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Platinum(II) Acetimino Cyclometalated Complexes Derived from Room Temperature Ammonia Activation

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Two Pt(II) rollover cyclometalated complexes, [Pt(bpy^{Ph}–H)(DMSO)Me] (**1**) and [Pt(bpy^{Ph}–H)(DMSO)Cl] (**2**), where bpy^{Ph}–H is the C_3-deprotonated 6-phenyl-2,2′-bipyridine, were reacted with aqueous ammonia in acetone at room temperature. In the case of the electron-poor complex **2** simple substitution of DMSO by NH_3 gave the amino complex [Pt(bpy^{Ph}–H)(NH_3)Cl] (**4**), whereas the electron-rich complex **1** produced the rare acetimine complex [Pt(bpy^{Ph}–H)(HN=CMe_2)Me] (**3**), which was isolated and characterized. Complex **3** is stable both in solution and in the solid state, in the presence of air and water. The result is noteworthy, as the condensation product of acetone and ammonia, acetimine, is not stable under mild conditions. The reaction likely requires a Pt(II) electron-rich complex and the presence of a carbon donor in *trans* position. An analogous reaction occurs with methylamine, allowing the synthesis of the secondary imine complex [Pt(bpy^{Ph}–H)(MeN=CMe_2)Me], **5**. Starting from this finding a series of cyclometalated acetimine complexes [Pt(N^C)(HN=CMe_2)Me] were isolated and characterized with other classical and rollover cyclometalated ligands with an array of different electronic and steric properties, indicating a possible extension of the reaction to various cyclometalated ligands. A preliminary study on the antimicrobial and antitumor properties of complex **3**, taken as a model for this class, showed no significant effects against Gram-positive, Gram-negative bacteria, or yeasts, but found activity in vitro against HT29 colon cancer cell line.

Introduction

Activation of small molecules is one of the most important topics in organometallic chemistry. This includes apolar or slightly polar molecules with multiple bonds, such as N_2, ethylene, CO or protic species, such as water or ammonia. Coordination of such species to a metal center usually results in an internal polarization and activation, leading to transformations usually not available for the free species.

Among the various species studied, water and ammonia play a particular role, being, *inter alia*, valuable sources for hydrogen and, especially for ammonia, useful precursors for organic derivatives. Condensation reaction of acetone and ammonia does not directly give the unstable and elusive acetimine.

Imines constitute an important class of intermediates in organic transformations.[1] N-substituted imines, *i.e.* secondary imines or Schiff bases, are generally fairly stable and may be used as ligands for coordination chemistry,[2] generating complexes with significant properties.[3] In contrast, the primary imine acetimine, HN=CMe_2, which is the simplest condensation product of ammonia and acetone, is not stable at room temperature, and rapidly decomposes to acetonine and ammonia.[4] The synthesis of acetimine requires harsh conditions and use of a catalyst,[5] but has vast interest due to the ample field of applications of acetone/ammonia condensation products.[6] Due to the difficult handling of acetimine under mild conditions, its coordination complexes are scarce and, to the best of our knowledge, none of them has been obtained by reaction of acetimine itself.

The few acetimine noble metals complexes reported in the literature were obtained following different procedures, such as starting from ammonia complexes in acetone or from solvato species in the presence of ammonia and acetone.

Vicente and coworkers reported the first gold acetimine complexes by reaction of several precursors, such as Au(acac)PPh_3 with $(NH_4)ClO_4$ in acetone at room temperature, or $[Au(NH_3)_2]^+$ with acetone. Successive oxidative addition reactions gave the corresponding Au(III) derivatives.[7] The same group obtained also the silver acetimine complexes [Ag(NH=CMe_2)$_2$]ClO_4, by reaction of $AgClO_4$ and NH_3 in acetone. Subsequent transmetalation reactions gave the first rhodium acetimine complexes.[8]

As for palladium, Ruiz reported a series of acetimine palladium(II) complexes, including the rare cyclometalated complexes $[Pd(N^C)(NH{=}CMe_2)_2]^+$ and $[Pd(N^C)(PPh_3)(NH{=}CMe_2)]^+$ by reaction of the corresponding

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solvato species with aqueous ammonia in acetone at room temperature.[9]

Also rare are platinum(II) acetimine complexes: in 2006 Natile and coworkers reported the synthesis the *cis* and *trans* isomers of $[PtX_2(NH{=}CMe_2)_2]$ and $[PtX_2(NH{=}CMe_2)(NH_3)]$ (X=Cl, I), starting from the corresponding platinum-ammine precursors by condensation with acetone. An important influence of the ligand in *trans* position was observed: the higher the *trans* effect of the ligand the easier the reaction to occur. The complexes showed antitumor activity and, in addition, the ability to circumvent, at least partially, cisplatin resistance.[10]

In the same year, Vicente and coworkers synthetized a series of Pt(II) and Pt(IV) acetimine complexes by transmetalation from previously the prepared gold and silver acetimine derivatives $[Ag(NH{=}CMe_2)_2]ClO_4$ and $[Au(NH{=}CMe_2)(PPh_3)]ClO_4$. Moreover, the study also allowed the isolation of the first heterodinuclear μ-acetimido complex.[11]

To the best of our knowledge, the only series of Pt(II) acetimino-cyclometalated complex appeared in the literature was reported in 2008 by Ruiz and coworkers, by reaction of cyclometalated complexes of 2-(dimethylaminomethyl)phenyl), after abstraction of the chloride ligand with a silver salt, in the presence of ammonia and acetone at room temperature.[12] Noteworthy, the new complexes showed a potent antitumor activity.

In the last years our interest has been focused on the chemistry of cyclometalated complexes of noble metals with nitrogen ligands: this family of organometallic compounds are characterized by a significant stability, due to the M(CN) chelation, and a variety of applications in different fields, from catalysis to biomedicine.[13,14] The studies have generated a series of subfamilies of complexes, such as the so-called pincer complexes,[15] carbene cyclometalates[16] and rollover derivatives,[17] with a great diversification of properties.

In a continuous effort to improve the comprehension of the chemistry of cyclometalated complexes we report here the results of our investigations on Pt(II) derivatives with ammonia, which produced a series of stable acetimine complexes [Pt(NC)(NHC=Me_2)Me], derived from room temperature activation of ammonia in the presence of acetone.

Results and Discussion

Among the vast series of different 2,2′-bipyridines, which have been described as "the most widely used ligands",[18] 6-phenyl-2,2′-bipyridine (bpy^{Ph}) revests a particular role, being a versatile ligand with a rich organometallic behavior. This ligand possesses several sites of potential C–H bond activation and has shown NNC,[19] NC[20] and bridging NC–CNC[21] coordination modes. Potential applications range from material chemistry to antitumor drugs.[22] Its behavior as a rollover ligand allowed the synthesis of the electron-rich Pt(II) complex **1**, [Pt(bpy^{Ph}–H)(DMSO)Me], and the analogous electron-poor chloride complex **2**, [Pt(bpy^{Ph}–H)(DMSO)Cl] (Chart 1).[23] The phenyl substituent plays an important role in the process of rollover C–H bond activation: we report here that the C–H activation process occurs even at room temperature, likely due to its moderately electron withdrawing properties, allowing an easy room-temperature cyclometalation to give the electron rich complex **1** starting from $[Pt(DMSO)_2Me_2]$.

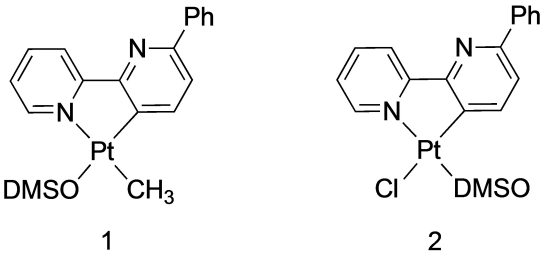


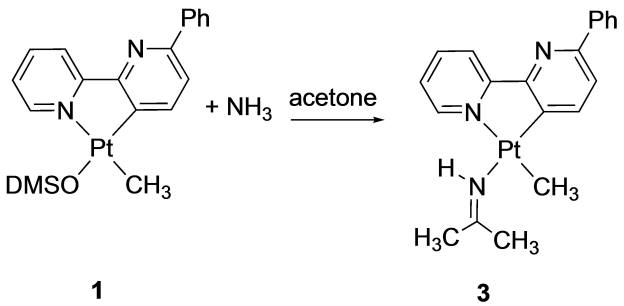
Chart 1. Starting complexes: the electron-rich rollover complex **1** and the electron-poor rollover complex **2**.

With the intention to obtain new ammino complexes under mild conditions we reacted complexes **1** and **2** with aqueous ammonia (30% v/v) in acetone at room temperature.

The reaction outcome of **1** with NH_3 gave an uncommon result: instead to simply substituting the labile DMSO ligand, ammonia reacted to give a complex with the rare acetimine ligand, [Pt(bpy^{Ph}–H)(HN=$C(CH_3)_2$)CH_3], **3** (Scheme 1).

The characterization of **3** was accomplished by several instrumental methods. The ^{1}H NMR spectrum in $CDCl_3$ shows the absence of the coordinated DMSO signal of **1**, at 3.26 ppm, and the appearance of two new singlets at 2.25 and 2.32 ppm, each corresponding to 3 protons, assignable to two acetimine methyls; one singlet with satellites, at δ 0.83 ppm (3H, J_{Pt-H} = 84.5 Hz), in line with a platinum-coordinated methyl, and, in addition, a broad singlet at 9.64 ppm (1H) identified as an acetimine hydrogen. This last signal is concentration dependent (ca 9.6–9.7 ppm) and disappears after addition of D_2O.

In view of the result of the reaction, with the aim of both identifying the product and understanding the reaction course, an in-depth study was undertaken by means of 1-D and 2-D NMR spectroscopy, including ^{13}C, H-H DQF COSY, H-H NOESY, H-C HMQC and HMBC spectra. The 2D COSY spectrum allowed to assign all the hydrogen signals, while the 2D NOESY spectrum showed interesting cross peaks (Figure 1). In particular, the spectrum revealed that the two imino methyls have different spatial interactions: the methyl at 2.32 ppm shows NOE contacts with the Pt-CH_3 (at 0.83 ppm) and the $H_{6'}$ protons



Scheme 1. Synthesis of complex **3.**

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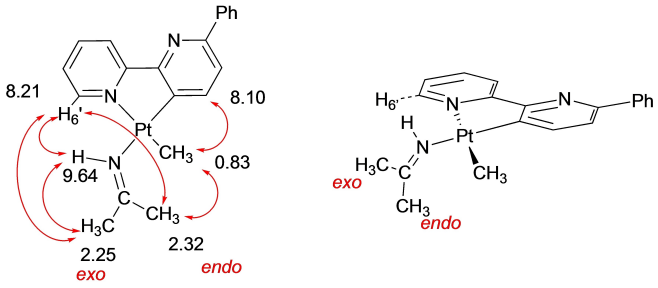

Figure 1. ^{1}H NOESY NMR contacts in **3.**

(at 8.21 ppm); at variance, the other imino methyl, at 2.25 ppm, shows NOESY cross peaks with the NH proton at 9.64 ppm, and a very small interaction with the $H_{6'}$. In addition, the NH proton shows contacts with the $H_{6'}$, the CH_3 at 2.25 ppm and the Pt-CH_3 protons.

Taken together, these data indicate that the methyl at 2.25 ppm seems to be much closer to the NH proton, while the methyl at 2.32 ppm seems much closer to the H6′. Of the two acetimine methyl signals, then, only the one at 2.32 ppm shows a cross peak with the coordinated methyl. The coordinated methyl also shows, as expected, a cross peak with the signal at 8.10 ppm (H_4).

All these signals account for the formulation given in Figure 1, with the acetimino HN=CMe_2 ligand coordinated in *trans* to the cyclometalated sp^2 carbon. Taken together, these data indicate a coordination of acetimine perpendicular to the coordination plane, with the imine methyl at 2.32 in *endo* position respect to the metal (and *trans* to the NH proton), and the other methyl at 2.25 in *exo* position (*cis* to NH, see Figure 1). The N=C double bond should also be responsible for the shielded position of the H6′ proton, at 8.21 ppm, often located beyond 9 ppm after coordination.

The ^{13}C NMR spectrum, together with two-dimensional HMBC and HMQC spectra, agrees with this formulation, showing the signals of the platinum-coordinated methyl at −18.29 ppm ($J_{Pt\text{-}C}$ = ca 800 Hz) and the two imino methyls at 26.61 and 30.46 ppm (correlated with the signals at 2.32 and 2.25 ppm, respectively, in the ^{1}H NMR spectrum). The spectrum also shows a signal at 181.96 ppm, which can be attributed to a nitrogen-bound sp^2 quaternary carbon (C=N). In the HMBC this signal correlates "long-range" with the two methyls in the proton spectrum at 2.25 and 2.32 ppm. In addition, a long-range correlation is also present between the NH proton in the ^{1}H spectrum and the imino methyls at 26.61 and 30.46 ppm in the ^{13}C spectrum.

Furthermore, the cyclometalated carbon (C_3) resonates at 150.53 ppm. The C=N double bond is confirmed by the FT-IR spectrum, which shows a band at 1606 cm^{-1} (C=N stretching).

Finally, high resolution mass spectrum shows the $[M+H]^+$ peak at *m/z* 499.14749 ($C_{20}H_{22}N_3Pt$). MS/MS spectrum shows additional peaks at 483.11457 ($C_{19}H_{18}N_3Pt$) and 442.08779 ($C_{17}H_{15}N_2Pt$) due to loss of methane and acetimine respectively.

The reaction was carried out under different experimental conditions, such as refluxing acetone, also using ammonium chloride in place of ammonia, always obtaining the same result. The reaction outcome is interesting: free acetimine is unstable at room temperature, especially in the presence of water, and it can be obtained by reaction of acetone and ammonia only at high temperature under high pressure, in the presence of a catalyst.

The formation of acetimine at room temperature is therefore attributable to the presence of the platinum complex. A search in the literature (reaxys.com) showed that imine complexes of this type are extremely rare,[12] and only a few examples of imine platinum cyclometalated complexes have been reported. Natile and co-workers have shown that *cis*- and *trans*-[PtX_2(HN=$C(CH_3)_2$)] (X=Cl, I) complexes are formed by reaction of the corresponding amine complexes with acetone. The reaction in some cases requires the presence of a base.[10]

In order to shed light into some aspects of the reaction, the behavior of **1** under different experimental conditions was studied. In the absence of acetone, the reaction of **1** with aqueous ammonia was followed by NMR in deuterated methanol. Under this experimental condition, coordinated DMSO was displaced, likely by the solvent. Even reproducing the reaction in non-deuterated methanol we were not able to isolate and characterize the product, which may be an unstable solvato species [Pt(NC)(S)Me], with S=NH_3, H_2O or MeOH, or a mixture of species.

When complex **1** is solubilized in aqueous acetone, under the same experimental conditions used for the synthesis of **3**, in absence of NH_3, no reaction was observed, indicating that both acetone and water do not react with the complex. Furthermore, when the electron-rich precursor [$Pt(DMSO)_2Me_2$] is reacted with aqueous ammonia in acetone no acetimine complex is formed, indicating that the presence of an NC cyclometalated complex is needed for the acetone/ammonia condensation reaction.

The mediation of the platinum center is not easily clarified. In the absence of further experimental data the mechanism of the reaction might only be speculated.

On the basis of the few literature precedents, we may suggest two possible reaction mechanisms. As suggested by Natile and coworkers[10] the acidity of coordinated ammonia is enhanced by coordination to a metal center so that a small quantity of coordinated Pt–NH_2 may exist in equilibrium with Pt–NH_3 (equilibrium A*char*/0*xEB*02*notimplemented*B, Scheme 2, path a). Condensation reaction with acetone, likely assisted by a molecule of water, finally generates complex **3**.

An alternative explanation is reported by Ruiz and co-workers in the synthesis of palladium(II) acetimine complexes (Scheme 2, path b):[10] the reaction between acetone and ammonia at room temperature could lead to an equilibrium with the formation of a small amount of free acetimine which is trapped and stabilized by coordination. Acetimine coordination also shifts the equilibrium leading to the formation of the final product. A third possibility, which cannot be completely ruled out, may consist in a first coordination of acetone in place of DMSO, with subsequent nucleophilic attack of free ammonia and final condensation reaction.

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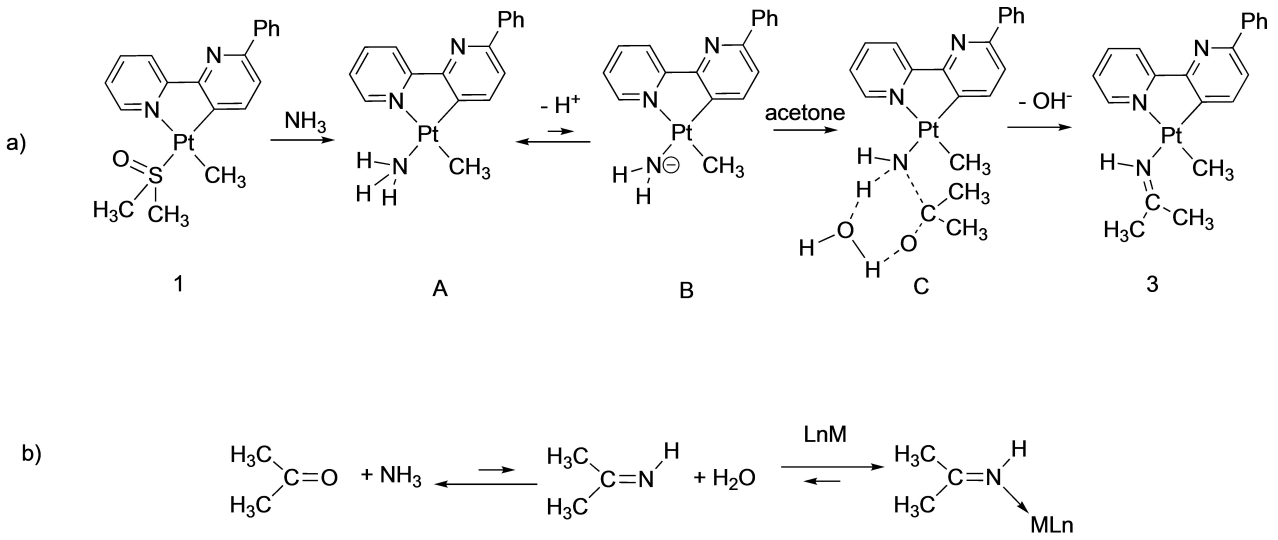

Scheme 2. Possible explanations on acetimine formation and coordination, as suggested by Natile *et al* (a)[10] and Ruiz *et al* (b).[12]

An important role may be played by the cyclometalated carbon atom in *trans* to the imine ligand, as reported by Natile and coworkers, who found that ligands with strong *trans* effect may have a role in favoring the acetimine formation and coordination.

The result is certainly interesting as imine complexes of transition metals have shown considerable anti-cancer activity in the past.[10]

Antitumor and Antimicrobial Preliminary Study

Organometallic drugs are considered a promising alternative in medicinal chemistry and several Pt(II) complexes are currently under consideration for their potential anticancer and antimicrobial properties. In particular, the few Pt(II) acetimino complex reported in the literature showed an interesting antitumor activity.[10,12]

For these reason we have tested this new platinum acetimino cyclometilated complex in vitro using the HT29 colon cancer cell line. Commercial human cell line HT29 (ATCC-HTPS://www.atcc.org), were obtained from the Istituto Nazionale per la Ricerca sul Cancro c/o CBA (ICLC, Genova). Confluent HT29 cells were isolated using trypsin/EDTA and 2–3×10^4 cells/cm^2 were plated with a mixture of MEM (EBSS), 10% fetal bovine serum (FBS), 100 units/ml penicillin, 100 μg/ml streptomycin, 2 mM L-Glutamine, 1% non-essential amino acids. Different amount of metal compound were added and after 24 hrs the MTT viability test was performed using the Cell proliferation Kit I (MTT), Roche REF number 11465007001. The results showed that increasing administration of this compound in vitro inhibits cell growth (see Figure 2)

This study also evaluated complex **3**'s antimicrobial properties against a range of bacteria and yeasts. These microorganisms belonged to the German Collection of Microorganisms and Cell Cultures GmbH, DSMZ, and they included: (i) the

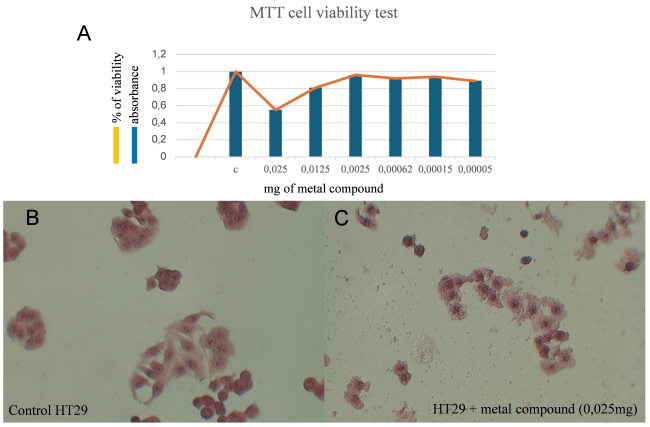

Figure 2. HT29 cell line was used in order to test the in vitro effect of metal compound administration. A) MTT test, B) hematoxylin-eosin stain of non treated HT29 cells, C) hematoxylin-eosin stain of treated HT29 cells.

Gram-positives group, *Streptococcus aureus* DSM 1104, *Streptococcus pyogenes* DSM 20565; (ii) the Gram-negatives group, *Escherichia coli* DSM 1103, *Klebsiella pneumoniae* DSM 681; and *Pseudomonas aeruginosa* DSM 1117. (iii) Yeasts: *C. albicans* DSM 1386; *C. krusei* DSM 70075; and *Candida glabrata* DSM 6425. The antimicrobial profile for each strain was evaluated by using the Kirby-Bauer method following a modified procedure based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) protocol. In brief, for each microbial strain a microbial suspension equal to 5*10^7/mL CFUs was inoculated in a Petri dish contained 15 mL of: Muller Hinton agar for bacteria strains and Sabouraud agar for yeasts. 50 mL of compound suspension was added to the plate in a well performed in the agar surface. The presence of an inhibition diameter in mm was evaluated after 30 hours of incubation at 37 °C in air for bacterial strains or with 5% CO_2 for yeasts.

The result (Table 1) showed that Complex **3** did not display any antibacterial activity, this result could be due to a diffusion or interaction problem with microbial cell wall, in fact, by

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Table 1. Antimicrobial profile for Pt(bpy^{Ph}–H)(HN=CMe$_2$)Me] with a set of Gram-positive, Gram-negative bacteria and Yeast.

Strain	[Pt(bpyPh–H)(HN=CMe2)Me]	Control
Gram negative		
E. coli	0.0 ± 0.0	Amp. 19.6 ± 0.7
K.pneumoniae	0.0 ± 0.0	Amp. 9.5 ± 0.8
P. aeruginosa	0.0 ± 0.0	Rif. 12.1 ± 0.5
Gram positive		
S. aureus	0.0 ± 0.0	Ox. 22.6 ± 1.5
S. pyogenes	0.0 ± 0.0	Amx 22.6 ± 1.5
Yeast		
C.albicans	0.0 ± 0.0	
C. krusei	0.0 ± 0.0	
C. glabrata	0.0 ± 0.0	

Legend: Legend: Amp = ampicillin; Ox = oxacillin; Rif = rifampin; Amx = amoxicillin.

considering the bacteria this structure containing peptidoglycan, which is rich in carboxyl and amino groups, most bacterial cells have a net negative charge at neutral pH. The negative charge on bacterial cell walls is also a result of phosphate-rich components found in teichoic acids. In the same way, Complex **3** could mainly exhibit the negative motif on part of the molecule surface, with a final repulsive force between these structures. By considering yeasts, its wall is a complicated network of biomolecules, phosphate and carboxyl groups which cause the surface to be negatively charged, with the same effects on the Complex **3**.

Electrochemical Behavior of 3

The electrochemistry of [Pt(bpy^{Ph}–H)(DMSO)Me] (**1**) and [Pt(bpy^{Ph}–H)(HN=CMe$_2$)Me] (**3**) has been investigated by cyclic voltammetry (Figure 3). The voltammetric response of complex **1** shows only one anodic process at 1.24 V, whereas two anodic processes are observed for complex **3**, located at 0.65 V and 1.08 V, respectively. In both cases, the processes appear irreversible in the timescale of the voltammetric experiment. The shape of the responses and the peak potential values, as well as the comparison between the parent complex **1** and the imine derivative **3** suggest to assign the process at 0.65 V of **3** to the imine ligand. On the other hand, the processes at 1.24 V (complex **1**) and 1.08 V (complex **3**) are reasonably due to a mixed involvement of the metal center and of the bpy-H ligand, as suggested from the comparison with [Pt(bpy–H)(Me)(L)] derivatives previously reported.[24,25] The irreversible behavior of this charge-transfer process is generally imputable to the low stability of the formally Pt(III) species resulting from the oxidation of the electroactive Pt(II) complex. As for the less anodic process in complex **3**, its irreversibility can be ascribed to the happening of a chemical reaction following the charge transfer. Experiments at increasing potential scan rates (from 0.02 V s^{-1} to 500 V s^{-1}) have been also performed, evidencing an increase of peak current with the scan rate. The resulting peak-current *vs* scan-rate square root curves show a linear fitting, suggesting electrode processes under diffusion control. Finally, the shift from 1.24 V (complex **1**) to 1.08 V (complex **3**) of the metal-centered process suggests a significative electron-donating effect of the imine ligand on the metal center.

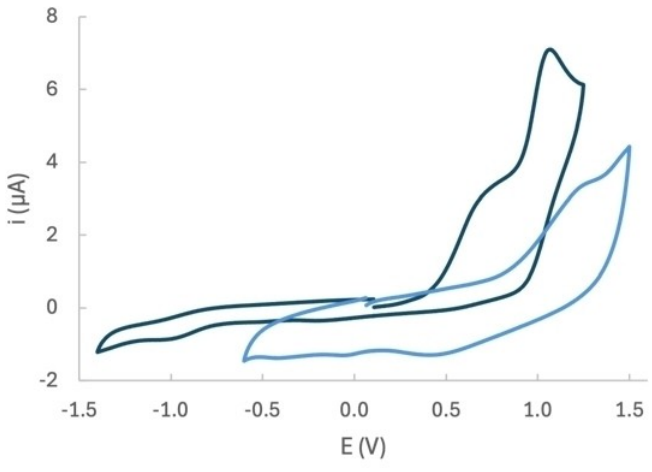

Figure 3. Cyclic voltammetry response of **1** (light blue) and **3** (dark blue) in CH_2Cl_2/TBAPF$_6$ 0.1 M. Potential scan rate: 100 mV s^{-1}.

In contrast with the behavior of complex **1**, the analogous reaction of complex **2** with ammonia gave the corresponding amino complex [Pt(bpy^{Ph}–H)(NH$_3$)Cl], **4**, after substitution of the labile DMSO ligand with ammonia. Even under different experimental conditions the same result was obtained, indicating the role of the anionic ligand (CH_3 in **1** *vs* Cl in **2**) on the reaction outcome. It is worth to remind that, due to the different donor properties of the two anionic ligands complexes **1** and **2** exist as different stereoisomers, *trans* C–Pt–S for **1** and *trans* N–Pt–S for **2**. For this reason, the different *trans* effect and influence of the C(sp^2) in **1** *vs* the N(sp^2) in **2** probably plays an important role in the reaction outcome.

Complex **4** was characterized on the basis of NMR spectroscopy and HRMS. The ^{1}H NMR spectrum shows a broad signal at 4.22 ppm, corresponding to three hydrogens, attributable to a coordinated ammonia molecule. The signal disappears after addition of D_2O to the solution. The ^{1}H NMR spectrum also shows a strongly deshielded signal, at 9.48 ppm, related to the H$^{6'}$ proton. The signal shift is typical of cyclometalated complexes with chlorides coordinated in the cis-position to a pyridine ring, and is due to a well-known through-space effect of the nearby halogen.[26] As usual for chloride rollover complexes only one isomer is observed in solution, *i.e.* the Cl-*trans*-C(sp^2) isomer (Scheme 3).

Complexes like **4**, with a formulation [Pt(NC)(NH$_3$)Cl], may be of interest, as the presence of the NH$_3$ and Cl ligands could allow the formation of interesting intermolecular interactions, as reported by Rourke and coworkers for the [Pt(NC)(NH$_3$)Cl] complex derived from 2(4-fluorophenyl)pyridine.[27] The X-ray structure of this latter complex showed the presence of chains of parallel molecules of complexes, with each successive molecule in the chain rotated by 180°, leading to an alternating pattern of chloride and amine. This sequence was stabilized by

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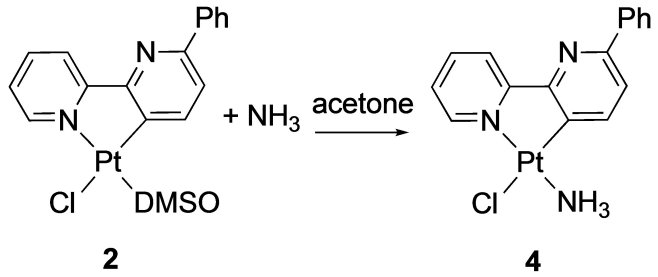


2 **4**

Scheme 3. Synthesis of complex **4**.

NH_3–Cl intermolecular interactions, due to N–H–Cl hydrogen bonds, as well as by Pt–Pt interactions, allowing chains with almost linear Pt–Pt sequences (Pt–Pt–Pt angles of 176.68○, Pt–Pt distances of 3.3634(3) Å). Further stabilization came from p-stacking of the aromatic rings.

The HRMS spectrum of **4** is in agreement with the proposed formulation, showing a peak at m/z 443.08264, corresponding to loss of chloride $[M-Cl]^+$ ($C_{16}H_{14}N_3Pt$). A second peak at m/z 484.10953 corresponds to $[M-Cl+CH_3CN]^+$ ($C_{18}H_{17}N_4Pt$).

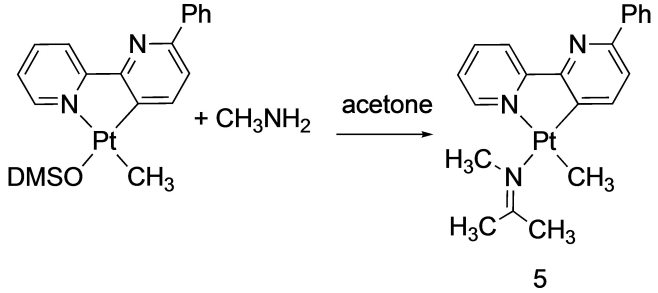
The different behavior of complexes **1** and **2** towards ammonia and acetone are connected with the different *trans* influence of carbon and nitrogen: in complex **1** the labile DMSO ligand is coordinated *trans* to a Csp^2 atom, whereas in complex **2** a *trans* Nsp^2 is observed. In addition, the electron richness of complex **1** may also play a role in the ammonia activation.

Extendibility of Imine Synthesis

The synthesis of imines is a problematic task: this fact, added to the formation of the rare cyclometalated acetimine complex **3** prompted us to investigate the extendibility of the reaction to different amines or cyclometalates.

As for the amine, we studied the behavior of methylamine with complex **1**, under the same experimental conditions used for ammonia.

The reaction, performed with aqueous methylamine in acetone gave with high yields (ca 80%) the imine complex [Pt(bpy^{Ph}–H)(MeN=CMe$_2$)Me], **5**, analogous to **3** (Scheme 4). The same result was obtained both at room temperature and in refluxing acetone. The ^{1}H NMR spectrum of **5** shows three



5

Scheme 4. Synthesis of complex **5**

different methyl groups, in addition to coordinated one (at 0.86 ppm, J_{Pt-H} = 84.9 Hz): 3.62 ppm (J_{Pt-H} = 19.7 ppm), 2.66 and 2.19 ppm. Two-dimensional NMR spectra (H-H COSY and NOESY, H-C HSQC and HMBC) allowed the assignment of most of the proton signals.

As for the cyclometalated ligand, we investigated the reaction with ammonia and acetone using a series of rollover cyclometalated [Pt(N^C)(DMSO)Me] complexes, derived from an array of ligands with different electronic and steric properties: the chosen ligands where the unsubstituted 2,2′-bipyridine (bpy), 2-pyridylquinoline (pyqui), 2,2′-bipyridine-N-oxide (bpy^{NO}) (see chart 2). In addition, in order to verify the behavior of a classical cyclometalated complex, the reaction of the corresponding complex with 2-phenylpyridine (Phpy) was studied.

In this way we would be able to compare cyclometalated complexes with different donor properties, with 2-phenylpyridine as the better donor, and 2,2′-bipyridine-N-oxide as the less donating ligand.

The rollover complexes [Pt(bpy–H)(DMSO)Me], **6**; [Pt(pyqui–H)(DMSO)Me], **7**; [Pt(bpy^{NO}–H)(DMSO)Me] **8**; [Pt(Phpy–H)(DMSO)Me], **9**, synthesized according to literature data,[25,28–30] were reacted with NH_3 in acetone under the same conditions followed for complex **1**.

The study showed that the complexes **6**–**9** react similarly to **1**, with, however, some important differences. A first difference is the elevated solubility of the obtained complexes, which makes it difficult to isolate the pure acetimino complex in the solid state. Thus, we were able to isolate as a pure compound in the solid state the complexes [Pt(bpy–H)(HN=C(CH$_3$)$_2$)CH$_3$], **10**, [Pt(pyqui–H)(HN=C(CH$_3$)$_2$)CH$_3$], **11**, [Pt(bpy^{NO}–H)(HN=C(CH$_3$)$_2$)CH$_3$], **12**, and [Pt(Phpy–H)(HN=C(CH$_3$)$_2$)CH$_3$], **13**; but only with scarce yields. The effective yields are higher, but the presence of minor secondary products, combined with the high solubility of the complexes reduced the amount of isolated pure compounds. Due to its high solubility, complex **10** was isolated with some impurities. Characterization of the acetimino complexes **10**–**13** is based on their ^{1}H NMR spectra, all exhibiting the same characteristic signals found in complex **3**, *i.e.*, a broad N–H signal between 9 and 10 ppm, with a shift variable with concentration, the coordinated methyl, close to 1 ppm, with a coupling constant with ^{195}Pt of about 84 Hz, and two singlets due to the imino methyls in the 2.20–2.40 ppm region.

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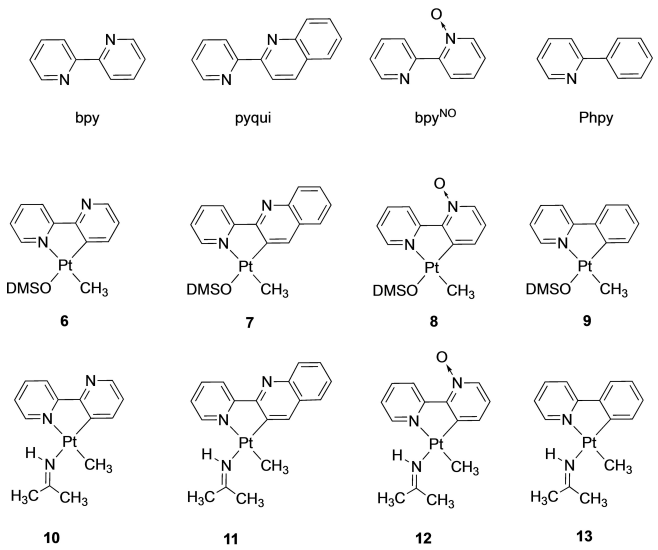

Chart 2. Other ligands used 2,2′-bipyridine (bpy), 2-pyridylquinoline (pyqui), 2,2′-bipyridine-N-oxide (bpy^{NO}), 2-phenylpyridine (Phpy) (above); DMSO-rollover complexes 6–9 (middle); acetimine-rollover complexes 10–13 (below).

The reaction outcome, however, is not so obvious and predictable: when the reaction is performed with the [Pt(NC)(DMSO)Me] rollover complex of the electron-rich 6-ethyl-2,2′-bipyridine (bpy^{et}), the process follows a more complex course: it is indeed possible to identify the acetimine complex [Pt(bpy^{et}–H)(HN=C(CH$_3$)$_2$)CH$_3$], **14**, among the products, but the yield is very low. In this case, only a mixture of products is obtained, from which the desired product could not be isolated.

It is therefore evident that small electronic and steric differences in the nature of the cyclometalated complex can influence the course and result of the reaction even considerably.

Conclusions

The participation of imines in several synthetic processes, such as functional group transformations or carbon–carbon bond formation, makes them important intermediates in synthesis. In contrast to secondary imines, which are generally stable and serve as ligands in numerous metal complexes, NH primary dialkyl imines, such as acetimine, are unstable compounds that need to be trapped in some way to reach stability. For this reason, some acetimine complexes have been reported in the literature, even though in a scarce number, and one of them has been obtained by direct coordination of free imine.

In this paper we have shown that electron-rich cyclometalated Pt(II) complexes are able to mediate the condensation reaction of ammonia with acetone, stabilizing the formed acetimine through coordination to give a new series of acetimine complexes. A preliminary study on the antimicrobial and antitumor properties of complex **3**, taken as a model for this class of cyclometalated acetimine complexes, showed no significant effects against Gram-positive, Gram-negative bacteria, or yeasts, but revealed activity in vitro against HT29 colon cancer cell line.

In conclusion, the chemistry of platinum(II) acetimino complexes is an almost unexplored field, although it may be of considerable interest due to difficulty to obtain and coordinate acetimine and to the potential applications of these complexes. For this reason, the preparation of the imine cyclometalated complexes reported in this work represents a starting point for a systematic study of these species.

Experimental Section

All the solvents were purified and dried according to standard procedures. The ligands 6-phenyl-2,2′-bipyridine, 2-pyridylquinoline and 6-ethyl-2,2′-bipyridine were synthesized according to previously published procedures.[24,29,31] The complexes *cis*-[PtCl$_2$(DMSO)$_2$], *cis*-[Pt(DMSO)$_2$Me$_2$],[32] **1**, **2**, **6**, **7**, **8** and **9** were synthesized as previously or elsewhere described.[25,28–30] The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance III 400 spectrometer operating at 400.1 and 100.6 MHz, respectively. Chemical shifts were given in ppm relative to TMS. 2d-NMR spectra (DQF-COSY, NOESY, HSQC e HMBC) were performed by means of standard pulse sequences.

Electrochemical investigation was performed under argon atmosphere in a three-electrode, single compartment cell, with an AUTOLAB PGSTAT12 instrument interfaced with a PC, with the specific software NOVA 2.1. A 2 mm diameter Pt disk was used as the working electrode, Ag/AgCl with a suitable salt bridge as the reference electrode, and a platinum wire as the auxiliary electrode. Before each experiment, the working electrode was polished with 1 and 0.3 μm alumina powder, then rinsed with distilled water. All the experiments were carried out in CH_2Cl_2 (Aldrich, anhydrous, ≥99.8%, packaged under nitrogen) as solvent, using 0.1 M tetrabutylammonium hexafluorophosphate ($TBAPF_6$) as supporting electrolyte, at a potential scan rate equal to 100 mV s^{-1}. The concentration of the complex was 1.0×10^{-3} M. All potential values are reported against Ag/AgCl.

The HRMS spectra were acquired on a Thermo Finnigan Q Exactive instrument with API-HESI source. Samples were introduced as 0.1 mg/L solutions in a mixture of MS grade methanol and acetonitrile.

Cell Culture

Commercial human cell line Ht29 (ATCC-HTPS://wwwatcc.org), were obtained from the Istituto Nazionale per la Ricerca sul Cancro c/o CBA (ICLC, Genova). Confluent HT″) cells were isolated using trypsin/EDTA and $2–3\times10^4$ cells/cm^2 were plated with a mixture of MEM (EBSS), 10% fetal bovine serum (FBS), 100 units/ml penicillin, 100 μg/ml streptomycin, 2 mM L-Glutamine, 1% non-essential amino acids. Different amount of metal compound were added and after 24 hrs the MTT viability test was performed using the Cell proliferation Kit I (MTT), Roche REF number 11465007001.

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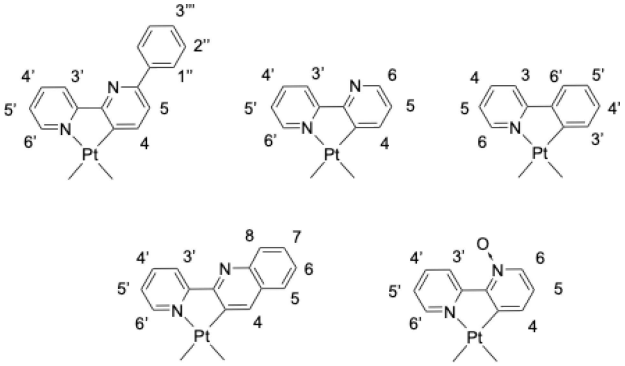
Numerical Scheme used in the NMR Characterization



Synthesis of [Pt(bipy^{Ph}–H)(HN=C(CH$_3$)$_2$)Me], 3

Method A. To a stirred solution of [Pt(bpy^{Ph}–H)(DMSO)Me], **1**, (100.0 mg, 0.1924 mmol) in acetone (20 mL) was added 200 μL of 30% v/v aqueous solution of NH_3. The solution was stirred at room temperature for 6 h, then it was concentrated to small volume and treated with diethyl ether, to give a precipitate that was filtered off and washed with diethyl ether to give the analytical sample. Yield: 65%.

Method B. To a stirred solution of [Pt(DMSO)$_2$Me$_2$] (119.3 mg, 0.313 mmol) in acetone (20 mL) was added 6-phenyl-2,2′bipyridine (75.0 mg, 0.323 mmol). The solution was stirred under argon atmosphere and heated to 60 °C for 3 h 30′. Then it was added 30% v/v aqueous solution of NH_3 (200 μL). The solution was stirred at room temperature for 25 h, then it was concentrated to a small volume and treated with diethyl ether, then it was filtered off and washed with diethyl ether. Yield: 55%.

Method C. To a stirred solution of [Pt(bpy^{Ph}–H)(DMSO)Me] (50.3 mg, 0.0968 mmol) in acetone (20 mL) was added NH_4Cl (10.8 mg, 0.2019 mmol) and 30% v/v aqueous solution of NH_3 (100 μL). The solution was stirred at room temperature for 5 h, then it was concentrated to a small volume and treated with diethyl ether; the precipitate formed was filtered off and washed with diethyl ether. Yield: 38%.

M.p. 216–220 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) = 9.66 (s, 1H, NH) 8.41 (d, 1H, J = 8.0 Hz, H3′) 8.19 (d, 1H, J = 5.5 Hz, H6′) 8.13 (m, 2H, H2″) 8.11 (d with sat, 1H, J_{Pt-H} = 57.4 Hz, H4) 7.89 (t, 1H, J = 7.6 Hz, H4′) 7.55 (d with sat, 1H, J_{H-H} = 7.9 Hz, J_{Pt-H} = 14.5 Hz, H5) 7.44 (t, 2H, J = 7.3 Hz, H3″) 7.36 (m, 1H, H4″) 7.16 (t, 1H, J = 6.5 Hz, H5′) 2.32 (s, 3H, CH_3) 2.25 (s, 3H, CH_3) 0.83 (s with sat, 3H, J_{Pt-H} = 84.5 Hz, Pt-CH_3). The signal at 9.66 ppm disappears after addition of a drop of D_2O.

^{13}C NMR ($CDCl_3$) ^{1}H NMR ($CDCl_3$): δ (ppm) −18.29 (Pt-CH_3), 26.61 (C=CH_3, corr. methyl at 2.32 ppm), 30.45 (C=CH_3 corr. methyl at 2.25 ppm), 120.83 (C5), 121.46 (C3′), 123.85 (C5′), 126.15 (C2″), 127.69 (C4″), 128.55 (C3″), 137.36 (C4′), 139.92 (C1″), 140.65 (C6), 141.47 (C4), 146.01 (C6′), 150.52 (C_3-Pt), 163.50 (C2′), 164.50 (C2), 181.96 (C=N).

Assignments based on H-H DQ-COSY, H-H NOESY, H-C HSQC and H-C HBQC.

Notable cross-peaks in the NMR NOESY spectrum: δ 0.83 ppm: cross peaks with 2.32 (CH_3), 8.10 (H4), 9.64 (NH); weak cross peak with 2.25 (CH_3); δ 2.25 ppm: cross peaks with 9.64 (NH, strong), 8.22 (H6′, weak); δ 2.32 ppm: cross peaks with 9.64 (very high), 8.22 (H6′, strong), 0.83 (Pt-CH_3, strong); δ 9.60 ppm: cross peaks with 8.22 (H6′); 2.25 (CH_3, very strong), 0.83 (Pt-CH_3, weak). IR (nujol, cm^{-1}): 1606 m, 752 m, 690 m. HRMS (ESI) *m/z* calculated for $C_{20}H_{22}N_3Pt$: 499.14578 $[M+H]^+$; found: 499.14749.

Synthesis of [Pt(bipy^{Ph}–H)(NH$_3$)Cl], 4

To a stirred solution of [Pt(bpy^{Ph}–H)(DMSO)Cl] (50.3 mg 0.0932 mmol) in acetone (20 mL) was added 30% v/v aqueous solution of NH_3 (200 μL). The solution was stirred and heated to 50 °C for 6 h 30′, then it was concentrated to a small volume and treated with diethyl ether, then it was filtered off and washed with diethyl ether. Yield: 60%. M.p. > 260 °C. ^{1}H NMR ($CDCl_3$, MM15): δ (ppm) = 9.48 (d, 1H, J = 6.2 Hz, H6′) 8.12 (d, 1H, J = 7.8 Hz, H3′); 8.06 (d, 2H, J = 8.2 Hz, H2″); 8.02 (t, 1H, J = 7.9 Hz, H4′); 7.64 (d, 1H, J = 8.5 Hz, H5); 7.49 (d with sat, 1H, J = 7.9 Hz, H4), 7.34 (m, 3H, H3″ + H5′) 7.27 (m, 1H, H4″) 4.22 (s, 3H, NH_3). HRMS (ESI) *m/z* calculated for $C_{16}H_{14}N_3Pt$: 443.08314 $[M-Cl]^+$; found: 443.08264 ; calculated for $C_{18}H_{17}N_4Pt$: 484.10976 $[M-Cl+CH_3CN]^+$; found: 484.10953.

Synthesis of [Pt(bpy^{Ph}–H)(MeN=CMe$_2$)Me], 5

The reaction was carried out at room temperature following the same procedure used for **3**, reacting aqueous methylamine in place of ammonia. Yield 80%. M.p. = 180–184 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) = 8.44 (d, 1H, J = 8.0 Hz, H3′); 8.20–8.02 (m, 4H, H6′-H2″-H4); 7.92 (td, 1H, J = 7.5 Hz, H4′); 7.53 (d with sat, 1H, J = 8.0 Hz, H5); 7.44 (t, 2H, J = 7.5 Hz, H3″); 7.35 (m, 1H, H4″); 7.16 (ddd, 1H, H5′); 3.62 (s br with sat, 3H, J_{Pt-H} = 19.9 Hz, N–Me); 2.66 (m br, 3H, Me); 2.19 (s br, 3H, Me); 0.86 (s with sat, 3H, J_{Pt-H} = 84.5 Hz, Pt–Me). ^{13}C NMR ($CDCl_3$) δ (ppm) 174.58 (C=N), 164.38 (C2 or C2′), 163.59 (C2 or C2′), 150.48, 145.61, 141.63, 140.73, 138.49, 137.31, 128.53, 127.63, 126.17, 124.04, 121.59, 120.82, 43.16 (N–Me, correlation with ^{1}H at 3.61 ppm), 29.81 (correlation with ^{1}H at 2.54 ppm), 21.67 (correlation with ^{1}H at 2.19 ppm), −18.66 (s with sat, J_{Pt-C} = 815 Hz, Pt-CH_3). ^{1}H-^{13}C correlations based on based on H–C HSQC spectrum.

IR (ATR, Neat, cm^{-1}): 3391 br, 1652 m, 1599 m, 1016 s, 695 m.

Synthesis of [Pt(NC)(NHMe$_2$)Me] 10–13

Complexes **10**–**13** were obtained following the same procedure used for complex **3**, starting from the corresponding Pt-(NC)(DMSO)Me] complexes **6**–**9**.

[Pt(bpy–H)(HNC=CMe$_2$)Me] 10. Yield 40%. ^{1}H NMR ($CDCl_3$): δ (ppm) = 9.82 (s, 1H, NH), 8.27 (m, 1H, H6 o H6′), 8.19 (d, 1H, J = 8.6 Hz, H3′), 8.15 (d, 1H, J = 5.8 Hz, H6 o H6′), 8.04 (d, 1H, J = 7.5 Hz, J = 56 Hz, H4), 7.84 (t, 1H, J = 7.9 Hz, H4′), 7.11 (t, 1H, J = 6.6 Hz, H5′ o H5), 7.05 (t, 1H, J = 5.9 Hz, H5 o H5′), 2,27 (s, 1H, CH_3), 2.21 (s, 1H, CH_3), 0.77 (s with sat, 1H, J = 84.4 Hz, CH_3-Pt).

[Pt(pyqui–H)(HN=CMe$_2$)Me], 11. Yield: 30%. ^{1}H NMR ($CDCl_3$): δ (ppm) = 9.92–9.45 (s, 1H, NH); 8.55 (d, 1H, J = 7.7 Hz, H3′) ; 8.43 (s with sat, 1H J_{Pt-H} = 64 Hz, H4); 8.31 (d, 1H, J = 5.6 Hz, J_{Pt-H} = ca 15 Hz, H6′) ; 7.99 (d, 1H, J = 8.4 Hz, H5 o H8); 7,94 (t, 1H, J = 7.9 Hz, H4′); 7.73 (d, 1H, J = 8.5 Hz, H5 o H8); 7.53 (t, 1H, J = 8.4 Hz, H7 o H6); 7.39 (t, 1H, J = 6.7 Hz, H7 o H6); 7.19 (m, 1H, H5′); 2.36 (s, 3H, CH_3); 2.30 (s, 3H, CH_3); 0.90 (s, 3H, J_{Pt-H} = 84.5 Hz, Pt-CH_3).

[Pt(bpy^{NO}–H)(HN=CMe$_2$)Me] 12. Yield: 40%. M.p = 204 °C–208 °C.[1] H NMR ($CDCl_3$, MM29): δ (ppm) = 9.84 (d, 1H, J = 8.3 Hz, H3′); 9.69 (s, 1H, NH); 8.25 (d, 1H, J = 5.5 Hz, J_{Pt-H} = 14 Hz, H6′); 8.03 (d, 1H, J = 6.3, Hz, H6); 7.93 (t, 1H, J = 8.0 Hz, H4′); 7.71 (d with sat, 1H, J = 7.9 Hz, J_{Pt-H} = 66 Hz, H4); 7.19 (t, 1H, J = 6.5 Hz, H5′); 7.00 (t, 1H, J = 7.3 Hz, J_{Pt-H} = 22 Hz, H5); 2.27 (s, 6H, CH_3); 0.72 (s with sat, 3H, J_{Pt-H} = 83.0 Hz, CH_3). IR (nujol, cm^{-1}): 1662 m, 795 m, 715 m.

[Pt(Phpy−H)(HN=CMe$_2$)Me], 13. Yield: 20%. M.p.=169 °C–173 °C. ^{1}H NMR ($CDCl_3$, MM54): δ (ppm)=9.84 (s, 1H, NH), 8.19 (d, 1H, J=5.2 Hz J_{Pt-H}=13 Hz, H6), 7.81–7.72 (m, 2H, H5+H3 o H6′), 7.71 (d with sat partially superimposed, 1H, J=8.6 Hz, J_{Pt-H}=47 Hz, H3′), 7.54 (d, 1H, J=8.2 Hz, H3 o H6′), 7.18(t, 1H, J=7.5 Hz, J_{Pt-H}=15 Hz, H4′), 7.05 (t, 1H, J=7.5 Hz, H5′), 6.97 (t, 1H, J=6.4 Hz, H5), 2.26 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 0.78 (s with sat, 3H, J_{Pt-H}=84 Hz, CH_3-Pt).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Pt(II) cyclometalated compounds · Rollover cyclometalation · Acetimine complexes · Laboratory medicine

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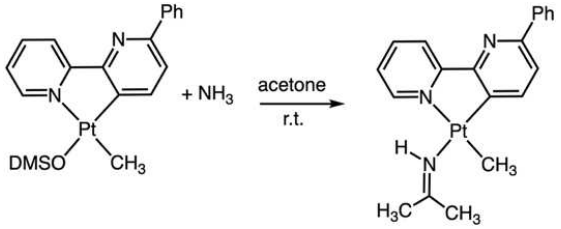

Reaction of electron-rich platinum(II) rollover cyclometalated complexes [Pt(N^C)(DMSO)Me] with aqueous ammonia in acetone gives rare acetimine complexes [Pt-(N^C)(HN=CMe$_2$)Me]. The reaction has been proven to be effective also with the classical cyclometalated complex derived from 2-phenylpyridine.

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