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Diarylplatinum(II) scaffolds for kinetic and mechanistic studies on the formation of platinacycles *via* an oxidative addition/reductive elimination/oxidative addition sequence

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ABSTRACT

Oxidative addition and reductive elimination reactions are fundamental steps in processes related to synthetic chemistry involving organometallic compounds. In these reactions a metal in two available oxidation states (generally differing in two units) is needed, platinum centres being a very good example. The relative inertness of diamagnetic Pt^{II} and Pt^{IV} organometallic species (having respectively d^8 square-planar or d^6 octahedral arrangements), enables an easy monitoring of time-resolved reactivity, including its posterior kinetic analysis. Specifically, imine ligands containing C-X bonds have been observed to oxidatively add to $\{Pt^{II}(Aryl)_2\}$ moieties, which sequentially undergo C-C reductive elimination and C-H bond activation on the new ligand formed. These new species have been found to contain mostly seven-membered metallacycles, despite the obvious thermodynamic preference for five-membered cycles, which are found only in some rather specific instances. The kinetic preference of the complexes obtained has been studied from a kinetico-mechanistic perspective, that included obtaining thermal and pressure derived activation parameters, and a dramatic influence on the spectator halido ligands and the substituents on the aryl groups has been established. To complete this kinetic and mechanism (kinetico-mechanistic) study, theoretical calculations have also been conducted to model the data collected and propose both the elementary steps and the factors determining the specificity of the full process.

Keywords: kinetico-mechanistic studies; DFT calculations; oxidative addition/reductive elimination sequence; platinacycles

1. Introduction

Kinetics experiments in solution lead to the collection of kinetic data that can be analyzed in terms of rate laws, which together with activation parameters acquired from temperature and pressure variable experiments, may lead to mechanistic proposals. The value of such analyses and proposals is compromised unless due diligence regarding reactant and solvent purity is followed, and furthermore reproducibility of measurements is assured, and primary data and derived secondary data and parameters are subject to appropriate error analysis.

In the last several decades the throughput of kinetics experiments has changed dramatically by instrument improvement, automation and validated data analysis software. Developments in chemical synthesis have yielded a wider range of subtle reactant variations leading to wider data sets. Consequently, provided the caveats within the experimental approach are followed, reliable new reaction mechanisms frequently ensue.

In order to understand further the detail of reaction mechanism pathways, the experimentalists have, over the last two to three decades, at their disposal, the ability to take advantage of the application of density functional theory (DFT) computation methodology. This methodology represents a significant and appealing addition to the overall repertoire of approaches by investigators for a detailed explanation of the time course, energetics and structural aspects of their chemical reaction systems. Successes in using this computational approach are widely reported. Indeed it will be shown in this contribution that a combination of kinetics and mechanism studies and modeling by DFT computations has led to a comprehensive understanding of the formation of platinacycles through various stages starting from diarylplatinum(II) scaffolds.

Oxidative addition and reductive elimination are fundamental reactions in organometallic chemistry in both stoichiometric and catalytic processes. The inertness of platinum compounds and the availability of different oxidation states make them suitable for mechanistic studies of these reactions. In particular, although cyclopalladated complexes are much used in catalytic processes, their equivalent platinum compounds have been often used as model compounds for fundamental reactions due to their high stability and inertness. The syntheses of cyclometallated compounds traditionally involves intramolecular C-H bond activation, but a great deal of interest is also focused in intramolecular C-X bond activation since, in these cases, the initial oxidative addition can be followed by a subsequent reductive elimination producing new σ bonds such as C-C, C-O, C-H or C-X. Among the large plethora of cycloplatinated compounds available, those containing aryl ligands might give rise to oxidative addition/reductive elimination process involving C-X and C-H bond activation as well as C_{aryl}-C_{aryl} reductive elimination. Therefore arylplatinum compounds provide a useful platform for a thorough study of these fundamental processes.

The relative inert character of such complexes allows the monitoring of their time-dependent reactivity in an easy and reproducible way. Furthermore, the possibility of detecting and isolating reaction intermediates precisely increases with the increase of the inert character on the reactivity involved. Unfortunately the possible actuation of dead-end processes also increases along the same line, and a comprehensive monitoring off all the processes involved in the reactivity studied is desirable. In this respect, the use of experimental mechanistic procedures has been suffering a decrease in use owing to the preference by some for computational methods, which usually come into play when the situation becomes too complicated to monitor experimentally, or when the

number of experiments needed is excessive. However, we have to keep in mind that computational methods have to be employed wisely; although calculations may corroborate or even guide experiments, the final conclusions have always to be ascertained by proper real experimental situations.

Platinum chemistry is a terrain that has been explored thoroughly by computational means. A tremendous number of publications regarding homogeneous catalysis, surface science or medicinal applications are reported each year. Bond activation by platinum complexes, and its implication in homogeneous catalysts, has been explored thoroughly. In particular cycloplatination reactions are a convenient computational area of study. Association and dissociation steps, along with well-known oxidative addition and reductive elimination processes between closed-shell diamagnetic Pt^{II}/Pt^{IV} species, are involved in the reactivity. Furthermore, relativistic effects for platinum, which should be the most remarkable issue in computational studies of these reactions, can be effectively tackled nowadays by most DFT methods. Either the use of scalar relativistic calculations, or basis sets with pseudopotentials (that include the corresponding corrections for the heavier atoms), represent a standard solution to the issue.

This chapter describes a series of experimental, kinetics, mechanistic and computational studies on the formation of five- and seven-membered metallacycles obtained from diarylplatinum(II) precursors with *N*-donor ligands. One aim of the material presented is to illustrate the enormous advantage of synergic collaborations between specialized research groups that adds great value to the studies conducted. However, by doing so, some aspects, which are normally taken for granted, have to be discussed and reformulated to account for the overall set of observations and results.

2. Compounds

Although the complexes [$PtMe_2$(***NN***)], where ***NN*** is a diimine ligand, such as 2,2′-bipyridine or 1,10-phenanthroline, are among the most reactive transition-metal complexes in intermolecular oxidative addition of alkyl halides, aryl halides fail to react with these Pt^{II} complexes. In this respect, the first reported oxidative additions of directed aryl halides to Pt^{II} have been achieved using ligands of formula $RCH{=}NCH_2CH_2NMe_2$.[1-3] In these, R is an *ortho*-halogenoaryl group, and the ligand coordinates *via* both nitrogen atoms to a dimethylplatinum(II) center producing a [$PtMe_2$(RCH=***N***CH_2CH_2***N***Me_2)] species that ultimately leads to intramolecular oxidative addition of the aryl-halogen bond. This strategy was successful in producing C-X (X = Br, Cl, F) bond activation leading to Pt^{IV} compounds of type [$PtMe_2X(C_5$***C***$H_4CH=$***N***CH_2CH_2***N***Me_2)]. In the same studies C-H bond activation was also achieved; in this case a final Me-H reductive elimination producing methane and Pt^{II} compounds of type [$PtMe(C_5$***C***$H_4CH=$***N***CH_2CH_2***N***Me_2)] takes place (Scheme 1, top).

Further work in this area involved the use of ligands with the same type of organometallic moieties, but with a single *N*-donor directing group, with a general formula 2-$XC_6H_4CH{=}NCH_2$-2′-$X'C_6H_4$.[4-6] In this case, the reaction of these ligands with [$Pt_2Me_4(\mu\text{-}SMe_2)_2$] may produce different types of five-membered platinacycles, either containing (*endo*cycles) or not (*exo*cycles) the imine functionality. As for the amino-imino ligands indicated above, intramolecular oxidative addition of C-X bonds (X = Br, Cl, F) produced cyclometallated Pt^{IV} compounds, while activation of C-H bonds with loss of methane gave the corresponding cyclometallated Pt^{II} compounds. Interestingly, formation of *endo*-platinacycles (Scheme 1, bottom) is favored in all cases for these ligands. *Exo*-platinacycles have only been found when imines 2,4,6-

$C_6Me_3H_2CH{=}NCH_2(2\text{-}XC_6H_4)$ (X = Br, Cl), in which formation of *endo*-metallacycles is precluded by the presence of methyl substituents in the *ortho* positions of the benzal ring, are used.

SCHEME 1 HERE

Scheme 1. Oxidative addition reaction mechanism for ligands of general formulae $RCH{=}NCH_2CH_2NMe_2$, $2\text{-}XC_6H_4CH{=}NCH_2Ar$ and $ArCH{=}NCH_2(2\text{-}XC_6H_4)$ on $[Pt_2Me_4(\mu\text{-}SMe_2)_2]$.

Given the successful results obtained for the intramolecular C-X activation mechanisms at the $\{Pt^{II}Me_2\}$ moieties, our attention was focused on substrates having the $\{Pt^{II}(Aryl)_2\}$ organometallic unit. The purpose being both to determine whether or not this type of compound could produce cyclometallated compounds under similar mild conditions, and to compare the mechanism operating for both series of compounds. The initial work involved preparative studies using *cis*-$[PtPh_2(SMe_2)_2]$ as substrate, indicated that intramolecular C-X (X = Br or Cl) bond activation may occur for both ligands containing one[7,8] or two nitrogen donor atoms.[9,10] Analogous results were obtained using the better spectroscopically handled $[Pt_2(4\text{-}MeC_6H_4)_4(\mu\text{-}SEt_2)_2]$ [11,12] or $[Pt_2(4\text{-}FC_6H_4)_4(\mu\text{-}SEt_2)_2]$ [13,14] starting materials. As previously reported for $[Pt_2Me_4(\mu\text{-}SMe_2)_2]$, C-X (X = Br or Cl) bond activation at diarylplatinum(II) compounds leads to cyclometallated Pt^{IV}compounds, or Pt^{II} after reductive elimination of arene for C-H bond activations. On the other hand, although intramolecular C-F bond activation has been achieved upon reaction of $[Pt_2Me_4(\mu\text{-}SMe_2)_2]$ with the ligand $C_6F_5CH{=}NCH_2CH_2NMe_2$ [3] such a process has not been observed for precursors $[PtPh_2(SMe_2)_2]$ or *cis*-$[Pt(4\text{-}MeC_6H_4)_2(\mu\text{-}SEt_2)]_2$. This result can be related to the

strength of the C-F bond and the lower reactivity of the arylplatinum reagents when compared to methyl analogues.

A distinct feature of the mentioned reactions on *bis*-aryl Pt^{II} compounds was disclosed in the preliminary study of compound *cis*-[$PtPh_2(SMe_2)_2$] with ligand 2-$BrC_6H_4CH{=}NCH_2C_6H_5$ [7] in which the initially formed cyclometallated Pt^{IV}compound has evolved to a novel type of seven-membered platinacycle that was structurally characterized (Figure 1) as the compound [$Pt^{II}Br(\boldsymbol{C}C_5H_4C_6H_4CH\boldsymbol{N}CH_2C_6H_5)(SMe_2)$] containing a biaryl linkage. This seminal work was followed by the report of further examples of seven-membered platinacycles such as [$Pt^{II}Br(\boldsymbol{C}C_5H_4C_6H_4CH\boldsymbol{N}R)(SMe_2)$] (R = Me or CH_2Mes) obtained from the reaction of *cis*-[$PtPh_2(SMe_2)_2$] with the corresponding *N*-donor ligands.[8] Further examples based on the reaction of [$Pt_2(4\text{-}MeC_6H_4)_4(\mu\text{-}SEt_2)_2$] or [$Pt_2(4\text{-}FC_6H_4)_4(\mu\text{-}SEt_2)_2$] with analogous imines containing one single *N*-donor atom proved that not only initial C-Br bond activation but also C-Cl bond activation may lead to such seven-membered platinacycles as indicated in Scheme 2.[11,12] It is interesting to note that these compounds are obtained in good yields not only when the *ortho* position of the imine is blocked with a fluorine substituent (Y = F) but also when Y = H, where a C-H bond activation leading to more stable five-membered Pt^{II} metallacycles is also possible.

FIGURE 1 HERE

Figure 1. Molecular structure of the seven-membered cyclometalated platinum(II) compound [$Pt^{II}Br(CC_5H_4C_6H_4CHNCH_2Ph)(SMe_2)$].

For these compounds, the fate of the substituent in position 4 of the aryl group (Z = Me or F), which in the final seven-membered platinacycles, is *meta* to the platinum center, is consistent with the reaction sequence indicated in Scheme 2. The process thus consists of: *i)* initial C-X (X = Br or Cl) bond activation to produce a starting Pt^{IV} derivative; *ii)* reductive elimination coupling with formation of a C_{aryl}-C_{aryl} bond between one of the aryl ligands and the metallated aryl of the imine ligand; *iii)* final cyclometallation with elimination of an arene molecule. As discussed in detail below, combined ^{1}H NMR and UV-Vis kinetico-mechanistic studies carried out recently for the formation of seven-membered [C,N]-platinacycles from cyclometallated Pt^{IV} compounds [13] indicate that the formal cyclometallation process *iii)* in fact involves an isomerization step (*iv*, Scheme 2) where the resulting non-cyclometallated intermediate adopts the required geometry for the final cycloplatination reaction (step *v*, Scheme 2). The distinct values of *J*(H-Pt) for the imine *trans* to C (*ca.* 44 Hz) or *trans* to X (*ca.*140 Hz) allows identification and monitoring of the isomerzation reaction. NMR spectroscopic monitoring of the full reaction indicates that the rate-determining step of the process is found to depend on the nature of the substituent (Z = H, Me or F) at the *para* position of the aryl ligand; no relevant differences in the synthesis of seven-membered [C,N]-platinacycles were found when SMe_2 or SEt_2 derivatives were used or even when the halido ligand was Br or Cl.

SCHEME 2 HERE

Scheme 2. Formation of seven-membered [C,N]-Pt^{II} metallacycles.

Interestingly, the reaction of *cis*-[Pt(C_6F_5)$_2$(SEt_2)$_2$] with imine 2-BrC_6H_4CH=NCH_2(4-ClC_6H_4) (Scheme 3) produced exclusively a five-membered metallacycle with an *exo* C_{aryl}-C_{aryl} bond. In this case, formation of a seven-membered platinacycle which requires C-F bond activation is not favored and indeed is not observed. ^{19}F NMR monitoring allows the detection of all proposed intermediates,[15] *i.e.* initial formation of a Pt^{IV} compound arising from the activation of the C-Br bond of the imine, C_{aryl}-C_{aryl} reductive elimination and final C_{aryl}-H bond activation leading to a five-membered cyclometallated Pt^{II} compound with concurrent elimination of pentafluorobenzene.

SCHEME 3 HERE

Scheme 3. Formation of a five-membered [C,N]-Pt^{II} metallacycle.

In order to analyze the scope of the formation of biaryl linkages in the coordination sphere of platinum, the reactions of [Pt_2(4-MeC_6H_4)$_4$(μ–SEt_2)$_2$] with *N*-benzylidenebenzylamines for which formation of *exo*-metallacycles is favored (as indicated above), were also studied. Imines containing a C-Br or a C-Cl bond in an *ortho* position of the more flexible benzyl ring effectively also lead to formation of biaryl linkages between one of the 4-tolyl ligands and the benzyl group of the imine ligand. However the biaryl linkage formed was found to be not necessarily involved in the subsequent metalation which produced either *endo*-five, *endo*-six or *exo*-five membered platinacycles as shown in Scheme 4.[16,17] The reactions observed follow the general sequence indicated before, but with the final cyclometallation step being more favored for $C_{aromatic}$-H than for $C_{aliphatic}$-H bonds and for *endo*- than for *exo*-

metallacycles, so that the latter are formed only when the *ortho* positions of the benzylidene rings are blocked with fluorine atoms.

Summarizing, all the reactions shown in Schemes 2-4 for the formation of [C,N]- Pt^{II} metallacycles containing a biaryl linkage, included or not in the final platinacycle, involve intramolecular C-X (X = Br or Cl) bond activation followed by C_{aryl}-C_{aryl} reductive elimination to produce non-cyclometallated intermediates that could be detected when the reactions were monitored by ^{1}H or ^{19}F NMR spectroscopy.[13,15] However, none of these intermediates could be isolated and characterized crystallographically. Nevertheless, ligands containing two nitrogen donor atoms such as *Ar'*CH*N*CH_2CH_2*N*Me_2 would be expected to produce more stable intermediates containing a [N,N']-chelate.

SCHEME 4 HERE

Scheme 4. Formation of several types of [C,N]-Pt^{II} metallacycle.

In contrast to the results indicated so far for [C,N] systems (Scheme 2, compounds of type **A**), early studies carried out with [C,N,N']-Pt^{IV} cyclometallated compounds of the general formula [$PtXAr_2$(***Ar'***CH***N***CH_2CH_2***N***Me_2], revealed a distinct behavior for X = Br or X = Cl with respect to the reactivity indicated in Schemes 2 and 3.[18] For X = Cl, seven-membered [C,N,N′]-Pt^{II} cyclometallated compounds of general formula [PtCl(***Ar***-Ar′CH=***N***CH_2CH_2***N***Me_2)] are easily obtained [10-12,14,18,19] (Scheme 2) and crystal structure determinations have been reported for representative examples (see Figure 2). Moreover antitumor properties have been studied for some of them.[14,19]

FIGURE 2 HERE

Figure 2. Molecular structure of [$Pt^{II}Cl(2\text{-}F\boldsymbol{C}C_5H_4(4MeC_6H_3CH\boldsymbol{N}CH_2CH_2\boldsymbol{N}(CH_3)_2]$.

In contrast, a five-membered [C,N,N′]-Pt^{II} cyclometallated compound containing an external biaryl linkage (Scheme 3) is formed from [$PtBr(4\text{-}MeC_6H_4)_2(\boldsymbol{C}C_5H_4CH\boldsymbol{N}CH_2CH_2\boldsymbol{N}Me_2]$ under analogous conditions. In an attempt to understand the different chemical behavior observed for bromo or chloro-[C,N,N′] systems, these reactions have been thoroughly studied.[18] Careful selection of the reaction conditions extracted from the kinetic studies indicated in the following section allowed the detection and characterization, including by X-ray crystallography, of two isomers of the non-cyclometallated Pt^{II} compound arising from C_{aryl}-C_{aryl} reductive elimination, thus supporting the existence of the reaction intermediates assumed for the reactivity with [C,N] systems.

In this respect and in an attempt to obtain a seven-membered [C,N,N′]-Pt^{II} cyclometallated compound for X = Br, the reaction of [$Pt_2(4\text{-}MeC_6H_4)_4(\mu\text{-}SEt_2)_2$] with imine 2-Br,6-$FC_6H_3CH{=}NCH_2CH_2NMe_2$ has also been studied [11] and, effectively, the presence of an inert C-F bond at the *ortho* position of the aryl ring of the imine ligand, prevents the C-H activation at the imine and thus, the reaction is driven towards the formation of a seven-membered platinacycle containing an internal biaryl linkage (Scheme 5). Again, for this system two isomers of the non-cyclometallated compound containing a biaryl ligand were isolated and crystallographically characterized.

SCHEME 5 HERE

Scheme 5. Formation of five- or seven-membered [C,N,N′]-platinacycles.

3. Kinetic studies

Reactions involving platinum organometallic complexes with simple *cis*-{$Pt^{II}R_2$} units (R = Me, Ph) have been proved to be extremely well-behaved for the directed oxidative addition reaction of C-X or C-H bonds indicated in the previous section (Scheme 1).[4-6,9,20,21] This has allowed us to study from a kinetico-mechanistic perspective the reaction with the ligands indicated in Scheme 6 having monofunctional (imine) or bifunctional (amino-imine) directing units.[22]

SCHEME 6 HERE

Scheme 6. Ligands utilised in the preliminary studies of oxidative addition reactions on *cis*-{$Pt^{II}R_2$} units.

Independently of the directing groups used, the process has been found to be occurring *via* the initial formation of an unsaturated tri-coordinated species that reacts in a concerted oxidative addition fashion to produce a penta-coordinated intermediate.[23,24] The rapid coordination of the sixth (dangling or available in the medium) ligand produces the final compound (Scheme 1). Figure 3a collects the isokinetic plot generated with all the data available, indicating that the process occurs indeed *vi*a the same concerted tri-centered mechanism.[22] Even the available data for systems lacking hydrogen bonding characteristics show a very good and extended enough $\Delta V^{\ddagger}/\Delta S^{\ddagger}$ correlation[25] (Figure 3b).

FIGURES 3a AND 3b HERE

Figure 3.- Isokinetic, a), and $\Delta V^{\ddagger}/\Delta S^{\ddagger}$, b), correlation plots for the series of concerted oxidative addition C−X and C-H activation reactions of compounds indicated in Scheme 6 on $\{Pt^{II}R_2\}$ (R = Me, Ph) moieties.

Interestingly, as stated in the previous section, for C-X and R = Ph bond activation reactions, the isolation of the final Pt^{IV} compound, type **A**, indicated in Scheme 1 proved to be rather difficult.[7,8] Both kinetics and time-resolved NMR spectra indicate the existence of a subsequent consecutive process (Scheme 2) that produces a seven membered platinacycle, type **7C**, as the final crystallized species (Figure 1). Detailed kinetic studies of the oxidative addition of some of the ligand molecules indicated in Scheme 6 on a series of *cis*-$\{Pt^{II}(Aryl)_2\}$ units proved, in fact, to have a rather complex and diverse behavior. Although, in some cases well-behaved two consecutive kinetic steps were observed, leading initially to complexes of type **A** and finally to species of type **7C**,[13] in some other cases the kinetic profiles showed up to four recognizable time-resolved steps.[11,18] Parallel NMR time-resolved monitoring was thus needed in order to ascertain what are the processes observed. Furthermore, the nature of the final platinum species formed was also found to be extraordinarily dependent on a plethora of variables.

The general reaction scheme that could be generalized from the data collected is already shown in Scheme 2, where the first step, *i)*, corresponds to the process indicated in Scheme 1 for X ≠ H (formation of compounds of type **A**).[22] The steps following this first oxidative addition reaction, *ii)* and *iii)*, correspond to a reductive elimination

coupling (formation of compound of type **B**),[15] and a new oxidative addition process of the biaryl ligand formed (formation of compound of type **C**).[11,13,18] With these data at hand, and given the good time-profile knowledge acquired for the formation of complexes of type **A**, isolation of such a Pt^{IV} five-membered metallacycle has been possible in most of the cases. Consequently the *ii)+iii)* set of reactions (producing compounds of type **B** and **C**) could be studied independently. Interestingly, the careful time-resolved isolation/characterization of the species involved in the process lead to the obtention of rather diverse reaction intermediates and products, which corresponds to the more detailed reaction sequence indicated in Scheme 5. As a whole, the species indicated in Scheme 7 have been characterized thanks to the existence of kinetically collected time/temperature data. Clearly from the experimental observation of these complexes, step *iii)* in Scheme 2 should effectively include two processes: an equilibrium isomerzation reaction, indicated by *iv)*, *plus* a final metalation reaction, *v)*.[11,18]

SCHEME 7 HERE

Scheme 7. Models of characterized products and intermediate species occurring during the set of reactions indicated in Scheme 2; L = SMe_2, SEt_2 or $Me_2N_{(chelate)}$ from ligands in Scheme 6.

3.1. Spontaneous processes with monodentate $N_{(imine)}$ ligands

The serendipitous seminal kinetico-mechanistic work of this reactivity series has been successfully concentration-tuned to evaluate in a separate manner, reductive elimination coupling and final cycloplatination reactions (Scheme 2).[7,8] The studies have been conducted taking advantage of the comprehensively studied substitution reactions on

the initial Pt^{IV} complexes (**A**, L = SMe_2, Aryl = Ph, X = Br, Scheme 8), found to react *via* a pentacoordinated intermediate (*i***A**).[26-30] This knowledge allowed for the sequestering of the reductively coupled intermediate appearing in the reaction mechanism (*i***B**) with excess of SMe_2.[7] For studies without excess of sequestering ligand a rather different set of kinetic and activation parameters was obtained, which should, consequently, be associated with the **B → 7C** reaction steps.[8] The relevant kinetic features determined for the two steps observed for this system, including thermal and pressure derived activation parameters are collected in Table 1. The possible isomerzation reaction occurring on the complex of type **7C** has also been studied with relevance to the final stereochemistry of the species isolated.[8]

SCHEME 8 HERE

Scheme 8. Concentration-tuned reactions for the spontaneous reductive elimination/oxidative addition sequence on complexes of type **A**.

As a follow up from these studies the kinetico-mechanistic monitoring of the reaction of the *cis*-{$Pt^{II}(C_6F_5)_2$} unit with ligand **6**, where R = H and R′ = 4-Cl, was also pursued (Scheme 6).[15] The process shows a neat two step rate-limiting sequence perfectly associated with reactions *ii) + iii)* in Scheme 2. That is, reaction Scheme 9 (with L = SMe_2, Aryl = C_6F_5, X = Br) applies to this process which modifies the reactivity indicated above. In this case the final compound corresponds to a five-membered platinacycle with a dangling C_6F_5 unit of type **5C**. Interestingly, the measured kinetics indicates that process *ii)* is very fast and the initial oxidative addition of ligand **6** (with R = H and R' = 4-Cl) on *cis*-[$Pt^{II}(C_6F_5)_2(SEt_2)_2$] (step *i)* in Scheme 2) cannot be

resolved; *i.e.* the compound of type **A** is not observed, only species **B** is initially present as an intermediate. Table 1 collects the relevant kinetic and activation parameters collected for the resolved reaction in Scheme 9 (**B → 5C**).

SCHEME 9 HERE

Scheme 9. Modification of the reactivity shown in Scheme 8 for the L = SEt_2, Aryl = C_6F_5, X = Br system producing a five-membered final platinacycle.

Further kinetico-mechanistic studies have also been carried out on complexes with a systematic variation of the Pt^{II}-attached aryl ligands in the starting *cis*-{$Pt^{II}(Aryl)_2$} moiety. Furthermore, an *ortho* substituent on the initial metallated ligand has been introduced (ligand **6** in Scheme 6, with R = 2-F and R′ = H).[13] The systems have been tuned from Aryl = Ph to 4-MeC_6H_4 and 4-FC_6H_4; in all cases the final characterized compound corresponds exclusively to an organometallic complex of type **7C**. That is, the reaction sequence indicated in Scheme 8 is operative for the spontaneous reactivity on these complexes.

For the two systems, as for the previous *cis*-{$Pt^{II}(C_6F_5)_2$} system, a single step leading to the final complex is observed from the isolated complexes of type **A**. Careful parallel time-resolved NMR monitoring of the reaction samples indicates that such rate-determining step monitored corresponds to the reaction **B → 7C** indicated in Scheme 8 for the Aryl = 4-MeC_6H_4 and 4-FC_6H_4 complexes, while for the Aryl = Ph compound the rate-determining step corresponds to the reductive **A → B** coupling. Table 1 collects the relevant kinetic and thermal and pressure derived activation parameters determined

for these systems. Clearly the kinetic and activation parameters of reactivity observed fall within the expected values for the Aryl = Ph compound, but two distinct sets are observed for Aryl = 4-MeC_6H_4 and 4-FC_6H_4 complexes; Figure 4 shows clear indication of the diverse trends observed for these systems.

FIGURE 4 HERE

Figure 4. Eyring and ln*k versus P* plots for the rate-determining step observed in the reaction indicated in Scheme 8 with Aryl = Ph, L = SMe_2, X = Br, ligand **4** from Scheme 6 with Aryl = Ph (circles) and ligand **4** from Scheme 6 with Aryl = 4-FC_6H_4, Ph (squares).

A close examination of time-resolved NMR monitoring indicated that the reductively eliminated type **B** complex undergoing the final formation of the seven-membered platinacycle (compound type **7C**) is not the same in both cases. While for the Aryl = 4-MeC_6H_4 complexes the reaction is seen from a **B** species with a *cis*-$N_{(imine)}$/Aryl stereochemistry (**B*cis***, Scheme 7), for the Aryl = 4-FC_6H_4 compounds the stereochemistry is *trans* (**B*trans***, Scheme 7). Clearly the activation process leading to the final **7C** complexes is either very distinct for the **B*cis*** and ***Btrans*** complexes, or one of the processes monitored corresponds to a rate-determining isomerzation reaction between these two stereochemical entities (*i.e.* slow **B*cis*** ⇄ ***Btrans*** and fast **B*cis*** or ***Btrans*** → **7C**). DFT studies (see next section) were conducted to ascertain the thermodynamic stereochemical preference of compounds of type **B** and effectively compounds of type **B*cis*** are found to lie lower in energy than the corresponding *trans* isomers.[11] Consequently the full **A** to **C** process can be better described as in Scheme 10 (similar to Scheme 2) with the penta-coordinated and tri-coordinated *i***A** and *i***B** intermediates maintaining the original stereochemistry of compounds **A** or **B**. The

kinetic and activation parameters associated with the rate determining step for Aryl = 4-FC_6H_4 thus do not correspond to a cyclometalation reaction, but to an isomerization from ***Btrans*** to **B*cis*** thus explaining the differences observed.

SCHEME 10 HERE

Scheme 10. Complete reductive elimination/isomerization/oxidative addition spontaneous reactivity of cyclometallated Pt^{IV} complexes of type $[Pt(Aryl)_2X(C_5\boldsymbol{C}H_4CH=\boldsymbol{N}\sim)L]$.

Table 1. Relevant kinetic and activation parameters of the spontaneous reductive elimination/oxidative addition reactions measured on compound of type **A** (Scheme 8).

TABLE 1 HERE

3.2. Spontaneous processes with chelate $N_{(amino)}$-$N_{(imine)}$ ligands

In view of the data shown so far the studies were extended to systems where the relatively labile ligand on the structure (L in the previous schemes) was substituted by the dangling arm of a chelate ligand. The purpose of such change is the isolation of some of the reductively coupled species of type **B** (Scheme 8, 9, 10), owing to the increase in stability expected by chelation. That is, ligands of the family **1**, **2**, and **3** shown in Scheme 6 were used in the scaffold for the initial oxidative addition of *cis*-$\{Pt^{II}(Aryl)_2\}$ moieties to produce compounds of type **A** with L = $Me_2N(CH_2)_2$-. Scheme 11 collects the drawing of the structures of the compounds which have been studied and

described in the previous section, but with the bidentate chelating $N_{(amino)}$-$N_{(imine)}$ ligands instead of the $N_{(imine)}$ *plus* L monodentate ligands set (Schemes 7-10).

SCHEME 11 HERE

Scheme 11. Models of the species occurring during the set of reactions indicated in Scheme 2 for ligands of type **1**, **2** or **3** from Scheme 6.

As indicated in Table 1, for the L, $N_{(imine)}$ systems isolation of the final compound as a **5C** species was only registered for the *cis*-{$Pt^{II}(C_6F_5)_2$} moiety (Scheme 9), possibly due to the difficulty of the activation of a C-F bond in the species **B** formed as an intermediate. For the rest of the systems studied the final compounds isolated have always the structure of complexes of type **7C** (Scheme 8). Nevertheless for the systems with the $N_{(amino)}$-$N_{(imine)}$ chelating ligands the outcome of the full process from the {$Pt^{II}(Aryl)_2$} units is more diverse, the reactivity indicated in Scheme 5 from the previous section being a clear summary. As a general rule substituting the ligands of type **2** and **3** in Scheme 6 at the remaining *ortho* position leads to a complex of type **A** that reductively couples with one of the Aryl = 4-MeC_6H_4 ligands to produce compounds of type **B** that only produce final cyclometallated complexes of type **7C** as found for the systems indicated before. Nevertheless, for the *ortho* unsubstituted complexes of type **A** the formation of the more thermodynamically stable complexes of type **5C** is also observed in some cases. This fact indicates that for these chelate complexes the formation of seven-membered metallacycles of type **7C** can be associated, at least in part, with the presence of a C-Y bond that is too strong to produce such a cyclometalation reaction.

The summary of this chemistry is indicated in Scheme 5 from the previous section. Scheme 12 collects the full series of species of type **5C** and **7C** encountered as the final compounds produced from the spontaneous reductive elimination/oxidative addition sequence occurring on complexes of type **A**. The kinetic study of the process occurring on compounds of type **A** proved to be much more complex than expected, with a very diverse behavior,[11,18] in line with that observed for the complexes in the last entries of Table 1. Figure 5 shows the Eyring plot of all the time-resolved reaction steps observed for the spontaneous reactivity of the bromo complex of type **A** with no chloro or fluoro substituents on the initial metallated ligand.

SCHEME 12 HERE

Scheme 12. Series of species of type **5C** and **7C** encountered as the final compounds produced from the spontaneous reductive elimination/oxidative addition sequence occurring on the complexes of type **A** indicated.

FIGURE 5a AND 5b HERE

Figure 5. Eyring plots for reactions observed by UV-Vis monitoring of the sequential spontaneous process occurring in toluene/xylene solutions of bromo complex with no chloro or fluoro substituents on the initial metallated ligand (Scheme 12) of type **A** (a) and **B*trans*** (b). Fitted lines are common to both graphs.

From the plot it is evident that at least three steps can be resolved by using carefully tuned conditions. Furthermore, careful choice of time/temperature conditions allowed for the isolation of some of the species appearing during the process. As indicated in

Scheme 11 reductively coupled intermediates have been isolated and fully characterized (Figure 6).

FIGURE 6 HERE

Figure 6. Reductively-coupled species of type **B*trans*** and **B*cis*** appearing during the spontaneous type **A** to type **5C** (top, no chloro or fluoro substituents on the initial metallated ligand) or **7C** (bottom, with fluoro substituent on the initial metallated ligand) reactions.

From these intermediate compounds the formation of the final type **5C** or **7C** compounds was also followed from a kinetic perspective. This procedure allowed the association of the steps observed to different single reactions by careful parallel time-resolved NMR monitoring. Figure 5b is a clear example of this association for the simplest system; the circle points in the plot corresponding to the formation of the final **5C** complex, while the triangle points in the plot corresponds to the **B*trans*** ⇄ **B*cis*** reaction, thus leaving the dashed line plot to the **A** → **B*trans*** reductive elimination reaction. Even the isomerization between the *E* and *Z* forms of the -CH=N- bond has been determined as for other simpler systems.[18,21] As a whole the full reaction sequence can be described by the previous Scheme 10, where most of the different steps have been resolved as a result of careful tuning of the reaction conditions of time and temperature. Parallel time-resolved NMR measurements have confirmed these assignments, and Table 2 collects the relevant associated data. Nevertheless for some of the systems studied the isomerization reaction has not been observed, thus indicating that the process is fast under the conditions studied, as already observed for some of the systems indicated in Table 1. As a whole, when the processes on the chelate $N_{(amino)}$-

$N_{(imine)}$ and monodentate $N_{(imine)}$-L systems are compared, both appear to be extremely complex and depending on the large number of variables involved. This is not surprising given the number of reaction steps involved in the full reactivity, which makes any claim such as *faster than* or *slower than* meaningless. Furthermore, the characterization of the intermediate species during the full process also brings in some news facts that have to be considered with respect to the isolation of only the less-reactive species of the full set.

Nevertheless, the most striking feature of the reactivity indicated in the previous pages relates to the five- or seven-membered platinacyclic nature of the final complex obtained. As seen in Table 2 only for one of the reactions studied, no doubt, the most thermodynamically stable five-membered platinacyclic compound is obtained, and the tuning of such specificity cannot be related to the different reaction sequences observed, all being rather equivalent. Only the detailed single step sequence occurring in the **B*cis*** → **7C** or **B*cis*** → **5C** process (Scheme 13) can explain such tuning. Further DFT calculations have been conducted (see next section) in order to establish the preferences once the empirical results are fully ascertained. A similar approach has been conducted in other organometallic systems with rather impressive synergic outcome.[31,32]

SCHEME 13 HERE

Scheme 13.- Detailed sequential reaction steps needed for the transformation of compounds of type **B*cis*** to cycloplatinated compounds of type **7C** or **5C** (Scheme 10).

Table 2. Relevant kinetic (xylene solution 340 K) and activation parameters of the spontaneous rate-determining steps involved in the reductive elimination/oxidative addition reactions measured on compound of type **A** (Scheme 10).

TABLE 2 HERE

4. Synergy with DFT calculations

DFT calculations have, nowadays, become a widely used powerful tool for studying reaction paths; quite a few examples are available in organometallic chemistry, catalysis and coordination chemistry studies.[33-37] The synergy between experiment and theory has also evolved considerably, allowing the development of both fields and producing some outcomes that would be hardly achievable using any of the single techniques. In this respect, the use of DFT calculations began by supporting results in a post-experimental manner. *i.e.* determining reaction mechanisms and selectivity when the rational chemical intuition and mechanistic experimental techniques have been exhausted. More recently, however, theory computations have begun to be used in parallel to experiments, or, even prior to them in some cases. By doing so, they have led, in some cases, to the discovery of new reactions and chemical systems.[38-40]

We have employed DFT theoretical calculations to ascertain some relevant aspects of the cycloplatination reactions explored from a kinetico-mechanistic perspective indicated in the previous sections. The aim has been to clarify some of the relative chemical stabilities, isomerization processes and kinetics observed.[11] Although the studies related to the Pt^{II} complexes having $N_{(amino)}$-$N_{(imine)}$ ligands have been reported, some new calculations related to monodentate $N_{(imine)}$ ligand systems have also been carried out and are reported here for the first time. The computational methodology used is equivalent to that utilized before,[11] and frequency calculations were carried out

to confirm stationary points and transition states. Additional single point calculations on the optimized geometries were also employed to obtain improved solvated free energy values with larger basis sets at the corresponding reaction temperatures; unless otherwise stated all the free energy values reported correspond to those obtained with these larger sets. As for the concentration/time kinetic models, they have been built using Copasi software[41] using the deterministic (LSODA) method with relative and absolute tolerance values of 10^{-6} and 10^{-12}, respectively.

4.1. Five- versus seven-membered platinacycle stability

As mentioned in the previous sections, the final five-membered platinacycle compounds, **5C**, are obviously expected to be more thermodynamically stable than the alternative seven-membered, **7C**, analogues. This fact has been confirmed in a facile manner using DFT calculations. The possible **5C** and **7C** products have been computed for different starting Pt^{II} complexes, **A** (even including some that have not been experimentally studied); the free energies of reaction (ΔG_R) thus derived are shown in Table 3. Clearly the five-membered platinacycles (**5C**) are the more stable in all cases, in agreement with what is expected for this kind of motif. Consequently, the obtention of the larger seven-membered platinacycles, from the isolated **B*cis*** intermediates indicated before, has to be due to kinetic preferences (see below). Furthermore, the calculated free energies for compounds **5C** and **7C** also confirm the expected larger stabilization of the $N_{(amino)}$-$N_{(imine)}$ chelated Pt^{II} species; in most cases these are found 5-20 kJ mol^{-1} more stable than their corresponding monodentate $N_{(imine)}$ analogues. Entries 9 and 10 do not include the calculated value for the corresponding **5C** complex given its non-feasibility due to the blocking indicated in Schemes 2, 5, and 12.

4.2. cis versus trans stability for B-type intermediates

As stated in the previous sections, the **B*trans*** ⇄ **B*cis*** interconversion plays an important role in the reactions studied,[11,18] in some cases the process even becomes the rate-determining step of the general cycloplatination reaction.[13] The full reaction consists of the sequence shown in Scheme 14. Initially, ligand L dissociates producing a T-shaped intermediate ***i*B*trans***, in which the imine group migrates from a *trans*- to a *cis*-aryl position, thus generating a ***i*B*cis*** intermediate. From this point back coordination of the L ligand (or moiety) produces the final **B*cis*** isomer.

Table 3. Computed free energies of reaction for products **5C** and **7C** of type **A** compounds; toluene solution at 70 ºC unless stated otherwise.

TABLE 3 HERE

SCHEME 14 HERE

Scheme 14. B*trans* ⇄ **B*cis*** isomerization reaction sequence.

In practice this isomerization process has been comprehensively computed only for compounds of type **A** with chelating $N_{(amino)}$-$N_{(imine)}$ ligands with Aryl = 4-MeC_6H_4 and X = Br or Cl (complexes on entries 7 and 8 on Table 3). The procedure used for the calculation was a linear transit potential energy surface scan, *i.e.* **B** and ***i*B** complexes were computed normally along with a set of structures in between, with the Aryl–Pt–$N_{(imine)}$ angle kept frozen at different decreasing values. The highest energy point along the reaction coordinate was thus associated with the isomerization transition state (**Isom_TS**) of the **B*trans*** ⇄ **B*cis*** rearrangement. Although the free energies shown in

Figure 7 were obtained using the smaller basis sets to simplify the scanning procedure, the relevant values for **Isom_TS** were recomputed with the bigger basis sets and found to lie at 138.4 and 140.1 kJ mol^{-1}, respectively, for complexes in entries 7 and 8 of Table 3.

FIGURE 7 HERE

Figure 7. Computed free energy profile for the **B*trans*** ⇄ **B*cis*** isomerization of complexes on entries 7 (solid) and 8 (dashed) in Table 3.

As shown, in the case of the L = $N_{(amine)}$ initial ligand release (Scheme 14), either from **B*trans*** or **B*cis***, requires a quite high amount of energy *ca.* 90-110 kJ mol^{-1}, which is obviously related to the chelating stabilization introduced by the bidentate ligand, lost when forming the corresponding T-shaped ***i*B** complexes. From this point on, the free energy rises steadily as the Aryl–Pt–$N_{(imine)}$ angle decreases, reaching a maximum around 140 ° for both complexes studied. These structures, considered to be the transition states of the isomerization reaction (**Isom_TS**), have an imaginary (*ca.* -100*i* cm^{-1}) frequency that resembles a rocking normal mode of vibration that moves the $N_{(imine)}$ ligand from a *trans*- to a *cis*-aryl geometrical position. As expected from the results collected in the previous sections, the **B*cis*** complexes are lower in energy than their *trans* counterparts (Table 4). Interestingly for the monodentate $N_{(imine)}$ ligands (L = SMe_2) this tendency is less pronounced.

Table 4. Computed relative free energies for **B*trans*** and **B*cis*** isomers derived from the type **A** compounds shown (Scheme 10); toluene solution at 70 ºC unless stated otherwise.

TABLE 4 HERE

4.3. Formation of five- or seven-membered platinaclycles from Bcis-type intermediates

Complexes with monodentate $N_{(imine)}$ ligands

The spontaneous reaction of three type **A** monodentate $N_{(imine)}$ complex systems (L = SMe_2 and X = Br, *i.e.* entries 1, 3 and 5 from Table 3), has been computationally explored in order to ascertain the preferential obtention of the seven-membered ring platinacycle product in all cases (type **7C**). As indicated in Scheme 15, two reaction pathways (**I** and **II**) from the intermediate **B*cis*** compounds described above are possible, each one leading to the formation of the five- or the seven-membered platinacycles, **5C** and **7C**, respectively.

SCHEME 15 HERE

Scheme 15. Reaction pathways leading to **5C** (**I**, top) and **7C** (**II**, bottom) type of compounds from Pt^{II} species of type **B*cis*** with monodentate $N_{(imine)}$ ligands.

Both reaction sequences involve a preliminary dissociation of the SMe_2 ligand from the starting **B*cis*** species, leading to the T-shaped ***i*B*cis*** intermediate. After this step a C–H bond activation, formally an oxidative addition process, should occur, either on the proximal ($\mathbf{H_A}$, **I**) or distal ($\mathbf{H_B}$, **II**) phenyl group of the biphenyl substituent of the imine ligand. Such activation entails the formation of the square pyramidal Pt^{IV} intermediates **B-CH$_5$** or **B-CH$_7$**, where the incoming hydride ligand is placed in the apical position.

Other conformers with a different ligand arrangement were also explored, but the calculated energies were found to be higher than the ones shown in Scheme 15. The final platinacycles of type **5C** or **7C** are finally obtained by the reductive elimination and release of the corresponding aryl by-products. Thus, the formation of the five- or seven-membered products should be dominated by the relative energy requirements of the oxidative addition (**OATS-CH$_x$**) and reductive elimination (**RETS-CH$_x$**) transition states. Experimentally, only the **7C** type of platinacycles is observed for the bromido complexes on entries 1, 3 and 5 in Table 3. Clearly the transition states along the route leading to **7C** (**II**) should be lower than those involved in the formation of **5C** (**I**). Indeed this is what is found when the relative free energies are computed (Table 5).

Table 5. Computed relative free energies (in kJ mol^{-1} and in toluene solution at 70 °C) for the reaction leading to Pt^{II} compounds of type **5C** and **7C** from complexes of type **A** with monodentate N$_{(imine)}$ ligands (entries 1, 3, and 5 of Table 3).

TABLE 5 HERE

As shown in Table 5, all the computed free energy profiles are quite similar, despite the diverse identity of the R group on the aryl ring. Nevertheless, the fact that the rate-determining step completely changes depending on the pathway followed by the reaction is rather interesting. For pathway **I**, that leading to the five-membered platinacycle product **5C**, the highest energy demanding stage corresponds to the final C–H reductive elimination producing the PhR moiety (**RETS-CH$_5$**). Contrarily, for pathway **II**, that leading to the seven-membered platinacycle product **7C**, the highest energy value corresponds to the initial C–H bond activation on the distal phenyl ring of the imine ligand (**OATS-CH$_7$**). These differences can be easily rationalized by the

careful observation of the structures of the transition states involved in each transformation. Figure 8 shows, as an example, the four transition states involved for the **A** compound on entry 1 of Table 3, including relevant bond distances. The analogous structures for the **A** compounds of entries 3 and 5 of the same table are very similar, thus the corresponding structures are not shown. The analysis of the bond distances in the transition states shown does not seem to provide a clear explanation of the observed reactivity, as they are rather similar in all cases. Obviously, the Pt–$N_{(imine)}$ bond is exceptional, being consistently longer in the route leading to product **7C**. A more thorough examination of the structures, nevertheless, provides a rather feasible explanation for the computed relative barrier heights. The smallest H–Pt–(Aryl) torsion angles found in the C–H oxidative addition and reductive elimination transition states (Table 6) is an indication of the relative orientation of the aryl ring and the hydrogen that is being cleaved or attached. The most favorable energy occurs when this torsion angle is close to 90 °, indicating that the C–H activation and reductive elimination reactions proceed naturally in the plane perpendicular to the aryl ring. Whenever this angle decreases, probably hindered by the arrangement of the other substituents on the platinum, the hydride group gets closer to one of the hydrogen atoms in the aryl ring and the free energy increases. Consequently, the torsion angles of the species shown in Table 6 indicate that the energy requirements to get to the transition state for the studied compounds are: **OATS-CH_5** < **RETS-CH_7** < **OATS-CH_7** < **RETS-CH_5**, in perfect agreement with the computed free energy values in Table 5.

FIGURE 8 HERE

Figure 8. Computed structures for the transition states leading to products **5C** (left, pathway **I**) and **7C** (right, pathway **II**) from compounds of type **B*cis*** originated form compound of type **A** in entry 1 of Table 3 (distances in Å, non-relevant H atoms have been omitted for clarity).

The computed relative free energy values collected in Table 5 have also been used to build a qualitative kinetic profile simulation model to evaluate the alternative formation of the final five- and seven-membered platinacycles, **5C** and **7C**, starting from the corresponding **B*cis*** parent intermediates of entries 1, 3 and 5 in Table 3 (Figure 9). The computed results totally agree with the experimental observations, and confirm that only products of type **7C** are expected in the reaction from bromido complexes of type **A** containing a set of monodentate $N_{(imine)}$ and a SMe_2 ligands. The possible amount of the analogous five-membered ring product **5C** remains, in all cases lower than 7 %, and the **5C**:**7C** ratios are 1:14, 1:30, and 1:73 for complexes involved in entries 1, 3, and 5 of Table 3, respectively.

Table 6. Smallest H–Pt–(Aryl) torsion angles (in degrees) and computed free energies (in kJ mol^{-1}) for the transition states indicated in Table 5 for the C–H activation and reductive elimination reactions studied.

TABLE 6 HERE

FIGURE 9 HERE

Figure 9. Qualitative time-resolved (arbitrary time scale) concentration profile for the complexes with monodentate $N_{(imine)}$ and SMe_2 ligands involved in entries 1, 3 and 5 of Table 3 (solid line, compounds of type **A**; dashed line, compounds of type 7**C**; dotted line, compounds of type **5C**).

Complexes with chelating $N_{(amino)}$-$N_{(imine)}$ ligands

The reactions of four different Pt^{II} complexes bearing chelate $N_{(amino)}$-$N_{(imine)}$ ligands, *i.e.* entries 7-10 in Table 3, have also been computationally studied in the same manner as that indicated above for the systems containing the monodentate $N_{(imine)}$ ligands. The experimental reactivity of the compounds of type **A** shown in entries 7 and 8 of this table, strongly depends on the nature of the halido ligand within the starting material, either bromido or chlorido. Results show a striking difference in the final products, which correspond to a five-membered platinacycle compound, type **5C**, for X = Br, but to a seven-membered analogue, type **7C**, for X = Cl. For the reactions occurring on the compounds of type **A** of the last two entries (9 and 10), only compounds of type **7C** are produced. Obviously this is a result of the hydrogen by fluoride substitution on the proximal aryl ring of the $N_{(amino)}$-$N_{(imine)}$ ligand; nevertheless, their reactivity was also theoretically calculated for comparison with the experimental data available.

As stated above for the monodentate systems, two possible pathways (leading to **5C** or **7C**) are possible for the systems on entries 7 and 8 of Table 3, once species of type **B*cis*** isomer are attained (Scheme 16). For the compound on entries 9 and 10 only route **II**, leading to platinacycles of type **7C** is possible. The reaction sequence for these mechanisms is quite similar to that described in the previous pages for the monodentate systems. Nevertheless, in this case the dissociation stage producing the T-shaped intermediate ($\mathbf{B}_{cis} \rightleftarrows \mathbf{\textit{i}B}_{cis}$) involves only the dechelation of a ligand, as the dimethylamino group still remains associated to the T-shaped species in a dangling arrangement. As for the previous systems, the relative energy requirements of the oxidative addition (**OATS-CH$_x$**) and reductive elimination (**RETS-CH$_x$**) transition states govern the selective formation of the final **5C** or **7C** product types.

SCHEME 16 HERE

Scheme 16. Reaction pathways leading to **5C** (**I**, top) and **7C** (**II**, bottom) type of compounds from Pt^{II} species of type **B*cis*** with chelate $N_{(amino)}$-$N_{(imine)}$ ligands.

For the bromido complex on entry 7 of Table 3, the energy requirements for pathway **I**, producing the thermodynamically preferred five-membered platinacycle **5C**, should be lower in energy than those leading to **7C**. Conversely, for the analogous chlorido system (entry 8 of Table 3), the energy requirements should favor pathway **II**, being the seven-membered platinacycle of type **7C** the one generated experimentally. Indeed, the computed relative free energies for these two systems confirm these trends, as shown in Table 7.

It may be noted that the dissociation of the chelating dimethylamino group requires a rather high input of energy (90.1 and 97.9 kJ mol^{-1} for systems in entries 7 and 8 of Table 3, respectively), which is in contrast to the much lower requirements (typically less than 40 kJ mol^{-1}) for the complexes having a monodentate $N_{(imine)}$ ligand. This difference can be easily explained by the entropic contributions of the ligand dissociation stage. On one hand, for the systems having monodentate $N_{(imine)}$ ligands, species $\mathbf{B}_{cis}$ dissociates into two different fragments, *i.e.* $i\mathbf{B}_{cis}$ and SMe_2, thus favoring entropy requirements. On the other hand, for the systems with chelating $N_{(amino)}$-$N_{(imine)}$ ligands, such dissociation produces a T-shaped intermediate with a dangling amino

group. This group still remains within the ***i*B$_{cis}$** coordination sphere, thus preventing an entropic stabilization to occur.

Table 7. Computed relative free energies (in kJ mol^{-1} and in xylene solution at 139 °C) for the reaction leading to Pt^{II} compounds of type **5C** and **7C** from complexes of type **A** with chelate N$_{(amino)}$-N$_{(imine)}$ ligands (entries 7 and 8 of Table 3).

TABLE 7 HERE

The computed free energies shown in Table 7 fully agree with the reactivity observed with respect to the nature and size of the final platinacycles. For the bromido complex in entry 7 of Table 3, the highest energy demands for pathways **I** and **II** are predicted to be 141.5 (**RETS-CH$_5$**) and 146.4 (**OATS-CH$_7$**) kJ mol^{-1}, respectively; this fact indicates that the preferred product should be the five-membered platinacycle of type **5C**. This behavior is totally contrary to that for the equivalent chlorido compound (entry 8 of Table 3), for which the highest barriers of pathways **I** and **II** are 155.6 (**RETS-CH$_5$**) and 149.8 (**OATS-CH$_7$**) kJ mol^{-1}, respectively. In this case the formation of the seven-membered ring, type **7C**, should be more favorable, as experimentally observed. It should be indicated that, both for X = Br and Cl (entries 7 and 8 of Table 3), the highest transition state for each pathway corresponds to the same process. For pathway **I** the rate-determining step corresponds to the final C–H reductive elimination of the aryl byproduct, while for pathway **II** it is the C–H initial bond activation that determines the energy requirements. Nevertheless, for the latter the final reductive elimination is almost as high in energy requirements.

The analysis of the bond distances of the transition state structures shows a similar behavior to the one indicated in the previous pages for systems with monodentate N$_{(imine)}$ and SMe$_2$ ligands. Nevertheless, for the H–Pt–(Aryl) torsion angles the trend is not as clear as before. Table 8 collects the smallest H–Pt–(Aryl) torsion angles found in

the C–H oxidative addition and reductive elimination transition states for the computed reactivity of the complexes of type **A** in entries 7 and 8 of Table 3. Nevertheless, as in the previous section, a correlation exists between the torsion angle values and the energy demands of the corresponding transition state (Table 7). Angles closer to 90 º are associated with the lower energy transition states, while smaller angles relate to an increase of the energy requirements. However, for the system of entry 7 in the previous tables, the reductive elimination transition state **RETS-CH$_5$** (on the way to a type **5C** species) appears to be quite low in energy when associated with the torsion angle value (Table 8). Even so, a careful analysis reveals that the relatively small torsion angle is in fact larger than those found for the analogous transition states of the reactivity of the systems of entries 1, 3, 5, and 8 from Table 3 (**RETS-CH$_5$** H–Pt–(Aryl) torsion angles being 52.5, 52.3, 53.8 and 53.2° respectively). This, somehow, low energetic requirement could be directly related to the preferential formation of compound of type **5C** in this case, thus explaining the switching in reactivity from the obtention of type **7C** complexes.

Table 8. Smallest H–Pt–(Aryl) torsion angles (in degrees) and computed free energies (in kJ mol^{-1}) for the transition states indicated in Table 7 for the C–H activation and reductive elimination reactions studied.

TABLE 8 HERE

The experimental observation that the spontaneous reaction of type **A** complex in entry 7 on Table 3 is much faster than that of the system of entry 8, can be immediately associated with the calculated energy demands above (Table 8).[11] The computed free energies for the reactions, despite differences in reaction conditions and calculations, indicate that for the bromido complex (entry 7) the energy requirement is 8 kJ mol^{-1} less

than for the chloride analogue (entry 8). Furthermore, for the systems from entries 7 and 8 of Table 3, the reactivity shown in Scheme 16 has been found to take place after a kinetically and spectroscopically detected **B*trans*** ⇄ **B*cis*** rearrangement (see Kinetic studies section). Consequently, the highest barrier found in the preferred reaction pathway for each compound in Scheme 16 has to be lower than that for the isomerization reaction. Indeed, this is observed for the computed data for both systems; even for some other systems the isomerization reaction has been found to be rate-determining.[13] For the bromido compound (entry 7 of Table 3) the isomerization (**Isom_TS**) and reductive elimination (**RETS-CH$_5$**) barriers are 138.4 and 141.5 kJ mol^{-1}, respectively; for the chlorido compound of entry 8 the isomerization transition state (**Isom_TS**) and the C–H oxidative addition transition state (**OATS-CH$_7$**) have values of 140.1 and 149.8 kJ mol^{-1} respectively.

As a whole, the data collected in Table 7 allow the building of a qualitative kinetic simulation model for evaluating the formation, over time of the final five- and seven-membered platinacycle compounds of types **5C** and **7C** from the starting **B*cis*** complexes of entries 7 and 8 in Table 3 (Figure 10). A very satisfactory qualitative agreement is found, even though the minor product is present in significant amounts in both complexes: for the bromido compound in entry 7 the **5C**:**7C** ratio is 87:13, while for the chlorido complex in entry 8 the ratio diminishes to 73:24. These results indicate that, unfortunately, the computed free energy differences between pathways **I** and **II** are not as important as they should be from the experimentally collected results. Nevertheless the overall trend and selectivity is successfully explained.

FIGURE 10 HERE

Figure 10. Qualitative product concentration evolution over time for Pt^{II} complexes with chelate $N_{(amino)}$-$N_{(imine)}$ ligands (Entries 7 and 8 in Table 3) in arbitrary time scale (solid line, compounds of type **A**; dashed line, compounds of type 7**C**; dotted line, compounds of type **5C**).

In order to validate the employed methodology, the mechanism indicated in Scheme 16 has been also computed for the reaction of the fluorinated compounds on entries 9 and 10 in Table 3. As stated before, for these systems the formation of the five-membered platinacycles of type **5C** is not possible, thus only pathway **II** has been computed (Table 9).

Table 9. Computed relative free energies (in kJ mol^{-1} and in toluene solution at 110 °C) for the reaction leading to Pt^{II} compounds of type **7C** from complexes of type **A** with chelate $N_{(amino)}$-$N_{(imine)}$ ligands (entries 9 and 10 of Table 3).

TABLE 9 HERE

The calculated energy requirements for the process producing the compounds of type **7C**, although very similar for both complexes, are slightly lower (*ca.* 1 kJ mol^{-1}) for the system containing the chlorido ligand (entry10 on Table 3). The experimental data collected, as indicated in the previous section indicate that the rate of formation of the chlorido compound of type **7C** is *ca.* four times faster than that of the analogous bromido complex (entry 9 on Table 3).[11] The qualitative kinetic model built for these processes totally agrees with this observation. Figure 11 shows the concentration-time profile for the formation of seven-membered platinacycles of type **7C** from complexes

of type **A** in entries 9 and 10 of Table 3; as predicted, the product ratio obtained is 1:4 in favor for the chlorido species.

FIGURE 11 HERE

Figure 11. Qualitative product concentration evolution over time for Pt^{II} complexes with chelate $N_{(amino)}$-$N_{(imine)}$ ligands (Entries 9 and 10 in Table 3) in arbitrary time scale.

5. Concluding remarks

In this contribution, we have illustrated how a series of oxidative addition and reductive elimination reactions, occurring on platinum(II) organometallic complexes, can be resolved experimentally by the use of an appropriate interlock between preparative and kinetic methodologies. Namely, the reaction of bis(aryl)platinum(II) precursors with imine or amino-imine ligands leads to the formation of platinacyclic compounds with five- or seven-membered metallacycles *via* a sequence that involves C-X bond oxidative addition *plus* reductive C-C coupling *followed by* C-H oxidative addition with a *final* C-H reductive elimination. Given the fact that the process includes a series of non-simple and fairly slow processes, several intermediates have been proposed and fully characterized in the reaction media. Nevertheless, with the precision of the approach some of these characterized species are found to be completely irrelevant in the sequential reaction pathway; that is they are *de facto* false intermediates or dead-end compounds.

The kinetico-mechanistic studies carried out on this time-resolved reactivity has provided series of thermal and pressure derived activation parameters that has allowed a fairly comprehensive description of the reaction sequence involved in the full process.

Nevertheless, a careful and comprehensive analysis has had to be applied, since the rate sequence is not uniformly applicable for the full series of complexes. That is, the combination of two reactions having only slightly different activation energies produces dramatic changes when taken jointly, and the rate-determining step of the full process could differ within a series of very similar reactions.

In this respect, the synergy between experiments and DFT calculations has been found to be very important in order to improve the understanding of both the mechanisms involved and the observed reactivity. DFT calculations have not only ascertained the elementary reaction steps of the process, they have also explained the kinetic preference for the less thermodynamically stable products, found in the majority of cases. Furthermore, the presence and incidence in the overall process of dead-end false intermediate compounds can be also assessed through calculations.

It is thus clear that computational studies, when fully supported by the empirical results, are able to fill in the areas of the puzzle that cannot be experimentally explored and resolved. In this respect, the set of studies presented in this contribution constitute a perfect example of how a close collaboration between experimentalists and theoreticians, with their specific perspectives when observing and interpreting data, provides remarkable value-added results to the work carried out.

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