm^{-1} (*p*-toluidine), typical of *trans*-isomers. Yield: 55%

Results and Discussion

The results of the element analysis of the platinum compounds are shown in Table I.

The *cis*-compounds are more soluble in organic solvents than the *trans*-isomers. For example, *cis*-[Pt(aniline)$_2Cl_2$] completely dissolve in DMF and isomerize to *trans*-[Pt(aniline)$_2Cl_2$] which precipitates out from the DMF solution. *Cis*-[Pt(2,5-dimethylaniline)$_2Cl_2$] is very soluble in acetone, while the *trans*-isomer is almost insoluble.

When aniline reacts with K_2PtCl_4 in water (Dhara's method) a greenish impurity precipitates along with [PtL_2Cl_2]. The infrared spectrum of the compound is not well defined. After the removal of the greenish impurity, a yellow compound can be obtained. When [PtL_2Cl_2] is prepared by this method, it is always accompanied by the green impurity even when freshly distilled aniline is used. Furthermore, the yellow compound [PtL_2Cl_2] is not isomerically pure. When an excess of potassium chloride is added to the solution of K_2PtCl_4 and aniline, the portion of the *cis*-isomer increases. When an excess of aniline is used, the portion of the *trans*-isomer increases. Since aniline is not completely miscible with water, the tiny oil droplets of aniline in water catalyse the *cis* → *trans* isomerization of the platinum compound. When aniline is used as the reaction medium instead of water, only the *trans*-isomer is obtained. The above results show that the *trans*-compounds can be easily obtained pure, but the preparation and identification of the *cis*-compounds should be done with great care since they can easily isomerize to the *trans*-isomers. Our method to prepare the *cis*-compounds is reliable and no isomerization occurs when followed carefully. *Cis*-[PtL_2Cl_2] is obtained pure. Our method consists in isolating first K[$PtLCl_3$] which is prepared from the reaction of K_2PtCl_4 and L (1:1 proportion) in the presence of potassium chloride at pH = 2:

$$K_2PtCl_4 + L \xrightarrow[pH=2]{H_2O,KCl} K[PtLCl_3] + KCl$$

K[$PtLCl_3$] can then react with L in a mixture of water and ethanol to give *cis*-[PtL_2Cl_2]:

$$K[PtLCl_3] + L \xrightarrow[ethanol]{H_2O} \textit{cis}\text{-}[PtL_2Cl_2] + KCl$$

Cis-[PtL_2Cl_2] dissolves completely in DMF and isomerizes to *trans*-[PtL_2Cl_2]

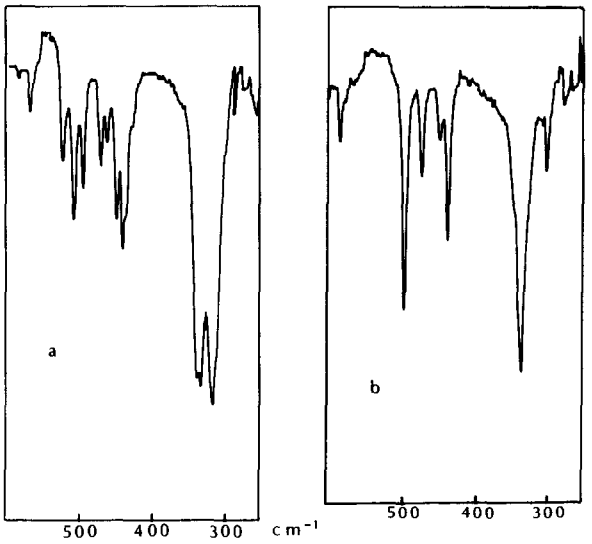

Fig. 1. Infrared spectra of a) *cis*-[Pt(2,5-dimethylaniline)$_2$-Cl_2] and b) *trans*-[Pt(2,5-dimethylaniline)$_2Cl_2$] in Nujol mull.

$$cis\text{-}[PtL_2Cl_2] \xrightarrow{DMF} trans\text{-}[PtL_2Cl_2]$$

Lock and Zvagulis [6] have already observed that several *trans*-complexes have been prepared from a procedure which was supposed to give the *cis*-complexes. The authors came to the conslusion that the *cis*-procedure gave the correct isomer, but, in the process of recrystallization, the *cis*-complex was converted to the *trans*. We also agree that in most of these procedures, the *cis*-isomer is first formed. But we think that in many instances, depending on the ligands and the reaction medium, the isomerization process starts before the recrystallization process.

The infrared spectra of the compounds were measured. The Pt–Cl stretching region of *cis*- and *trans*-[Pt(2,5-dimethylaniline)$_2Cl_2$] is shown in Fig. 1. The *cis*-isomers have two bands while the *trans*-isomers have only one.

The isomers' pair [Pt(2,5-dimethylaniline)$_2Cl_2$] respond to Kurnakov's test in acetone solution at room temperature. *Trans*-[Pt(2,5-dimethylaniline)$_2$-(thiourea)$_2$]Cl_2 was isolated and characterized. However, other aniline complexes do not respond to this test under the same conditions. No isomers' pairs respond to Kurnakov's test in DMF or in water.

The aniline platinum compound has been reported to have a slight activity on tumors [5]. Since the *trans*-isomers are not thought to have any antitumor activity and since the *cis*-isomers of aniline and aniline derivatives isomerize very easily, even in water, to the *trans*-isomers, we cannot expect at this moment that these platinum compounds will be good drugs for cancer.

However this work can give us some information about *cis*-platinum complexes of amines with large organic substituents. These complexes might behave as aniline complexes and isomerize easily to the *trans*-isomers. We intend to study these compounds very soon.

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