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Solution Behavior of Amidine Complexes: An Unexpected *cis/trans* Isomerization and Formation of Di- and Trinuclear Platinum(III) and Platinum(II) Species

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Platinum bis-amidine complexes (both the *cis* and *trans* isomers) are stable in acetone and chlorinated solvents but are unstable in protic solvents such as methanol or water. In the latter solvents an initial *cis/trans* isomerization leads to formation of an equilibrium mixture with a *cis/trans* ratio of about 1:4; subsequently a dinuclear platinum(III) complex (**1**) is formed under aerobic conditions while, under anaerobic conditions, a trinuclear platinum(II) compound (**2**) is obtained. We hypothesize that the process of isomerization and formation of polynuclear compounds (**1** and **2**) have a common precursor: a dinuclear platinum(II) species supported by two bridging amidinato ligands (**3**), formed in small yield, which can either dissociate back to monomers of *cis/trans* configuration or evolve in two different polynuclear species depending upon the aerobic/anaerobic conditions. In aerobic conditions, oxidation of platinum(II) to platinum(III) together with formation of two additional amidinato bridges across the two platinum centers takes place leading to compound **1**. In contrast, in anaerobic conditions, oxidation of platinum is prevented and the dinuclear platinum(II) precursor remains in solution until it reacts with an extra molecule of the starting mononuclear complex which loses its two amidine ligands and cross-links the two bridging amidinato ligands of **3** to yield compound **2**. This latter features two triply bridging amidinato ligands linking the three platinum units to form a pocket. Complexes **1** and **2** have been characterized by means of IR and NMR spectroscopy, mass spectrometry, elemental analysis, and X-ray crystallography.

Introduction

Among the platinum drugs approved by Food and Drug Administration (FDA) for clinical use (cisplatin, carboplatin, and oxaliplatin), there are no cases in which the complex geometry is different from *cis*. Indeed, the *trans* isomer of cisplatin (transplatin) has no antitumor activity and this is probably a consequence of its kinetic instability which renders the complex unable to reach the target in the active form. Therefore, for a long time the *cis* geometry has been retained as a necessary requisite for a platinum compound to be antitumor active.[1]

More recently, however, several groups have reported that, upon a careful choice of the non-leaving ligands, the *trans* isomer can gain cytotoxicity comparable to (or even greater than) that of the *cis*-isomer and even of cisplatin. [2]

We have contributed to this field[3] by first reporting an active *trans*-platinum compound bearing two chlorido and two iminoether ligands [iminoesther should be a more appropriate name for this ligand but, since it was reported the first time as "iminoether", we have kept the initial terminology] and, subsequently, by extending the investigation to platinum complexes with other imino ligands such as ketimines[4] and amidines (Figure 1).[5−7] A common feature of the imino ligands is the possibility of *E* or *Z* configuration about the azomethine double bond. In the case of iminoethers and amidines (formed by addition to a coordinated nitrile of an alcohol or an amine, respectively), the *Z* configuration is kinetically favored. In solution, however, *E*/*Z* isomerization

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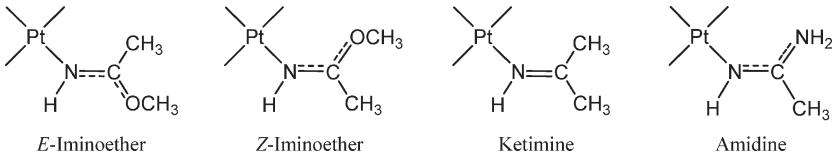

Figure 1. Sketches of imine ligands.

can take place, the thermodynamically favored isomer having the bulkier iminic-carbon substituent *trans* to platinum with respect to the C=N double bond.

In the case of addition of ammonia to a coordinated nitrile, the resulting amidine complexes were found to have stable *Z* configuration (favored both kinetically and thermodynamically).[5] Moreover these complexes were endowed with a relevant cytotoxic activity, which was quite similar for the *cis* and the *trans* isomers and in some cases was even greater than that of cisplatin.[8]

In this paper we wish to report on some intriguing aspects of the chemistry of amidine complexes. Differently from iminoethers and ketimines, amidine complexes, in water solution, readily undergo *cis*/*trans* isomerization, oligomerization, and oxidation, under ambient aerobic conditions, to platinum(III) species.

The spontaneous oxidation of a *trans* diam(m)inedichlorido platinum(II) complex to a Pt^{IV} species has recently been described in a paper from Sadler's group, which also includes full spectroscopic characterization of the new species.[9]

Spontaneous oxidation under aerobic conditions was also responsible for formation of the so-called "platinum blue" species obtained starting from diaqua-cisplatin and polyuracil. Platinum blue was detected to have high antitumor activity and low renal toxicity;[10,11] however, it was found to be a mixture of polymeric species with an average platinum-oxidation state intermediate between II and III.

Binuclear platinum(III) complexes, bridged with nucleobases, acetates, amidates, phosphates, sulphates, and so forth, are very common and generally obtained by the action of an oxidant.[12] The number of bridges can vary from two to four, while dimeric species without bridging ligands are very rare.[12,13] These dinuclear platinum(III) complexes have been widely investigated as chemotherapeutic agents,[10,14,15] luminescent probes,[16] catalysts,[17] and "molecular cages" for host−guest chemistry.[18]

This study has disclosed a rich chemistry of platinum-amidine complexes stemming from the presence, in the amidine ligand, of a second donor atom (the aminic nitrogen). This allows the amidine ligand to interact with another metal center (or even more than one) favoring the formation of polynuclear species. A dinuclear platinum(II) intermediate appears to be responsible for the spontaneous *cis*/*trans* isomerization, the easy oxidation to a platinum(III) dimer, and formation of a trinuclear platinum(II) compound.

Experimental Section

Starting Materials. Commercial reagent grade chemicals were used without further purification. The *cis* and *trans*-[$PtCl_2$-($N{\equiv}CCH_3$)$_2$] complexes were prepared by using the Hofmann reaction,[19] and subsequently separated according to a reported procedure.[20] All reactions were performed without exclusion of atmospheric oxygen, unless otherwise specified.

Preparation of the Amidine Complexes *cis* and *trans*-[$PtCl_2$-{$HN{=}C(NH_2)CH_3$}$_2$]. *cis* and *trans* acetamidine complexes were prepared using an already reported procedure, but with some modifications so as to increase their purity.[8] Briefly, a suspension of *cis*-[$PtCl_2(N{\equiv}CCH_3)_2$] (0.50 g, 1.4 mmol) in tetrahydrofuran (thf, 100 mL) was treated with a 5-fold excess of NH_3 (0.24 g, 7.0 mmol). The mixture, kept under stirring at 25 °C for 24 h, affords a yellow microcrystalline precipitate of the *cis* amidine complex. Elemental analysis: Calcd for $C_4H_{12}Cl_2N_4Pt$ (382): C, 12.57; H, 3.16; N, 14.66%. Found: C, 12.55; H, 3.33; N, 14.50%. ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.29 and 6.56 (s, 2H each, NH_2), 6.04 (s, 2H, NH), 2.07 (s, 6H, CH_3) ppm. ^{195}Pt-NMR (64.3 MHz, dmso-d_6): −2108 ppm. ESI-MS: m/z 405 $[M + Na]^+$. Similarly, the *trans* isomer was obtained from a suspension of *trans*-[$PtCl_2(N{\equiv}CCH_3)_2$] (1.40 g, 4.0 mmol) in thf (170 mL) treated with a 5-fold excess of NH_3 (0.68 g, 20.0 mmol). After stirring the mixture at 25 °C for only 2 h, the solution was filtered, to remove the white precipitate of *trans*-[$PtCl(NH_3)${$HN{=}C(NH_2)CH_3$}$_2$]Cl, and then taken to dryness by evaporation of the solvent under reduced pressure. The resulting solid was the desired *trans* amidine complex. The white precipitate of *trans*-[$PtCl(NH_3)${$HN{=}C(NH_2)CH_3$}$_2$]Cl could be converted into *trans*-[$PtCl_2${$HN{=}C(NH_2)CH_3$}$_2$] by reaction with potassium iodide, affording *trans*-[PtI_2{$HN{=}C(NH_2)CH_3$}$_2$], followed by reaction with $AgNO_3$ and then with LiCl. Elemental Analysis: Calcd for $C_4H_{12}Cl_2N_4Pt$ (382): C, 12.57; H, 3.16; N, 14.66%. Found: C, 12.72; H, 3.19; N, 14.29%. ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.27 and 6.51 (s, 2H each, NH_2), 5.82 (s, 2H, NH), 2.09 (s, 6H, CH_3) ppm.

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^{195}Pt-NMR (64.3 MHz, acetone-d_6): −2000 ppm. ESI-MS: m/z 405 $[M + Na]^+$.

Synthesis of the ^{15}N-Labeled Complex *cis*-[PtCl$_2${HN=C(^{15}NH$_2$)CH$_3$}$_2$]. For the preparation of the ^{15}N labeled complex *cis*-[PtCl$_2${HN=C(^{15}NH$_2$)CH$_3$}$_2$], the above-described procedure was adapted to the use of $^{15}NH_4Cl$ instead of aqueous ammonia. Briefly, $^{15}NH_4Cl$ (126.6 mg, 2.32 mmol) was treated with a solution of KOH (130 mg, 2.32 mmol) in 325 μL of water. This solution was treated with thf (16 mL) which caused the precipitation of KCl. After filtration, the $^{15}NH_3$ solution was added to the *cis*-[PtCl$_2$(N≡CCH$_3$)$_2$] complex (80.0 mg, 0.23 mmol), and the mixture was stirred at room temperature for 2 h. A yellow precipitate of the desired complex separated from the solution. It was recovered by filtration of the solution, washed with thf and dried in a current of dry air.

Preparation of [Pt$_2^{III}$Cl$_2${HN=C(NH)CH$_3$}$_4$] (1). A solution of *trans*-[PtCl$_2${HN=C(NH$_2$)CH$_3$}$_2$] (200.0 mg, 0.52 mmol) in water (50 mL) was heated to 60 °C meanwhile a stream of air was bubbled through it. The starting yellow solution turned to blue in a few minutes. After 24 h (always at 60 °C and aerobic conditions) a brown precipitate of **1** separated from the solution. After filtration of the mother liquor, the precipitate was washed with water and dried under dry air (50 mg, 0.07 mmol). The mother solution was brought again to 60 °C for 7 more days meanwhile a second solid fraction separated out; this was collected, redissolved in hot dimethyl sulfoxide, and allowed to precipitate by cooling to room temperature. A pure microcrystalline red solid was recovered (32 mg, 0.046 mmol). The overall yield was 45%. The compound was characterized by IR, ^{1}H, and ^{195}Pt NMR spectroscopy, ESI-MS, elemental analysis, and X-ray crystallography. Elemental analysis: Calcd for $Pt_2Cl_2N_8C_8H_{22}O$ (707.38): C 13.58, H 3.13, N 15.84%. Found: C 13.13, H 2.82, N 15.54%. ^{1}H NMR (300 MHz, dmso-d_6): 5.10 (s, 8H, NH), 1.90 (s, 12H, CH$_3$).^{195}Pt NMR (64.3 MHz, dmso-d_6): −990 ppm. ESI-MS: m/z 653.9 $[M - Cl]^+$.

Preparation of [Pt$_3$Cl$_4${HN=C(NH$_2$)CH$_3$}$_2${HN=C(NH)CH$_3$}$_2$] (2). A solution of *trans*-[PtCl$_2${HN=C(NH$_2$)CH$_3$}$_2$] (51.4 mg, 0.13 mmol) in methanol (5 mL) was stirred at 45 °C for 5 days in a vial, meanwhile a dark precipitate of impure **2** separated from the solution. The solution was filtered off, and the precipitate was washed with methanol and dried under vacuum. The dark precipitate was recrystallized from *N,N*-dimethylformamide (dmf), affording pure complex **2** as green crystals (0.025 mmol, 58% yield). The compound was characterized by IR, ^{1}H, and ^{195}Pt NMR spectroscopy, ESI-MS, elemental analysis, and X-ray crystallography. Elemental analysis: Calcd for $Pt_3Cl_4N_8C_8H_{26}O_2$(993.39): C 9.67, H 2.63, N, 11.28%. Found: C 9.73, H 2.60, N 10.94%. ^{1}H NMR (300 MHz, dmf-d_7): 10.20 (s, 2H, NH), 7.55 and 7.48 (s, 2H each, NH$_2$), 7.02 (s, 2H, NH), 4.50 (s, 2H, NH), 2.50 (s, 6H, CH$_3$), and 2.01 (s, 6H, CH$_3$). ^{195}Pt NMR (64.3 MHz, dmso-d_6): −2126 (1Pt, PtN$_2$Cl$_2$) and −2326 (2Pt, PtN$_3$Cl) ppm. ESI-MS: m/z 955.7 $[M - H]^-$.

NMR Study of the Transformation of the *trans*-[PtCl$_2$-{HN=C(NH$_2$)CH$_3$}$_2$] Complex in the Presence or Absence of Oxygen in Water Solution. *trans*-[PtCl$_2${HN=C(NH$_2$)CH$_3$}$_2$] (3.0 mg, 8.0×10^{-3} mmol) was dissolved in 3 mL of a mixture of H_2O/D_2O 9:1. The solution was divided in two portions and transferred into two NMR tubes. Oxygen was bubbled through one sample, while the other sample was deoxygenated with argon and kept under inert atmosphere. Both samples were submitted to ^{1}H NMR analysis from time to time over a period of one month.

NMR Study of the Transformation of *cis* or *trans*-[PtCl$_2$-{HN=C(^{15}NH$_2$)CH$_3$}$_2$] in Methanol-d^4. The *cis or trans*-[PtCl$_2$-{HN=C(^{15}NH$_2$)CH$_3$}$_2$] complex (5.0 mg, $1.3 \cdot 10^{-2}$ mmol) was dissolved in 0.6 mL of methanol-d^4, and the resulting solution was poured into an NMR tube and kept at 22 °C. The solution was analyzed from time to time by means of ^{1}H and ^{195}Pt NMR spectroscopy. After 18−20 days green needles of **2** were formed in the tube. The identity of the latter complex was confirmed by means of ^{1}H NMR in dmf-d_7.

Transformation of ^{15}N-labeled *cis*-[PtCl$_2${HN=C(^{15}NH$_2$)-CH$_3$}$_2$] into the trans Isomer in Methanol. *cis*-[PtCl$_2${HN=C-(^{15}NH$_2$)CH$_3$}$_2$] (40 mg, 0.10 mmol) was dissolved into 10 mL of methanol, and the resulting yellow solution was kept at room temperature in a sealed vial. After 3 days, the formed yellow crystals were collected onto a glass filter, washed with cold methanol, and dried under vacuum. They were characterized by IR and ^{1}H and ^{195}Pt NMR. They resulted in the complex *trans*-[PtCl$_2${HN=C(NH$_2$)CH$_3$}$_2$] in which the ^{15}N isotope is uniformly distributed between the amino and the imino nitrogens. In the following 18 days green needles of **2** precipitated from the solution. They were isolated and characterized by IR and ^{1}H NMR spectroscopy.

Physical Measurements. NMR spectra were collected at 295 K on a Bruker AVANCE DPX 300 MHz instrument. Standard Bruker automation programs were used for two-dimensional NOESY experiments. ^{1}H chemical shifts were referenced to TMS by using the residual protic peak of the solvent (D_2O, methanol-d_4, acetone-d_6, dmf-d_7, and dmso-d_6) as internal reference. One-dimensional ^{195}Pt spectra were acquired using ^{1}H-decoupling sequences. ^{195}Pt chemical shifts were referenced to K_2PtCl_4 (1 M in water, $\delta = -1614$ ppm). FT-IR spectra were recorded on a Perkin-Elmer mod. 283 Spectrum One System using KBr as a solid support for pellets. Elemental analysis were carried out on a CHN Eurovector EA 3011 equipment. ESI-MS analysis were performed on a Agilent 1100 series LC-MSD Trap system VL.

X-ray Diffraction Analysis. X-ray data for compounds **1** and **2** were collected on a Bruker AXS X8 APEX CCD system equipped with a four-circle Kappa goniometer and a 4K CCD detector (radiation Mo Kα). All calculations and molecular graphics were carried out using SIR2002,[21] SHELXL97,[22] PARST97,[23] WinGX,[24] and ORTEP-3 for Windows packages.[25] The crystallographic data for compounds **1** and **2** are listed in Table 1.

Red crystals of **1** were obtained by crystallization from water. Although the crystal was not of good quality, nevertheless we thought useful to perform an X-ray investigation. A total of 28600 reflections were indexed, integrated, and corrected for Lorentz, polarization, and absorption effects using multi−scan. A total of 2951 were independent reflections. The unit cell dimensions were calculated from all reflections. The structure was solved using the direct methods technique in the $C2/c$ space group. The model was refined by full-matrix least-squares methods. All non-hydrogen atoms were refined anisotropically; only the N1 atom necessitated isotropic treatment to maintain satisfactory thermal displacement parameters. All hydrogen atoms were placed in their geometrically calculated positions and were included in the full-matrix least-squares cycles with isotropic thermal parameter (U) fixed at 1.2 and 1.5 times the values of U of the attached nitrogen or carbon atom. The refinement converged to $R_1 = 0.0570$, $wR_2 = 0.1443$, and $S = 1.081$ for 2355 reflections with $I > 2\sigma(I)$, $R_1 = 0.0711$, $wR_2 = 0.1540$, and $S = 1.081$ for 2951 unique reflections and 92 parameters.

The final difference-Fourier map showed electron density peaks (up to 6.088 e·Å^{-3}) lying near the Pt atoms. Selected bond lengths and angles are listed in Table 2.

Green crystals of **2** were obtained by crystallization from methanol. A total of 20443 reflections were indexed, integrated,

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Table 1. Crystal Data and Structure Refinement Parameters for Complexes **1** and **2**

empirical formula	$C_8\ H_{20}\ Cl_2\ N_8\ Pt_2$	$C_8\ H_{22}\ Cl_4\ N_8\ Pt_3$
formula weight	689.40	957.41
temperature (K)	293(2)	293(2)
wavelength(Å)	0.71073	0.71073
crystal system	monoclinic	monoclinic
space group	*C*2/*c*	*C*2/*c*
a (Å)	14.0853(13)	13.848(1)
b (Å)	9.0037(8)	20.941(2)
c (Å)	13.6624(13)	10.819(1)
β (deg)	118.741(5)	136.64(1)
V (Å^3)	1519.2(2)	2154.0(3)
Z	4	4
D_{calc} (Mg/m^3)	3.014	2.952
μ (mm^{-1})	18.751	19.940
F(000)	1256	1712
crystal size (mm)	0.155 × 0.130 × 0.110	0.300 × 0.062 × 0.044
θ range (deg)	2.80 to 33.72	1.94 to 49.64
reflections collected	28600	20443
independent reflections	2951 [R(int) = 0.0770]	2127 [R(int) = 0.0663]
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/parameters	2951/0/92	2127/0/115
goodness-of-fit on F^2	1.081	1.014
final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0570, wR_2 = 0.1443	R_1 = 0.0282, wR_2 = 0.0670
R indices (all data)	R_1 = 0.0711, wR_2 = 0.1540	R_1 = 0.0373, wR_2 = 0.0717
largest diff. peak and hole (e·Å^{-3})	6.088 and −3.9462	1.271 and −0.727

Table 2. Selected Bond Lengths [Å] and Angles [deg] for Complex **1**

Pt1−Cl1	2.434(2)	N1−C4	1.300(11)
Pt1−N1	2.024(7)	N2−C4	1.318(12)
Pt1−N2	1.995(7)	N3−C3	1.319(12)
Pt1−N3	2.017(8)	N4−C3	1.321(11)
Pt1−N4	2.019(8)	C1−C3	1.495(12)
Pt1−Pt1^a	2.4748(6)	C2−C4	1.525(13)
N1−Pt1−N2	174.7(3)	N1−Pt1−Cl1	91.9(2)
N1−Pt1−N3	89.7(3)	N2−Pt1−Cl1	93.4(2)
N1−Pt1−N4	90.7(3)	N3−Pt1−Cl1	93.4(2)
N2−Pt1−N3	89.5(3)	N4−Pt1−Cl1	91.9(2)
N2−Pt1−N4	89.6(3)	N1−Pt1−Pt1^a	87.4(2)
N3−Pt1−N4	174.6(3)	N2−Pt1−Pt1^a	87.3(2)
Cl1−Pt1−Pt1^a	178.76(6)	N3−Pt1−Pt1^a	87.6(2)
		N4−Pt1−Pt1^a	87.1(2)

^{a} i = $-x, -y, 1-z$.

and corrected for Lorentz, polarization, and absorption effects using multi−scan. A total of 2127 were independent reflections. The unit cell dimensions were calculated from all reflections. The structure was solved using the direct methods technique in the *C*2/*c* space group. The model was refined by full-matrix least-squares methods. Anisotropic thermal parameters were applied for all non-hydrogen atoms. All hydrogen atoms were placed in their geometrically calculated positions and were included in the full-matrix least-squares cycles with isotropic thermal parameters (*U*) fixed at 1.2 and 1.5 (for methyl group) times the values of *U* of the corresponding nitrogen or carbon atoms (except for H21 and H4, which were found by Fourier difference and refined isotropically). The refinement converged to $R_1 = 0.0282$, $wR_2 = 0.0670$, and $S = 1.014$ for 1792 reflections with $I > 2\sigma(I)$, $R_1 = 0.0373$, $wR_2 = 0.0717$, and $S = 1.014$ for 2127 unique reflections and 115 parameters. The final difference-Fourier map showed electron density peaks (up to 1.271 e·Å^{-3}) lying near the Pt atoms. Selected bond lengths and angles are listed in Table 3.

Table 3. Selected Bond Lengths [Å] and Angles [deg] for Complex **2**

Pt1−Cl2	2.344(2)	N1−C1	1.285(11)
Pt2−Cl1	2.304(2)	N2−C1	1.329(12)
Pt1−N4	2.068(6)	N3−C3	1.289(10)
Pt2−N1	2.031(7)	N4−C3	1.414(10)
Pt2−N3	2.018(6)	C1−C2	1.497(12)
Pt2−N4^a	2.099(6)	C3−C4	1.507(11)
Cl2−Pt1−Cl2^a	96.3(1)	N1−Pt2−Cl1	89.8(2)
		N3−Pt2−Cl1	177.3(2)
N4−Pt1−Cl2	174.6(2)	N4^a−Pt2−Cl1	86.0(2)
N4−Pt1−Cl2^a	88.4(2)	C3−N4−Pt1	106.5(5)
N4−Pt1−N4^a	87.0(4)	C1−N1−Pt2	128.8(6)
N1−Pt2−N3	88.5(3)	C3−N3−Pt2	129.9(5)
N1−Pt2−N4^a	175.5(3)	C3−N4−Pt2^a	112.9(5)
N3−Pt2−N4^a	95.7(2)	Pt1−N4−Pt2^a	117.8(3)

^{a} i = $1-x, +y, 3/2-z$.

Results

In a previous study[8] we investigated the effectiveness of amidine complexes (*cis* and *trans*-[$PtCl_2${HN=C(NH_2)-CH_3}$_2$] and *cis* and *trans*-[$PtCl_2(NH_3)${HN=C(NH_2)CH_3}]) to inhibit tumor cell growth. The present investigation aims at unraveling the solution behavior of *cis*- and *trans*-[$PtCl_2$-{HN=C(NH_2)CH_3}$_2$] complexes under aerobic and anaerobic conditions. Analogous investigation was also performed under physiological-like conditions (water solution containing 100 mM NaCl). The investigation has revealed a series of unexpected processes occurring in solution, and we can propose a mechanism which can account for them.

The crucial observation was that the amidine complexes (*cis*- or *trans*-[$PtCl_2${HN=C(NH_2)CH_3}$_2$]), when dissolved in water, give a yellow solution which quickly tends to brown and, in the period of days, separates red crystals of a new compound (**1**). In contrast, a solution of the same compounds in methanol, left standing for quite a few days at room temperature (or for 5 days at 45 °C), affords green crystals of another compound (**2**). The extremely simple ^{1}H NMR spectrum of **1** contrasts with the great complexity of the ^{1}H spectrum of **2**. We will describe first the identification and characterization of the two compounds (**1** and **2**), and then describe the processes occurring in solution starting from pure *cis* or *trans* bis-amidine complex, monitored by ^{1}H and ^{195}Pt NMR.

Characterization of Compound 1. The elemental analysis of **1** was in accord with one chlorine and two amidines per platinum atom. The ESI-MS spectrum showed the parent peak at 653.9 *m*/*z* corresponding to the species [C_8H_{20}-N_8ClPt_2]$^+$ which presumably arises from a neutral species which has lost a chlorido ligand. The fragmentation spectrum (MS/MS) of the parent peak exhibits three signals at 617.8, 559.7, and 503.8 *m*/*z*, corresponding to species [M − HCl]$^+$, [M − HCl − $C_2H_6N_2$]$^+$, and [M − HCl − 2$C_2H_6N_2$]$^+$, corresponding to the sequential loss of HCl, one and two amidine ligands. The experimental isotopic pattern of the parent peak and the theoretical one match perfectly one another.

The IR spectrum exhibits characteristic N−H stretchings at 3398 and 3331 cm^{-1} and C=N stretching at 1615 cm^{-1}. The C=N stretching frequency is considerably lower than that observed in *cis* and *trans*-[$PtCl_2${HN=C-(NH_2)CH_3}$_2$] (1650 cm^{-1}). A Pt−Cl stretching could be detected at 292 cm^{-1} (polyethylene pellet), in analogy with values found for other platinum(III) dimers.[26]

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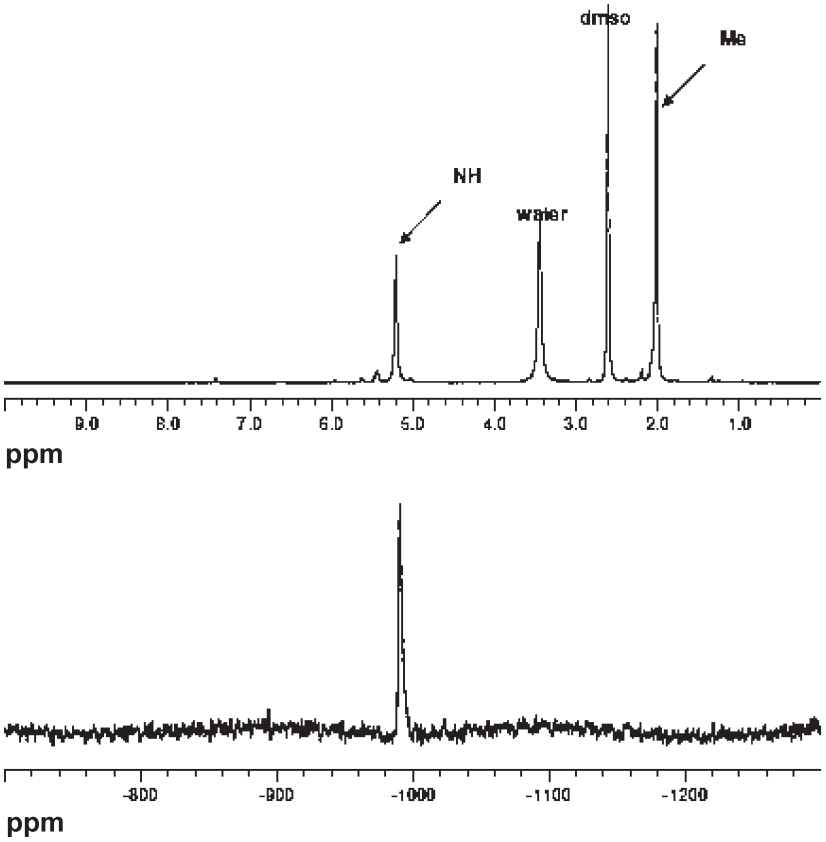

Figure 2. ^{1}H (above) and ^{195}Pt (below) NMR spectra of **1** in dmso-d_6.

A C=N stretching around 1615 cm^{-1} and a Pt−Cl stretching below 300 cm^{-1} were characteristic features of a compound previously isolated in our laboratory and having two platinum(III) atoms bridged by four acetamidato ligands and capped by two chlorido ligands, $[Pt_2^{III}Cl_2\{HN{=}C(O)CH_3\}_4]$.[27,28] Therefore compound **1** could have a structure similar to that of the acetamidato complex just mentioned. The deprotonation of an amidine ligand to yield a bridging amidinato ligand would slightly reduce the double bond character of the azomethine moiety and lower the C=N stretching. Moreover, the axial Pt−Cl bond would be weakened by the *trans* influence of the intermetallic bond and have its stretching below 300 cm^{-1}.

The ^{1}H NMR spectrum of **1** in dmso-d_6 is reported in Figure 2. The methyl groups of the amidinato ligands give rise to a signal at 1.90 ppm, while a signal at 5.10 ppm can be assigned to the N*H* protons. The observation of just one signal for the methyl and one for the NH protons is indicative of a high symmetry of the complex, where all the imino and all the methyl protons are equivalent. In the ^{195}Pt NMR spectrum (Figure 2) the platinum nuclei give a singlet at −990 ppm. This value of chemical shift is consistent with a dimeric platinum(III) having a N_4Cl set of donor atoms.[29]

Thus, the analytical and spectroscopic data are in accord with a Pt^{III} dimer having four equatorial amidinato bridging ligands and two chlorides in axial positions.

X-ray Structure of 1. Figure 3 illustrates the molecular geometry and the labeling scheme of compound **1**. Table 2 lists selected bond lengths and angles. The asymmetric unit comprises a half molecule of complex, and the structure is generated by the inversion at the midpoint of the Pt−Pt bond. Around the Pt_2Cl_2 axis are located four amidinato ligands, featuring a "lantern-shaped" structure. The axial Pt−Cl distance [2.434(2) Å] is comparable to those already reported for axial Pt−Cl distances in dinuclear complexes of platinum(III) (average Pt−Cl distance of 2.44 Å).[12,30a,b]

The Pt−Pt distance (2.4748(6) Å) (Table 2) is shorter than the Pt−Pt distance observed in the quadruply bridged amidinato complex $[Pt_2Cl_2\{PhN{=}C(NPh)H\}_4]$ (2.517(1) Å)[30a] but larger than the corresponding distance in the amidato complex $[Pt_2Cl_2\{HN{=}C(O)^tBu\}_4]$ (2.448(2) Å).[28] Similarly, the N···N bite distance (average 2.29 Å) is shorter than the corresponding distance in the analogous amidinato complex $[Pt_2Cl_2\{PhN{=}C(NPh)H\}_4]$ (2.33 Å),[30a] but longer than the corresponding distance in the amidato complex $[Pt_2Cl_2\{HN{=}C(O)^tBu\}_4]$ (2.28 Å).[28]

The platinum coordination squares are perfectly eclipsed (maximum twist angle 0.6°) since such conformation allows for the greatest separation between the two

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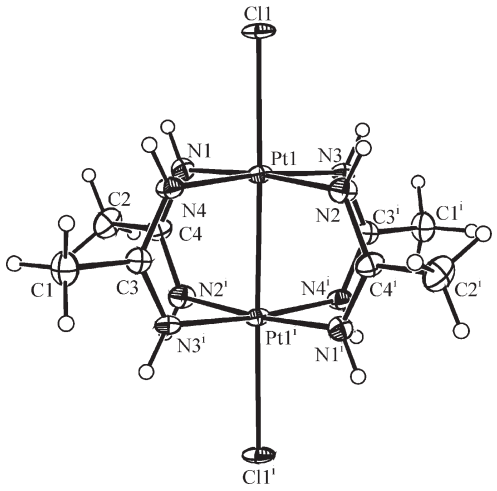

Figure 3. View of complex **1** showing the atomic numbering scheme ($i = -x, -y, 1 - z$). Displacement ellipsoids are drawn at 30% probability level.

platinum atoms. The platinum atoms are displaced from the equatorial coordination planes by 0.093 Å toward the axial chlorides, such a displacement being a measure of the strength with which the four bridging ligands pull together the two metal centers.

In the bridging amidinato ligands the C−N distances are equal within experimental error with a mean value of 1.31(1) Å.

In the crystal packing the complexes are bonded by a web of weak intermolecular interactions involving iminic hydrogen atoms and chlorine atoms (N3···Cl1^{i} = 3.72(1) Å, (N3)H3···Cl1^{i} = 2.89(1) Å, N3−H3···Cl1^{i} = 161(1)°; N4···Cl1^{ii} = 3.44(1) Å, (N4)H4···Cl1^{ii} = 2.72(1) Å, N4−H4···Cl1^{ii} = 141(1)°; $i = -x, y, 1/2 - z$, $ii = 1/2 - x$, $1/2 - y, 1 + z$) (Supporting Information, Figure S1).

Characterization of Compound 2. The elemental analysis of **2** was in agreement with a species containing four chlorides and four amidine ligands and three platinum atoms. In the ESI-MS spectrum the parent peak occurred at 955.7 *m*/*z* in the negative ion current corresponding to the species $[C_8H_{21}N_8Cl_4Pt_3]^-$, presumably arising from dissociation of one proton from the parent neutral species. The fragmentation spectrum of the parent peak (MS/MS) showed three peaks at 918.7, 898.5, and 862.6 *m*/*z,* corresponding to the loss of an HCl $[M - HCl]^-$, an amidine $[M - C_2H_6N_2]^-$, and an HCl and an amidine $[M - HCl - C_2H_6N_2]^-$. There is a very good agreement between the experimental and the calculated isotopic patterns for the parent peak.

The ^{1}H NMR spectrum of compound **2** was taken in dmf-d_7, where no changes were observed over a time of weeks. In the 2D-NOESY spectrum (Figure 4) the proton signals were labeled by letters from **a** to **g**, starting from that at lowest field, while the cross peaks were labeled with capital letters. It is to be noted that the seven signals, corresponding to five NH and two methyl groups, account for the presence of an amidine [HN=C(NH_2)CH_3] (three N*H* and one CH_3) and an amidinato [HN=C(NH)CH_3]$^-$ ligand (two N*H* and one CH_3). Therefore, the two N*H* signals resonating at 10.2 (**a**) and 4.5 ppm (**e**) and the methyl signal at 2.5 ppm (**f**), which have two strong NOE cross peaks (**B** and **E**), ought to be assigned

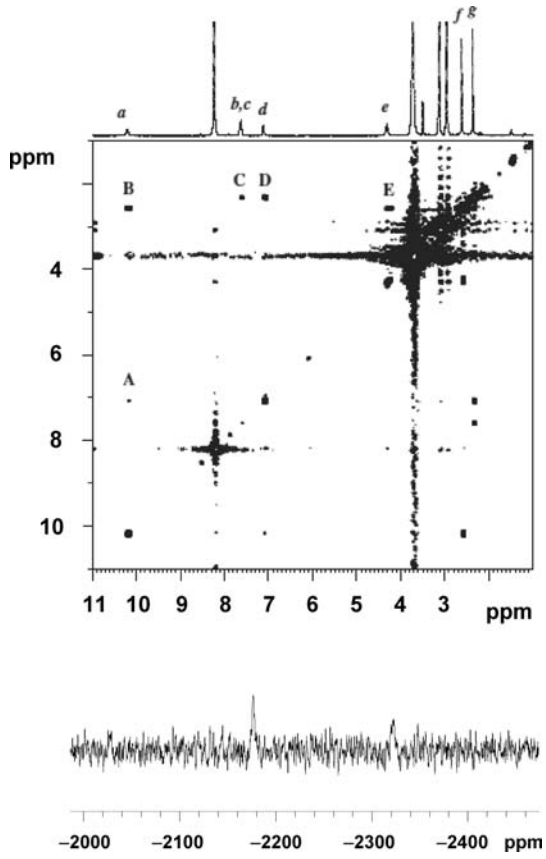

Figure 4. ^{1}H 2D-NOESY (above) and ^{195}Pt (below) NMR spectra of **2** in dmf-d_7.

to the amidinato ligand. The remaining three N*H* signals around 7.5 (**b** and **c**) and 7.0 ppm (**d**) and the methyl signal at 2.0 ppm (**g**), which also have strong NOE cross peaks (**C** and **D**), must belong to the amidine ligand. Moreover, on the basis of the already observed trend for coordinated amidines, the **d** signal has to be assigned to the iminic proton while the **b** and **c** signals have to be assigned to the two aminic protons. The very large chemical shift separation between the two NH protons of the amidinato ligand (5.7 ppm) indicates that this ligand is coordinated to the platinum atoms in a highly asymmetric way; moreover, the presence of a cross-peak (**A**) between **a** and **d** indicates that amidine and amidinato ligands are *cis* coordinated to the same platinum atom.

The ^{195}Pt NMR spectrum (Figure 4) shows two signals at −2126 (Pt1) and −2326 ppm (Pt2), of relative intensity 1:2, which are in good agreement with one platinum(II) having an N_2Cl_2 set of donor atoms and two platinum(II) having an N_3Cl set of donor atoms. Therefore, two chlorides must be bound to Pt1 and the remaining two chlorides one per each Pt2 atom. The two amidine ligands are equivalent, and must be bound one per each Pt2 atom (if both bound to Pt1 this would result in Pt1 being a monomeric dichlorido bis amidine complex). The two amidinato ligands are also equivalent; each of them must be bound to a Pt2 atom through one nitrogen (NOE cross peak with the iminic proton of the amidine coordinated to the same metal core) and to the second Pt2 and to Pt1 through the second nitrogen. A triply bridging amidinato ligand is required to saturate all coordination positions

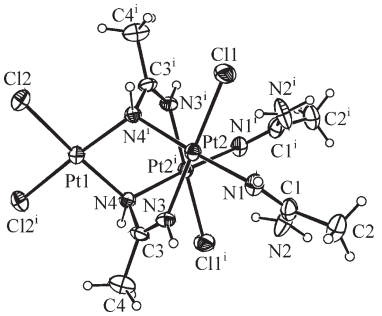

Figure 5. View of complex **2** showing the atomic numbering scheme ($i = 1 - x, +y, 3/2 - z$). Displacement ellipsoids are drawn at 30% probability level.

on the platinum atoms. Moreover, the very large separation in chemical shifts between the two NH of the amidinato ligand can find an explanation in one NH being coordinated to two platinum atoms (tetrahedral aminic nitrogen with highly shielded proton), while the second NH is coordinated to only one platinum atom (trigonal iminic nitrogen with highly deshielded proton). For the exact stereochemistry of the compound we had to wait for the X-ray diffraction analysis.

X-ray Structure of 2. Figure 5 illustrates the molecular geometry and the labeling scheme of complex **2**. Table 3 lists selected bond lengths and angles. The asymmetric unit comprises a half molecule of complex, and the overall structure is generated by a 2-fold axis. One platinum atom is in a special position. The trinuclear complex contains two *cis*-Cl{HN=C(NH_2)CH_3}Pt units (Pt2) doubly bridged by two amidinato ligands; these latter ligands also bind a third *cis*-Cl_2Pt unit (Pt1). The Pt atoms have square planar coordination: Pt1 has two chlorine and two nitrogen (sp^3) atoms in *cis* positions, while Pt2's have one chlorine and three (one sp^3 and two sp^2 hybridized) nitrogen atoms. The Pt−N(sp^3) distances (2.068(6) and 2.099(6) Å for Pt1−N4 and Pt2−N4, respectively) are larger than the Pt−N(sp^2) distances (2.031(7) and 2.018(6) Å for Pt2−N1 and Pt2−N3, respectively).

The Pt1 coordination plane has a slight tetrahedral distortion (the atoms are coplanar within ± 0.06 Å). On the other hand, the Pt2 units have a slight pyramidal distortion with the platinum atoms displaced by 0.03 Å from the mean plane defined by the four donors, the latter atoms are coplanar within ± 0.005 Å. The pyramidal distortion might be caused by weak intramolecular Pt−Pt interaction (Pt2···Pt2($1 - x, +y, 3/2 - z$) distance of 3.381(1) Å).

In the bridging amidinato ligand, the C−N(sp^3) distance (1.41(1) Å for C3−N4) is much longer than the C−N(sp^2) distance (1.29(1) Å for C3−N3). In contrast the two C−N distances are much closer in the monodentate amidine ligand (1.29(1) and 1.33(1) Å for C1−N1 and C1−N2, respectively). The monocoordinated amidine ligands are rotated in such a way as to direct an hydrogen atom of NH_2 toward the platinum and the chlorine atoms of the symmetrical subunit (N2···$Cl1^i$ = 3.76(1) Å, (N2)H21···$Cl1^i$ = 2.98(8) Å, N2−H21···$Cl1^i$ = 144(6)°; N2···$Pt2^i$ = 3.89(1) Å, (N2)H21···$Pt2^i$ = 3.02(12) Å, N2−H21···$Pt2^i$ = 158(6)°; $i = 1 - x, +y, 3/2 - z$).

In the crystal packing the complexes are piled along the *c* axis (Supporting Information, Figure S2). In the pile, adjacent complex molecules are rotated by about 180° one with respect to the other and are bonded by weak intermolecular interactions involving =NH hydrogen atoms and chlorine atoms (N1···$Cl2^{ii}$ = 3.40(1) Å, (N1)-H11···$Cl2^{ii}$ = 2.62(1) Å, N1−H11···$Cl2^{ii}$ = 152(1)°; N3···$Cl2^{iii}$ = 3.60(1) Å, (N3)H31···$Cl2^{iii}$ = 2.76(1) Å, N3−H31···$Cl2^{iii}$ = 169(1)°; ii = $-x, 1 - y, 1/2 + z$; iii = $1 - x, 1 - y, 2 + z$). Between piles there are weak intermolecular interactions involving hydrogen atoms of NH_2 and chlorine atoms (N2···$Cl1^{iv}$ = 3.31(1) Å, (N2)H22···$Cl1^{iv}$ = 2.55(1) Å, N2−H22···$Cl1^{iv}$ = 146(1)°; iv = $-1/2 + x, 1/2 - y, -1/2 + z$).

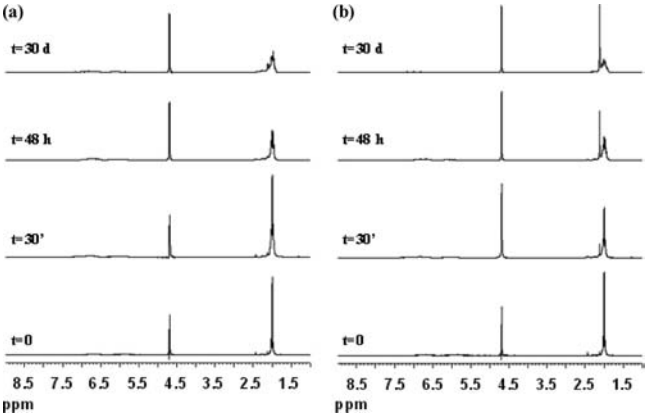

Figure 6. Sequential ^{1}H NMR spectra of *trans*-[$PtCl_2${HN=C(NH_2)CH_3}$_2$] in D_2O (13 mM) at 22 °C in anaerobic (a) and aerobic (b) conditions.

^{1}H NMR Investigation of *cis*- or *trans*-[$PtCl_2${Z-HN=C(NH_2)CH_3}$_2$] in Water or Methanol under Aerobic and Anaerobic Conditions. The obtainment of a platinum(III) species in water raises the question of which agent, present in the solvent, could be responsible for the oxidation of Pt^{II} to Pt^{III}.

To answer this question pure *trans*-[$PtCl_2${HN=C(NH_2)CH_3}$_2$] was dissolved in D_2O, and the solution divided in two portions. Argon was bubbled through one of them with the aim of removing the oxygen dissolved in the solvent, while oxygen was bubbled through the second solution. The transformations taking place in the two solutions were followed by acquisition of NMR spectra from time to time over a period of 1 month (Figure 6).

The solution kept under inert atmosphere showed only changes attributable to *cis*/*trans* isomerization and solvation processes (Figure 6a). In contrast, the second solution (the one treated with oxygen) showed, in addition to the *cis*/*trans* isomerization and solvation, also the appearance of a signal at 2.08 ppm characteristic of the methyl protons of compound **1** in water solution (Figure 6b).

Compound **1** is scantly soluble in water, and with time red crystals separate out. The reaction can be accelerated by heating to 60 °C as described in the Experimental Section. Rather facile oxidation of platinum(II) to platinum(IV) complexes in aqueous solutions and in the presence of oxygen has already been reported. For instance, oxidized Pt^{IV} species were detected by multinuclear NMR and ESI-MS techniques in a water solution of *trans*-[$PtCl_2(NH_3)$(*rac*-2-Me-butylamine)].[9] It was also reported that the oxidation of platinum(II) complexes

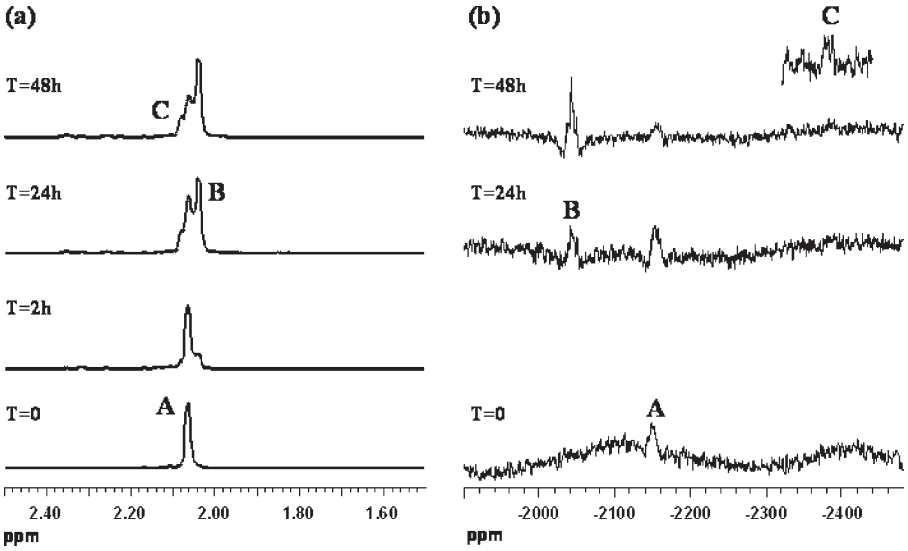

Figure 7. ^{1}H (a) and ^{195}Pt (b) NMR spectra of *cis*-[$PtCl_2${$HN{=}C(NH_2)CH_3$}$_2$], in methanol-d_4 (17 mM) and at 22 °C, taken at different time intervals.

can be triggered by hydrolysis of the Pt−Cl bond and that, in general, platinum(II) complexes with two am(m)ines and two hydroxo ligands are more easily oxidized than the corresponding dichlorido species.[31] A peculiar feature of our amidine complexes is that the oxidation process stops at the +3 oxidation state and does not proceed to the more common +4 state. This issue will be addressed in the discussion section.

We also noticed that in water solution the starting complexes undergo facile *cis*/*trans* isomerization. The isomerization process could be better investigated in anaerobic conditions where the oxidative pathway is ruled out; however, even in these conditions, the study is complicated by the occurrence of extensive solvolysis. Therefore, we decided to move to methanol which is quite similar to water, but its poorer coordinating ability reduces solvolysis. Therefore, pure *cis*-[$PtCl_2${$HN{=}C(NH_2)CH_3$}$_2$] was dissolved in methanol-d_4, and the solution monitored by ^{1}H and ^{195}Pt NMR spectroscopy. Figure 7 shows the spectra obtained at different time intervals. The initial *cis* complex (**A**) is converted within hours into another species (**B**) which becomes dominant after 24 h. We have identified **B** as the *trans* isomer. Moreover, the formation of a third species which reaches a steady state concentration (**C**) was clearly evident. The same transformations were confirmed by ^{195}Pt NMR spectroscopy (Figure 7). The initial signal at −2150 ppm, due to the *cis* isomer (**A**), is soon accompanied by a new signal at −2040 ppm, corresponding to the *trans* isomer (**B**), which grows and reaches a final *cis*/*trans* ratio of about 1:4. During this time a third species with a signal at −2377 ppm (**C**) is also present, the latter chemical shift is consistent with a platinum(II) having a N_3Cl set of donor atoms. We tried to better characterize the latter species; however, all the efforts have been so far unsuccessful. For longer time, green needles of compound **2** separate from the solution. The same results were obtained starting with the *trans* complex. In 3 days, the same equilibrium composition was obtained and, for longer time, green needles of compound **2** separated out. It is to be noted that compound **2** can also be obtained from water solution, but under strictly anaerobic conditions, while such stringent conditions are not required in methanol. A possible explanation for the different behaviors of water and methanol solutions is that platinum oxidation by oxygen is favored by solvolysis and methanol has poor solvolytic properties. For this reason methanol was used for preparing **2** in relevant amounts.

Study of the *cis*/*trans* Isomerization of the Amidine Complexes. The ready *cis*/*trans* isomerization observed in water or methanol does not occur in aprotic solvents. We wondered by which mechanism this process could take place.

In general, isomerization of 4-coordinate square-planar complexes takes place through an *associative* mechanism, which contemplates two consecutive steps (with ligands of each type entering and leaving the coordination shell) and requires a catalytic amount of free ligand.[32] Other two isomerization mechanisms are also possible: (i) a *dissociative* mechanism, observed in some special cases, which contemplates dissociation of one ligand (possibly assisted by loose association of a solvent molecule), isomerization of the T-shaped intermediate, and subsequent reassociation of the ligand dissociated in the first step;[33] (ii) a *photochemical* mechanism, observed in some cases under light irradiation, which does not contemplate dissociation and reassociation of ligands but passing through a tetrahedral transition state.[34] The latter two mechanisms are rare and take place only under special conditions.

The non-observation of easy *cis*/*trans* isomerization in the other imino-complexes investigated by us (iminoethers

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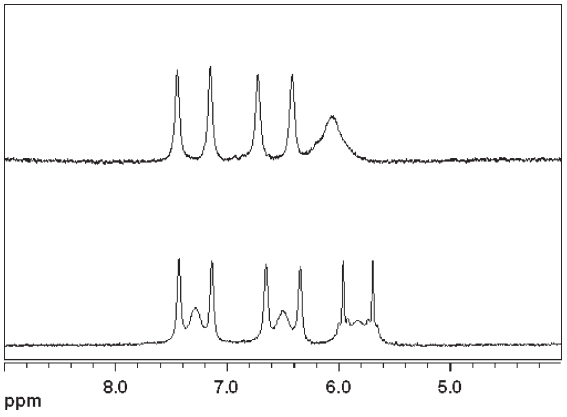

Figure 8. Detail of the ^{1}H NMR spectra of *cis*-[$PtCl_2${HN=C-($^{15}NH_2$)CH_3}$_2$] (above) and of the *trans* isomer (below) obtained by spontaneous isomerization of the *cis* isomer in acetone-d_6.

and ketimine derivatives) led us to hypothesize that the aminic residue could be involved in the process. Therefore, starting with a platinum-bonded amidine ^{15}N labeled at the $-NH_2$ residue, we hypothesized that the usual *cis*/*trans* isomerization process would not lead to scrambling of the ^{15}N between the $-NH_2$ and the $=NH$ sites. The ^{1}H NMR spectrum of the *cis*-[$PtCl_2${HN=C-($^{15}NH_2$)CH_3}$_2$] complex, ^{15}N-enriched solely to the NH_2 residue, is shown in Figure 8. The $^{15}NH_2$ proton signals (the two protons are not equivalent) are doublets due to $^{1}H-^{15}N$ coupling; in contrast, the signal that originates from the iminic proton bound to the ^{14}N atom, is a broad singlet. The *cis* compound is more soluble in methanol than the *trans* isomer; therefore, starting with a concentrated solution of the *cis* isomer, pale yellow crystals of the *trans* isomer soon separate from the solution. The crystals were collected and characterized by NMR spectroscopy and found to be the pure *trans* isomer, where all NH proton signals are due to the overlap of a doublet (presence of ^{15}N) and a broad singlet (presence of ^{14}N), indicating that, simultaneously to the isomerization, also a scrambling of ^{15}N between the aminic and the iminic sites has taken place. This conclusion was also supported by the ^{195}Pt NMR spectrum. In the case of two ^{14}N (nuclear spin = 1) coordinated to platinum, the resulting signal should be a quintet. The same signal would be a triplet in the case of two ^{15}N (nuclear spin = 1/2) coordinated to platinum. If instead one ^{14}N and one ^{15}N are coordinated to platinum, the result would be a doublet of triplets.[35] The platinum spectrum showed that the signal was a multiplet originated by the overlap of the three multiplets described above, confirming that the isomerization is accompanied by complete scrambling of the ^{15}N over the two N-sites of the amidine ligand.

A possible isomerization mechanism which involves coordination of the aminic nitrogen and can account for the scrambling of the ^{15}N is reported in Figure 9. It contemplates formation of an intermediate species with amidinato ligands bridging two metal centers. The propensity of ligands with multiple donor atoms (such as carboxilates, amidates, pyrophosphate, etc.) to bridge different metal atoms is well documented.[36] The overall process only requires that an amidine ligand coordinated to platinum through the iminic nitrogen uses the aminic nitrogen to bind a second metal atom (this step requires dissociation of a proton from the aminic nitrogen and displacement of a chlorido ligand from a complex molecule). After formation of the first bridge, a second bridge could be formed (compound **3**; doubly bridged Pt^{II} species are quite common with this type of ligands).[12,29a,37] Always with reference to Figure 9, the Cl^- released in the first step could react with **3** displacing a N-donor (possibly the nitrogen which suffers the strongest *trans* effect) and affording the *trans* isomer.

We noticed that, even in protic solvents, the isomerization, oligomerization, and oxidation reactions are prevented if free chloride is present (0.1 M). This is in accord with the mechanism proposed above since formation of **3** requires displacement of Cl^- from the starting mononuclear complex, and this reaction is obviously inhibited by the presence of excess Cl^-. A catalytic amount of chloride would instead favor a *cis*/*trans* isomerization taking place by the usual associative mechanism. Our hypothesis of a dimeric platinum(II) intermediate finds support also in the presence of a third signal (−2377 ppm), besides those attributable to the *cis* and *trans* isomers, in the ^{195}Pt NMR spectra of solutions of the dichlorido bisamidine compounds. Such a signal is very close to that at −2326 ppm found for the Pt2 atoms in complex **2**, and therefore consistent with a N_3Cl set of donor atoms around the metal center.

The hypothesis that the isomerization could take place through a binuclear intermediate with bridging amidinato ligands can also provide a straightforward explanation for the formation of a dinuclear Pt^{III} compound (**1**) under aerobic conditions and of a trinuclear Pt^{II} compound (**2**) under anaerobic conditions as it will be discussed in the following section.

Discussion

It is well documented that ligands with multiple donor atoms, but with a small bite, such as to prevent the formation of 5- or 6-membered chelate rings, have a propensity to bridge different metal cores and form polynuclear compounds. Platinum compounds have been widely investigated in this context with important contributions to the field of mixed valence compounds and molecular wires.[38] Amidine ligands fall in this category and, in the case presently investigated, have led to unexpectedly easy *cis*/*trans* isomerization, oligomerization, and oxidation to platinum(III). The formation of an intermediate dinuclear platinum(II) species with bridging amidinato ligands has been proposed. This was considered to be the key intermediate in a new reaction

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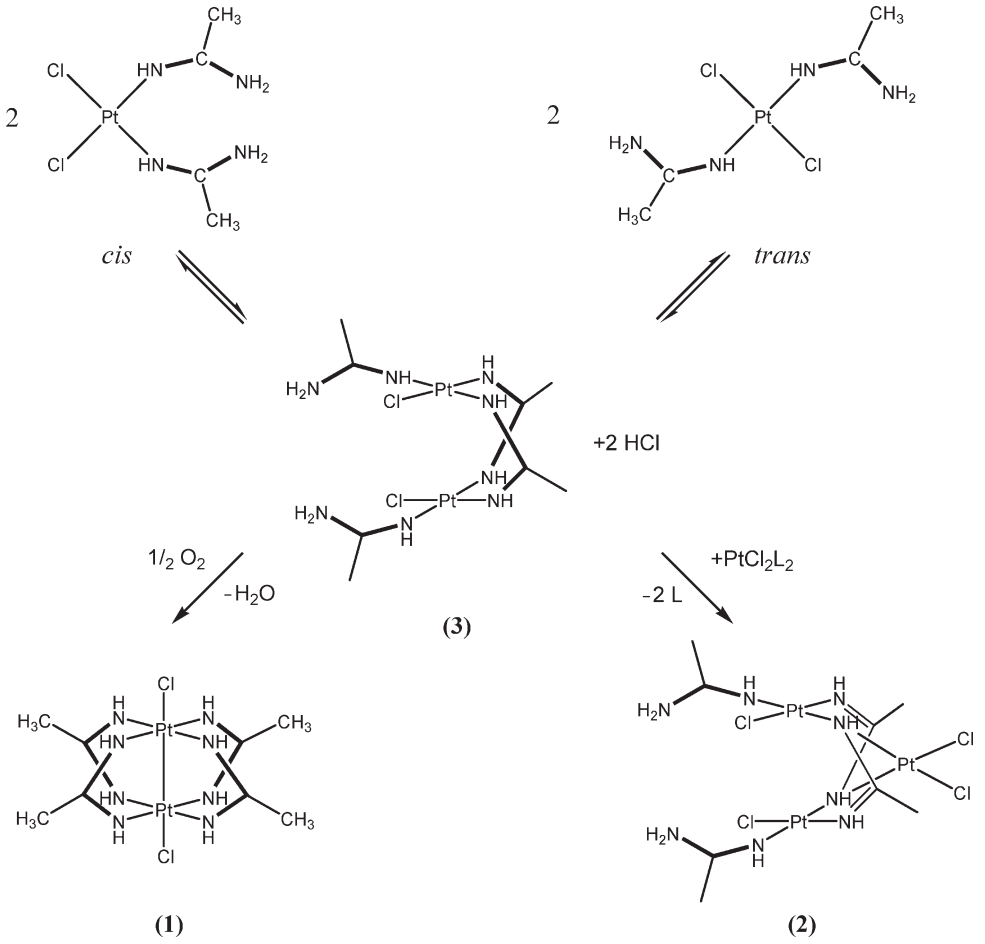

Figure 9. Overview of the processes occurring in solution. Greater thickness of the bond lines indicates π-bond delocalization. L = amidine.

pathway for *cis*/*trans* isomerization, and it will be worth looking to other examples where this mechanism could apply.

The same dinuclear platinum(II) species could also account for formation of the dinuclear platinum(III) species (**1**) under aerobic conditions and of the trinuclear platinum(II) compound (**2**) under anaerobic conditions.

It is known from literature that dimeric platinum(II) complexes with two bridging ligands are good precursors of platinum(III) species,[12] the oxidation being promoted by the closeness of the two metal centers fostered by the bridging ligands. The closer the two platinum atoms, the greater will be the overlap of the d_{z^2} orbitals. Thus a dimeric platinum(II) species with amidinato bridging ligands would be an ideal precursor for the formation of a Pt(III) complex under mild oxidative conditions. Apart from favoring the oxidation, the dimeric platinum(II) precursor could also account for the oxidation process stopping at the +3 stage and not proceeding to the +4 stage as usually occurs for monomeric platinum complexes.

The dimeric platinum(II) intermediate (**3**) can also account for the formation of compound **2**. If the oxidation is prevented by the absence of oxygen, the dinuclear intermediate can remain in solution until it reacts with another molecule of the starting mononuclear substrate yielding **2**. Compound **2** is sparingly soluble in water or methanol and this could be the driving force to its formation. The latter reaction has two unusual features: (i) the entering mononuclear substrate loses the two amidine ligands while keeping the two chlorides, usually the opposite trend is observed; (ii) in **3** the bridging amidinato ligands have a 4 electron π-system, delocalized over the N−C−N frame, lacking a free lone-pair suitable for coordination to an incoming metal center (Pt1). It is possible that the release of the amidine ligands is fostered by the small amount of HCl released in the dimerization reaction (Figure 9). Moreover, the ability of the bridging amidinato ligand to disengage a lone pair of electrons from the delocalized π-system and bind to a metal core (Pt1) indicates that the energy required for passing from a delocalized π-system to a limiting configuration with a lone-pair localized on one nitrogen and the second nitrogen π-bonded to carbon is not very high.

Unique features of compound **2** are also the large dihedral angle between the coordination planes of the two Pt2 units (53°), to be compared with an average value of 33° for platinum(II) dimers bridged by two amidinato or amidato ligands,[39] and a N−Pt···Pt−N torsion angle for the bridging amidinato ligands of about 38° while such an angle generally tends to be 0 so to allow full exploitation of the ligand bite. Both features originate from Pt1 cross-linking the aminic nitrogens of the two bridging amidinato ligands and reveal the large plasticity of this molecular edifice.

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This investigation has also highlighted different features of amidine and amidinato ligands. In the amidine ligand the $-NH_2$ nitrogen, similarly to the $=NH$ nitrogen, is hybridized sp^2; this allows formation of a 4-electron π-system extending over the N−C−N skeleton and results in two distinct ^1H resonances for the $-NH_2$ protons. Furthermore, the chemical shifts of the aminic protons are quite close to that of the iminic proton. When the amidine loses one proton from the $-NH_2$ group and acts as a bridging ligand between two metal units (this is the case of compound **1**), the resulting amidinato ligand is perfectly symmetrical and the 4-electron π-system remains essentially similar to that of amidines. A completely different case is that of a triply bridging amidinato ligand, as found in compound **2**. While one N terminus keeps the sp^2 hybridization (iminic nitrogen), the other N-terminus is hybridized sp^3. This has a dramatic effect on the chemical shifts of the two NH groups and on the lengths of the two C−N bonds. The iminic proton shifts about 3 ppm downfield, while the aminic proton shifts about 3 ppm upfield with respect to corresponding signals in monodentate amidine and bidentate amidinato ligands. The difference between the two C−N distances, that in monodentate amidine and bidentate amidinato ligands is $\leq$0.04 Å, becomes as large as 0.13 Å in full agreement with one C−N having single bond and the other C−N double bond character.[40]

Conclusions

The solution chemistry of *cis* and *trans* bis-acetamidine complexes of platinum appears to be dominated by the formation of a dinuclear complex which determines the rate of *cis*/*trans* isomerization, the oxidation to the not so common +3 state, and the formation of a trinuclear platinum(II) species featuring a chiral cage which could find applications in the field of host−guest chemistry and of catalysis as shown by other polynuclear complexes of platinum.[41,42]

In the present case the facile *cis*/*trans* isomerization was exploited for the preparation of the *trans* isomer. The direct synthesis of the *trans* isomer (by aminolysis of the *trans* bis-nitrile complex) is hampered by the simultaneous substitution of one chlorido ligand by the excess amine. Such a substitution does not take place in the case of the *cis* isomer because of the greater inertness of the chlorido ligands both *trans* to nitrogen donors.

The peculiar aqueous chemistry of amidine complexes here described should not represent an impediment to the biological exploitation of these complexes, since the described transformations are prevented if the starting compounds are dissolved in physiological solutions (100 mM NaCl concentration); moreover, inside the cell the drug concentration is expected to be sufficiently low to prevent formation of polynuclear species.

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Supporting Information Available: Additional information as noted in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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