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Multinuclear magnetic resonance spectroscopy and crystal structures of iodo-bridged dinuclear Pt(II) complexes with amines

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Abstract

Complexes of the types *cis*-Pt(amine)$_2$I$_2$ were transformed into the iodo-bridged dimers, which were characterized mainly by multinuclear (^{195}Pt, ^{1}H and ^{13}C) magnetic resonance spectroscopy. For bulby amines, the dinuclear species were synthesized directly from $K_2[PtI_4]$. Compounds with several primary aliphatic and cyclic amines and two secondary amines were studied. In ^{195}Pt NMR, two signals were observed between −3899 and −4080 ppm in acetone. These species were assigned to the *cis* and *trans* dinuclear compounds I(amine)Pt(μ-I)$_2$PtI(amine). We suggest that the most shielded compound is the *trans* isomer. The difference between the two isomers is 12–13 ppm for the primary amine system and 26–27 ppm for the two secondary amines. There seems to be a slight dependence of the proton affinity in the gas phase of the amine (linear amines) with the δ(Pt) chemical shifts of the dinuclear Pt(II) compounds. The $^{2}J(^{195}Pt–^{1}HN)$ coupling constants are slightly larger for the trans isomers (average 67 Hz, vs. 56 Hz). The $^{3}J(^{195}Pt–^{1}H)$ coupling constants were detected only for the dimethylamine compounds, 46 Hz (*trans*) and 44 Hz (*cis*). In ^{13}C NMR, the values of $^{2}J(^{195}Pt–^{13}C)$ and $^{3}J(^{195}Pt–^{13}C)$ were also found to be very slightly larger for the *trans* complexes (average 19 and 25 Hz vs. 15 and 18 Hz). The structures were confirmed by X-ray diffraction studies of the *n*-butylamine and diethylamine compounds. The two crystals were those of the *trans* dinuclear complexes.

Keywords: Crystal structure; Platinum; Amine; NMR; Iodo ligands

1. Introduction

The antitumor properties of the complex *cisplatin*, *cis*-Pt(NH$_3$)$_2$Cl$_2$ has been known now for several decades. Its chemistry has been studied by many authors and the compound is nowadays one of the most widely used anticancer drug. A good review of the influence of structure on the activity of Pt drugs has been published [1]. When NH$_3$ is replaced by primary amines, the antitumor activity can sometimes increase, depending on the amines [2–5], but these compounds have generally a more limited activity spectrum. Furthermore, several of the most active complexes (for example those with cyclic amines) are too insoluble to be useful anticancer drugs [6].

Most *cisplatin* analogues studied in the literature contain two identical amines since they are very easy to synthesize. A method was reported for the synthesis of mixed-amine complexes many years ago by our research group [7,8], but it has not been very popular. We have reported a few of these compounds and other complexes were reported in the literature by other groups. For example, the mixed-ligand compound *cis*-Pt(NH$_3$)(2-picoline)Cl$_2$ was found to be very active and it is currently in clinical trials [9,10]. These mixed-ligand complexes are usually prepared using the iodo-bridged dimer as the intermediate compound, which is synthesized from the Pt(amine)$_2$I$_2$ complex [7]. These two types

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of compounds are very insoluble and the reacting time is usually quite long (2–3 weeks). Furthermore, it is difficult to determine when the reaction is complete. The iodo-bridged dimers are usually brown and the diiodo complexes are yellow, but the color of the mixture is not a good criterion.

The cleavage of the iodo-bridged dimers can be done with a second amine to produce directly Pt(amine)(amine′)I_2, which can be converted into the dichloro species by reaction with a silver salt followed by the addition of KCl. The iodo dimers can also be converted to the complex salt K[Pt(amine)Cl_3] by reacting directly the dimer with a silver salt followed by the addition of KCl.

The purity of the mixed-ligand compounds is very important when the antitumor properties are determined. Therefore the purity of the dinuclear intermediate is also an essential criterion, since the quantity of the silver salt must be carefully controlled. Furthermore, if the formation of the dimer is not complete, the presence of Pt(amine)$_2$ species will always be present in the final product. We have therefore undertaken a systematic NMR study of the dinuclear species, although the latter are not very soluble. Iodo Pt(II) compounds tend to decompose in $CDCl_3$ [12]. It has been shown that *cis*-diamine compounds react rapidly with DMSO and often isomerize quite rapidly in DMF [13]. These solvents were therefore eliminated. We have decided to use acetone for the study, although it is not a completely inert solvent. But we have observed that the isomerization is either absent or very slow, unless it is heated.

In this paper, we report a systematic and detailed study of the multinuclear (^{1}H, ^{13}C and ^{195}Pt) NMR spectra of the dinuclear complexes I(amine)Pt(μ-I)$_2$Pt-(amine)I in acetone-d_6. Complexes with eight primary aliphatic amines, four cyclic amines and two secondary amines were studied. Amines cannot accept electron density from the metal. Therefore the σ bonds should cause a deshielding effect on the ligand and a shielding effect on the metal. The strength of the σ bond should be related to the pK_a value of the protonated amine or the proton affinity of the ligand, although few of the latter values have been reported in the literature. We have also determined the crystal structures of two iodo-bridged dimers and the results will be discussed below.

2. Experimental

$K_2[PtCl_4]$ was obtained from Johnson Matthey and was recrystallized in water before use. The amines were bought from Aldrich. CD_3COCD_3 was purchased from CDN Isotopes.

The NMR spectra were measured on a Varian Gemini 300BB in CD_3COCD_3. The fields were 300.075, 75.462 and 64.267 MHz, respectively for ^{1}H, ^{13}C and ^{195}Pt. The acetone peak was used as an internal standard for ^{1}H (2.04 ppm) and ^{13}C (29.80 ppm). The external reference used for ^{195}Pt was *cis*-Pt(tetramethylenesulfoxide)$_2Cl_2$ (in $CDCl_3$), adjusted at −3450 ppm from $K_2[PtCl_6]$ (δ(Pt) = 0 ppm in D_2O).

2.1. Synthesis

2.1.1. *cis*-Pt(amine)$_2I_2$

These complexes were synthesized by a modified version of Dhara's method [11] and as described in details more recently [12,13]. For *t*BuNH_2, the *cis* compound does not form. For Et_2NH, a brown product was formed and ^{195}Pt NMR has shown the presence of the iodo-bridged dimers (70%) and another compound, which was found to be *cis*-Pt($Et_2NH)_2I_2$ (30%) [12]. All these Pt(amine)$_2I_2$ complexes have already been characterized by IR, multinuclear magnetic resonance and a few by crystallographic methods [12,13].

2.1.2. I(amine)Pt(μ-I)$_2$Pt(amine)I

All the complexes, except those of *t*-butylamine and diethylamine were synthesized by slight variations of the published method [7]. The complex *cis*-PtL_2I_2 (0.2 mmol) was placed in 5 mL ethanol and 1.5 mL of perchloric acid 0.67 M and mixed until the formation of a brown or orange precipitate (one to three weeks). The yellow color of the starting material must have disappeared completely. The brownish product was filtered, washed with water and ethanol and dried under vacuum in a desiccator. For the four cyclic amines, the reaction time was 10 days. NMR spectroscopy has shown that the cyclopropyl dimer had not formed yet after 10 days since only the starting material was found. The reaction was then repeated and the mixture was left stirring for 3 weeks. At that time, there was no more starting material.

For the bulky amines *t*-butylamine and diethylamine, the dimeric compound was synthesized directly from the reaction of $K_2[PtI_4]$ with an excess of amine in water. The method described to synthesize *cis*-Pt(amine)$_2I_2$ was used [12].

The NMR characterization of the products are listed below. Because of the multiplicity of the proton signals and the formation of more than one product, the $^3J(^1H–^1H)$ couplings have not been assigned, except for the amines where the multiplicity is reduced as in $MeNH_2$ and Me_2NH.

I($MeNH_2$)Pt(μ-I)$_2$Pt($MeNH_2$)I, *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.498 and 4.390 (s); H_1 2.522 and 2.510 (t), $^3J(^1H–^1H) = 6.3$ and 6.3 Hz; ^{13}C: C_1 35.188 and 34.505, $^2J(^{195}Pt–C_1) = 19$ and 16 Hz.

I($EtNH_2$)Pt(μ-I)$_2$Pt($EtNH_2$)I, *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH not assigned (see text); H_1 2.838 and 2.794 (tq); H_2 1.297 and 1.249 (t); ^{13}C: C_1 44.022 and 43.354, $^2J(^{195}Pt–C_1) = 18$ and 15 Hz; C_2 16.656.

I(nPrNH$_2$)Pt(μ-I)$_2$Pt(nPrNH$_2$)I, *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.525 and 4.432 (s); H$_1$ 2.764 and 2.738 (tq); H$_2$ 1.753 and 1.802 (tt); H$_3$ 0.939 and 0.946 (t); ^{13}C: C$_1$ 50.838 and 50.184; C$_2$ 24.912 and 24.879; C$_3$ 11.161 and 11.387.

I(nBuNH$_2$)Pt(μ-I)$_2$Pt(nBuNH$_2$)I: *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.516 and 4.399 (s), $^2J(^{195}\text{Pt–NH}) = 66$ and 57 Hz; H$_1$ 2.784 and 2.761 (tq); H$_2$ 1.740 and 1.765 (tt); H$_3$ 1.395 and 1.400 (tt); H$_4$ 0.923 and 0.929 (t); ^{13}C: C$_1$ 48.787 and 48.120; $^2J(^{195}\text{Pt} - \text{C}_1) = 17$ and 14 Hz; C$_2$ 33.685; C$_3$ 20.239 and 20.390; C$_4$ 13.939.

I(*iso*PrNH$_2$)Pt(μ-I)$_2$Pt(*iso*PrNH$_2$)I, *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.492 and 4.381 (s), $^2J(^{195}\text{Pt–NH}) = 68$ and 56 Hz; H$_1$ 3.413 and 3.204 (thept); H$_2$ 1.345 and 1.363 (d); ^{13}C: C$_1$ 51.504 and 50.882; $^2J(^{195}\text{Pt–C}_1) = 23$ and 16 Hz; C$_2$ 24.199 and 24.154, $^3J(^{195}\text{Pt–C}_2) = 27$ Hz (*trans*).

I(*iso*BuNH$_2$)Pt(μ-I)$_2$Pt(*iso*BuNH$_2$)I: *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.452 and 4.347 (s), $^2J(^{195}\text{Pt–NH}) = 68$ and 55 Hz; H$_1$ 2.646 and 2.639 (td); H$_2$ 2.159 and 2.137 (thept); H$_3$ 0.982 and 0.959 (d); ^{13}C: C$_1$ 56.467 and 55.799, $^2J(^{195}\text{Pt–C}_1) = 20$ and 16 Hz; C$_2$: hidden by the solvent; C$_3$ 20.162 and 20.208.

I(*sec*BuNH$_2$)Pt(μ-I)$_2$Pt(*sec*BuNH$_2$)I, *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.431 and 4.325 (s); H$_1$ 2.986 and 2.959 (m); H$_2$ 1.471 and 1.509 (tq); H$_3$ 1.287 and 1.346 (d); H$_{2'}$ 0.954 and 0.930 (t); ^{13}C: C$_1$ 56.847 and 56.194, $^2J(^{195}\text{Pt–C}_1) = 16$ Hz (*trans*); C$_2$ 30.984, $^3J(^{195}\text{Pt–C}_2) = 27$ Hz (*trans*); C$_3$ 21.058 and 21.106; C$_{2'}$ 10.479 and 10.506.

I(tBuNH$_2$)Pt(μ-I)$_2$Pt(tBuNH$_2$)I, *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.326 and 4.009 (s), $^2J(^{195}\text{Pt–NH}) = 67$ Hz (*trans*); H$_2$ 1.526 and 1.415 (s); ^{13}C: C$_1$ 56.300 and 55.390, $^2J(^{195}\text{Pt–C}_1) = 16$ and 10 Hz; C$_2$ 32.168 and 31.075, $^3J(^{195}\text{Pt–C}_2) = 22$ and 18 Hz.

I(Me$_2$NH)Pt(μ-I)$_2$Pt(Me$_2$NH)I, *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.900 and 4.798 (s); H$_1$ 2.662 and 2.656 (d), $^3J(^1\text{H–}^1\text{H}) = 6.0$ and 6.0 Hz, $^3J(^{195}\text{Pt–H}_1) = 46$ Hz (*trans*) and 44 Hz (*cis*); ^{13}C: C$_1$ 46.086 and 45.145, $^2J(^{195}\text{Pt–C}_1) = 17$ and 14 Hz.

I(Et$_2$NH)Pt(μ-I)$_2$Pt(Et$_2$NH)I, *trans* and *cis*, respectively: RMN (δ (ppm)): ^{1}H: NH 4.763 and 4.332 (s); H$_1$ 2.955 and 2.858 (m); H$_2$ 1.488 and 1.452 (t); ^{13}C: C$_1$ 53.735 and 53.219, $^2J(^{195}\text{Pt–C}_1) = 19$ and 17 Hz; C$_2$ 15.184 and 15.305. This product contains 30% of *cis*-Pt(Et$_2$NH)$_2$I$_2$. Crystal data for **II**: $C2/c$ space group, $a = 20.655(5)$, $b = 7.2730(10)$, $c = 13.822(4)$ Å, $\beta = 100.35(2)°$, $\rho = 3.395$, $R_1 = 0.065$, wR_2 (all data) = 0.0826, and $S = 1.027$.

2.2. Crystal structures

The crystallographic study of the iodo-bridged nBuNH$_2$ (**I**) and Et$_2$NH (**II**) dimers were determined at room temperature on a Bruker P4 diffractometer using graphite-monochromatized Mo Kα ($\lambda = 0.71073$ Å) radiation. The crystals were selected after examination under a polarizing microscope for homogeneity. The cell dimensions were determined at room temperature, from a least-squares refinement of the angles 2θ, ω and χ obtained for well-centered reflections. The data collections were made by the $2\theta/\omega$ scan technique using the XSCANS program [14]. The coordinates of the Pt atoms were determined by direct methods. All the other non-hydrogen atoms were found by the usual Fourier methods. The refinement of the structures was done on F^2 by full matrix least-squares analysis. In crystal **I**, the two terminal C atoms of the butyl chains were found disordered and they intermingle. The hydrogen atom positions were fixed in their calculated position with $U_{eq} = 1.2\ U_{eq}$ (or 1.5 for methyl groups) of the carbon to which they are bonded, except for the C atoms of the butyl chains. Corrections were made for absorption (Gaussian integration for **I** and from ψ–scans for **II**), Lorentz and polarization effects. The residual peaks were located in the close environment of the platinum atoms. The calculations were done using the Bruker SHELXTL system [15]. The pertinent crystal data and the experimental details for crystal **I** are summarized in Table 1.

Table 1
Crystallographic data for crystal **I**

Crystal	**I**
Name	{Pt(nBuNH$_2$)I}$_2$(μ-I)$_2$
Chemical formula	C$_8$H$_{22}$I$_4$N$_2$Pt$_2$
M_w	1044.06
Space group	R-3 (No.148)
a (Å)	25.249(4)
b (Å)	25.249(4)
c (Å)	8.113(2)
Volume (Å^3)	4478.9(15)
Z	9
ρ_{calc} (g cm^{-3})	3.484
μ (MoKα) (cm^{-1})	20.228
F(000)	4068
Measured reflections	11 332
Independent reflections (R_{int})	1946 (0.1512)
Observed reflections ($I > 2\sigma(I)$)	1148
R_1 ($F > 2\sigma(I)$)	0.0626
wR_2 (all data)	0.1198
S	1.089

$R_1 = \sum(|F_o - F_c|)/\sum|F_o|, wR_2 = [\sum(w(F_{o^2} - F_{c^2})^2)/\sum(w(F_{o^2})^2)]^{1/2}$.

3. Results and discussion

3.1. Synthesis

The brown or orange iodo-bridged dinuclear complexes were synthesized mainly from the reaction of yellow *cis*-Pt(amine)$_2$I$_2$ in perchloric acid as described in our previous publication [7].

$$2Pt(amine)_2I_2 \xrightarrow[EtOH]{HClO_4/H_2O} I(amine)Pt(\mu\text{-}I)_2Pt(amine)I$$

Both types of compounds are very insoluble and the reaction time is very long (2–3 weeks). This method was used for the following amines: = methylamine ($MeNH_2$), ethylamine ($EtNH_2$), *n*-propylamine ($nPrNH_2$), *n*-butylamine ($nBuNH_2$), *iso*-propylamine ($isoPrNH_2$), *iso*-butylamine ($isoBuNH_2$), *sec*-butylamine ($secBuNH_2$) and dimethylamine (Me_2NH). For the four cyclic amines (cyclopropylamine (cpra), cyclobutylamine (cba), cyclopentylamine (cpa) and cyclohexylamine (cha)), the reaction time was 10 days. NMR spectroscopy has shown that the cyclopropyl dimer had not formed yet. Only the starting material was detected. The experiment was then repeated and the mixture was left stirring for 3 weeks. At that time, they were no more starting material and only the cyclopropyl dimers were observed in the NMR spectra.

A mechanism has been suggested in the literature for the formation of the dinuclear species [16]. The published scheme indicates a trans configuration of the dimer, although its configuration is not discussed in the paper.

For *t*-butylamine (*t*-$BuNH_2$) and diethylamine (Et_2NH), the *cis* disubstituted compound which is produced with other amines is not easily formed because of the bulkiness of the two ligands. The iodo-bridged dimer with these two sterically demanding ligands were synthesized directly from the reaction of $K_2[PtI_4]$ with the amine in water.

$$2K_2[PtI_4] + 2amine \xrightarrow{H_2O} I(amine)Pt(\mu\text{-}I)_2Pt(amine)I + 4KI$$

The product obtained with Et_2NH contained also about 30% of another compound which was identified as *cis*-$Pt(Et_2NH)_2I_2$. The ligand *t*-butylamine is too bulky to form a *cis* compound.

These dimers are very important intermediates in synthetic Pt(II) chemistry and therefore, it is essential to know the purity of these compounds, especially in the synthesis of potential antitumor compounds. They were characterized mainly by multinuclear NMR spectroscopy. The crystal structure of the $nBuNH_2$ and Et_2NH compounds were determined by X-ray diffraction, which confirmed the structure of the iodo-bridged dinuclear species.

3.2. Crystal structures

The crystallographic study of the $nBuNH_2$ (**I**) and Et_2NH (**II**) compounds confirmed the structure of the two iodo-bridged dimers. The structure of the Et_2NH complex has been published [17] and our crystallographic results on crystal **II** will not be discussed in detail. The structure of the $nBuNH_2$ complex (**I**) is shown in Fig. 1. The two terminal C atoms of the butyl chains

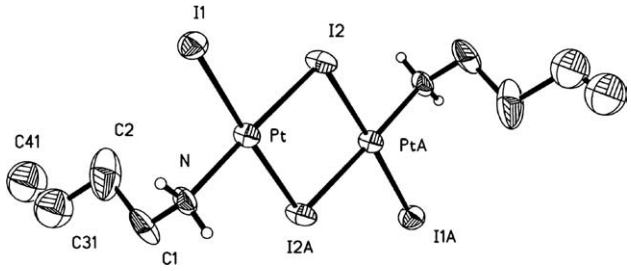


Fig. 1. Diagram of the *n*-butylamine iodo-bridged dimer (only one conformation is shown for C3 and C4).

are disordered as often seen in crystals containing $nBuNH_2$ ligands.

Both molecules are centrosymmetric and the compounds have the trans geometry. In crystal **I**, the two Pt atoms, the 4 I ligands and the two N atoms are all in the same plane (mean deviation is 0.0123 Å). The terminal Pt–I bonds are 2.5801(15) Å, while the bridging bonds are very slightly longer. The bond in trans position to the iodo ligand (2.5990(16) Å) is slightly longer than the one in trans position to the amine (2.5825(17) Å), suggesting that the trans influence of the iodo ligand is larger than the one of amines. There are some deformations from the perfect square plane around the Pt atoms caused by a strain inside the 4-membered ring. The internal angles I–Pt–I are smaller (85.71(5)°) than the ideal value, while the internal angles at the bridging iodo ligands are (94.29(5)°). These results agree with our results on **II** and those published for the Et_2NH dimer [17].

The Pt–N bond distances are 2.072(14) Å, which reflects the larger *trans* influence of the iodo ligand. In the Et_2NH dimer, our value is 2.081(7) Å, compared to 2.065(9) Å in the published structure [17]. In *cis*-$Pt(Et_2NH)_2I_2$, the Pt–N bonds are longer (2.113(10) Å) because of important steric hindrance caused by the presence of two secondary amines in *cis* positions [12].

3.3. NMR

The NMR spectra of all the dinuclear complexes were measured in CD_3COCD_3. Although several compounds are soluble in normal $CHCl_3$, they decompose quite rapidly in $CDCl_3$ to produce iodine. Attempts to purify $CDCl_3$ were not successful. We also encountered similar problems with CD_2Cl_2. Since our ^{13}C NMR spectra were accumulated for at least overnight, we have found that deuterated acetone was the best solvent, even if it is not a completely inert solvent. We have not found any change after one week of standing in CD_3COCD_3.

3.3.1. ^{195}Pt NMR

The δ(Pt) chemical shifts of all the compounds are listed in Table 2. For most products, three signals were observed, except for the $MeNH_2$ and Me_2NH compounds,

Table 2
$\delta(^{195}Pt)$ (ppm) of the products in CD_3COCD_3

Amine	$Pt(amine)_2I_2$	$I(amine)Pt(\mu\text{-}I)_2Pt(amine)I$		$\Delta\delta$ (*cis*–*trans*)
		trans	*cis*	
$MeNH_2$		−3999 (55%)	−3986 (45%)	13
$EtNH_2$	(*cis*)-3354 (50%)	−4010 (25%)	−3997 (25%)	13
n$PrNH_2$	(*trans*)-3364 (24%)	−4008 (38%)	−3995 (38%)	13
n$BuNH_2$	(*trans*)-3360 (10%)	−4005 (47%)	−3993 (43%)	12
iso$PrNH_2$	(*trans*)-3344 (18%)	−4015 (48%)	−4003 (34%)	12
iso$BuNH_2$	(*trans*)-3372 (8%)	−4011 (46%)	−3998 (46%)	13
sec$BuNH_2$	(*trans*)-3336 (23%)	−4013 (41%)	−4001 (36%)	12
t$BuNH_2$	(*trans*)-3368 (62%)	−4080 (19%)	−4069 (19%)	12
cpra[a] cpra[b]	(*cis*)-3354 (100%)	−4003 (60%)	−3990 (40%)	13
cba[a]	(*trans*)-3400 (10%	−4031 (60%)	−4021 (30%)	10
cpa[a]	(*trans*)-3364 (30%)	−4006 (55%)	−3994 (15%)	12
cha[a]	(*trans*)-3343 (25%)	−4013 (45%)	−4002 (30%)	11
Me_2NH		−3925 (65%)	−3899 (35%)	26
Et_2NH	(*cis*)-3302 (30%)	−3962 (35%)	−3935 (35%)	27

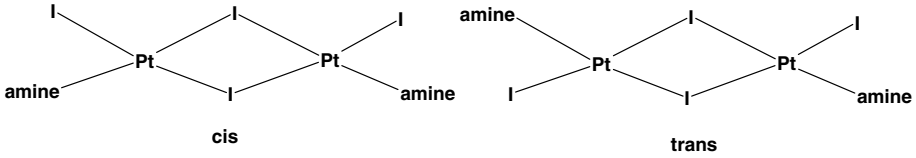
[a] After 10 days of reaction.
[b] After 3 weeks of reaction.

where only two were detected. Iodo bridged dimers of this type have two geometric isomers as shown in Scheme 1.

Both isomers should have very similar chemical shifts. They were observed between −3986 and −4080 ppm for the primary amines and between −3899 and −3962 ppm for the secondary amines. The proportion of each species is also shown in Table 2, although these numbers are very approximate. The two signals for the dinuclear species are very close. The separation is 10–13 ppm for the compounds containing a primary amine and slightly larger (26–27 ppm) for those containing secondary amines. For most of the amines, the intensity of one signal was higher than the second one. It is impossible for the moment to make definite assignment, but we suggest that the signal with the highest intensity corresponds to the *trans* isomers, which in fact is the one observed at highest field. We will therefore assume these configuration in the remaining discussion. The ^{195}Pt NMR spectra of a few similar dimers were reported in the literature by our group [18], mostly in DMF. For most compounds, two signals were also observed for the different isomers and our results agree well with these values.

The third signal for the $EtNH_2$ complexes was assigned to *cis*-$Pt(EtNH_2)_2I_2$, which was recently reported by our group [12]. The dimerization reaction was presumably stopped before it was completed. For Et_2NH, the third peak (30%) was assigned to *cis*-$Pt(Et_2NH)_2I_2$, since it was synthesized directly from the reaction of $K_2[PtI_4]$. It was observed at −3302 ppm, while the *trans* isomer was reported at −3128 ppm [12]. For all the other amines, the third signal was assigned to *trans*-$Pt(amine)_2I_2$, which we have also reported recently [12,13]. These monomers are observed in a lower field region, around −3350 ppm. The proportion of the disubstituted compound varied from one experiment to the other and seems to depend on the time of the reaction. For most of the amines, it seems that the *cis*-$Pt(amine)_2I_2$ compound has isomerized to the *trans* configuration in the long process of dimer formation. We do not think that it was formed in the NMR tube (in cold acetone), since the spectra were stable with time. The compound *cis*-$Pt(nPrNH_2)_2I_2$ was stirred in ethanol for 3 weeks and then slightly heated. The NMR spectrum of the product has shown the presence of only *trans*-$Pt(nPrNH_2)_2I_2$. Therefore these *cis* compounds can isomerize to the trans geometry in organic solvents, especially if it is heated. The disubstituted product could also result from the cleavage of the iodo-bridged dimers with the free amine although we are not sure if the reaction could happen in acid solution. The cleavage of the trans dimers with amines should lead to *cis*-$Pt(amine)_2I_2$, while the cleavage of the *cis* dimers might lead to the formation of a mixture of *cis*- and *trans*-$Pt(amine)_2I_2$, but this hypothesis has not been verified.

We have found a slight relation between the δ(Pt) chemical shifts of the dimers and the proton affinity of the linear primary amines in the gas phase and these are shown in Fig. 2. The ^{195}Pt signals are slightly shifted to higher fields as the proton affinity [19–21] increases,



Scheme 1.

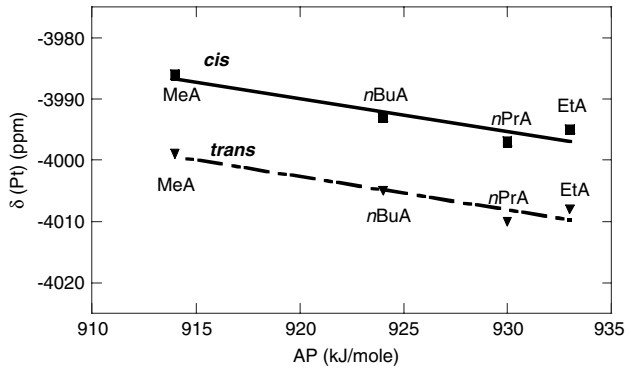


Fig. 2. δ(Pt) of the linear aliphatic amine dimers vs. proton affinity of the amine [19–21].

suggesting that the δ(Pt) chemical shifts are influenced by the basicity of the amine as expected.

3.3.2. ^{1}H NMR

The proton chemical shifts of the dimers are shown in the experimental section. Since there are three different species and because of the high multiplicity of several signals, the assignments are quite difficult. Since the ^{1}H NMR spectra of the disubstituted compounds have been recently published [12,13], their signals could be eliminated. The δ(NH) of the two iodo-bridged isomers are shown in Table 3. The assignments are based again on the relative intensity of the two signals. The most intense is the trans isomer and it was observed at lower fields. This is in agreement with our results obtained in ^{195}Pt NMR spectroscopy. An increase of electron density on the Pt atom (*trans* isomer found at higher field in ^{195}Pt NMR) will cause a decrease in electron density on the H atoms (*trans* isomer at lower field in ^{1}H NMR). The difference between the *cis* and *trans* isomers seems to be larger for more bulky amines. For most compounds, the difference varies between 0.092 and 0.117 ppm, but for *t*-butylamine and diethylamine, the difference is 0.317 and 0.431 ppm, respectively.

Table 3
$\delta(^{1}H)$ (ppm) and $^{2}J(^{195}Pt–N^{1}H)$ (Hz) of the NH protons in the complexes I(amine)Pt(μ-I)$_2$Pt(amine)I

Amine	δ*trans*	δ*cis*	$^{2}J(^{195}Pt–N^{1}H)$ *trans*	$^{2}J(^{195}Pt–N^{1}H)$ *cis*
$MeNH_2$	4.498	4.390		
n$PrNH_2$	4.525	4.432		
n$BuNH_2$	4.516	4.399	66	57
iso$PrNH_2$	4.492	4.381	68	56
iso$BuNH_2$	4.452	4.347	68	55
sec$BuNH_2$	4.431	4.325		
t$BuNH_2$	4.326	4.009	67	
cpra	4.620	4.522		
cba	4.759	4.667		
cpa	4.558	4.455	69	
cha	4.470	4.371		
Me_2NH	4.900	4.798		
Et_2NH	4.763	4.332		

Since the complexes are not very soluble, the intensity of the NH signals is quite low, but a few $^{2}J(^{195}Pt–N^{1}H)$ coupling constants could be measured and they are shown in Table 3. For the *trans* isomers, they are larger (average 68 Hz) than in the *cis* geometry (average 56 Hz). There are no reported values in the literature for these types of compounds. For monomers, the coupling constants are usually larger for the *cis* complexes than for the *trans* isomers. But the iodo-bridged compounds are very different, since the two amine ligands are located on two different Pt atoms. Therefore, their ^{195}Pt coupling constants cannot be compared with values obtained for monomers.

The $^{3}J(^{195}Pt–^{1}H)$ coupling constants of only the Me_2NH dimers could be calculated. The value is 46 Hz for the *trans* dimer and 44 Hz for the *cis* compound. The $^{3}J(N^{1}H–^{1}H)$ coupling constants are identical for the two isomers (6 Hz).

3.3.3. ^{13}C NMR

The δ(C) chemical shifts of the dimers are shown in Table 4. The signals corresponding to Pt(amine)$_2$I$_2$ were substracted. Again, the two isomers are observed and the most intense signal was assigned to the trans compound. The C atoms close to the binding site (C_1 and

Table 4
$\delta(^{13}C)$ (ppm) and $J(^{195}Pt–^{13}C)$ (Hz) of the dimers in CD_3COCD_3

Amine	C_1		C_2		^{2}J(Pt–C_1)		^{3}J(Pt–C_2)	
	trans	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*
$MeNH_2$	35.188	34.505			19	16		
$EtNH_2$	44.022	43.354	16.656		18	15		
n$PrNH_2$	50.836	50.184	24.912	24.879				
n$BuNH_2$	48.787	48.120	33.685		17	14		
iso$PrNH_2$	51.504	50.882	24.199	24.154	23	16	27	
iso$BuNH_2$	56.467	55.799	[a]		20	16		
sec$BuNH_2$	56.847	56.194	30.984			16	27	
t$BuNH_2$	56.300	55.390	32.168	31.075	16	10	22	18
Me_2NH	46.086	45.145			17	14		
Et_2NH	53.735	53.219	15.184	15.305	19	17		

[a] Hidden by the solvent.

C_2) in the *trans* isomers are observed at lower fields than the corresponding atoms in the *cis* complexes. For the primary amines (except *t*-butylamine), the difference in the chemical shits of C_1 is quite constant (average 0.659 ppm), but for *t*-butylamine and Me_2NH, the difference is larger (0.910 and 0.941 ppm). Again, these results are in agreement with the results observed in the ^{195}Pt and ^{1}H NMR spectra as discussed in the ^{1}H NMR section. An increase of electron density on the Pt atom (^{195}Pt NMR) will correspond with a decrease of electron density on the ligand (^{1}H and ^{13}C NMR).

Most of the $^{2}J(^{195}Pt–^{13}C_1)$ coupling constants could be calculated and are shown in Table 4. They are slightly larger for the trans isomers (average 19 Hz vs. 15 Hz), but these values are very approximate. For a few complexes, the $^{3}J(^{195}Pt–^{13}C_2)$ coupling constants were detected. The average value for the trans compounds is 25 and 18 Hz for the *cis t*-butylamine complex. No such values have been reported yet in the literature on similar types of complexes.

4. Conclusion

The iodo-bridged dimers are very useful molecules for many different types of syntheses. Its most important use is in the preparation of mixed-amine compounds [7,8] They can be cleaved in water by a second type of ligand to form mixed-ligands compounds as mentioned previously.

$$\mathrm{I(amine)Pt(\mu\text{-}I)_2Pt(amine)I} + 2\mathrm{L} \xrightarrow{\mathrm{H_2O}} 2\mathit{cis} - \mathrm{Pt(amine)(L)I_2}$$

The diiodo mixed-ligands compounds can be transformed into the dichloro species, which have better antitumor properties than the corresponding diiodo complexes. The dimers are also useful for the synthesis of the monoamine complexes $K[Pt(amine)Cl_3]$ [22]. They will react with a silver salt in water to produce aqua species, which can react with KCl to form $K[Pt(amine)Cl_3]$.

$$\mathrm{I(amine)Pt(\mu\text{-}I)_2Pt(amine)I} + 4\mathrm{Ag^+} \xrightarrow{-\mathrm{AgI}} \text{aqua species} \xrightarrow{\mathrm{KCl}} \mathrm{K[Pt(amine)Cl_3]}$$

The latter monosubstituted compounds are excellent starting materials for all kinds of mixed-ligands complexes ($Pt(amine)(L)Cl_2$). We have also used the iodo-bridged dimers to synthesize trans disubstituted compounds with bulky ligands. The normal method to synthesize trans compounds involve the use of the intermediate tetrasubstituted compound $[Pt(amine)_4]^{2+}$, but it cannot be used with bulky ligands (like *t*-butylamine). The second amine can also be replaced by another bulky ligand (B) to produce *trans*-$Pt(amine)(B)I_2$.

$$\mathrm{I(amine)Pt(\mu\text{-}I)_2Pt(amine)I} + 2\mathrm{B} \rightarrow 2\mathit{trans}\text{-}\mathrm{Pt(amine)(B)I_2}$$

The iodo-bridged dimers are very important intermediates in synthetic Pt(II) chemistry and it is essential to know their purity especially in the field related to chemotherapy. The crystal structure determinations have shown that the analyzed crystals are the *trans* isomers, but multinuclear and more specially ^{195}Pt NMR have shown that the two isomers coexist in solution. The *trans* compound is probably the most stable isomer, although the two amine ligands are far from each other. Therefore, steric hindrance is not an important factor in this type of compound.

The cleavage of the iodo-bridged dimers with a second amine (amine′) will produce *cis*-Pt(amine)(amine′)I_2, although it might be contaminated by the presence of *cis*-$Pt(amine)_2I_2$ or *trans*-$Pt(amine)_2I_2$ as shown in this work. These diiodo complexes are usually converted into the dichloro species by reaction with a silver salt followed by the addition of KCl. But the diamine compound will always be present as impurities in the mixed-amines complexes. Furthermore, the quantity of silver salt is very critical in these reactions and if the starting material is not pure, the quantity of silver salt added will not be adequate. Some reactions of Pt species with an excess of silver nitrate have been reported [23]. The purity of the different products is especially important in the synthesis of compounds which have an interest in chemotherapy. The purity of the compounds to be tested for their antitumor properties should be careful evaluated before any biological studies. It can be verified by multinuclear NMR, which is an excellent method to detect for example the presence of *cis*- or *trans*-$Pt(amine)_2Cl_2$ in the *cis*-Pt(amine)(amine′)Cl_2 complexes. ^{1}H NMR spectroscopy is particularly a very adequate method, since the accumulation time is relatively short even if the compounds are not very soluble. We have found than acetone is a relatively good solvent and no isomerization was observed for a few days, unless the sample is heated. We think that *cis* compounds should never be heated in an organic solvent. This work has shown that the *cis* disubstituted complexes isomerize to the *trans* isomer in warm ethanol. DMSO reacts quite rapidly with these types of complexes and should never be used to characterize them. Isomerization can also occur in cold DMF, faster than in cold acetone as shown by some previous work [13].

5. Supplementary material

The CIF table for crystal **I** has been deposited to the Cambridge Data File Centre. The deposit number is CCDC 269590.

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