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Synthesis and crystal structure of the dinuclear cyclopalladated compounds of methyl (*E*)-4-(benzylideneamino)benzoate with acetato and chlorido bridge ligands: Study of their splitting reactions with pyridine

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ABSTRACT

Reaction of methyl (*E*)-4-(benzylideneamino)benzoate $C_6H_5CH{=}N(C_6H_4\text{-}4\text{-}CO_2Me)$ with $Pd(OAc)_2$ produced the dinuclear acetato bridge *ortho*-cyclopalladated compound $[Pd\{C_6H_4CH{=}N(C_6H_4\text{-}4\text{-}CO_2Me)\text{-}\kappa\boldsymbol{C}_{ortho},\kappa\boldsymbol{N}\}]_2(\mu\text{-}OAc)_2$ (**1**). Compounds $[Pd\{C_6H_4CH{=}N(C_6H_4\text{-}4\text{-}CO_2Me)\text{-}\kappa\boldsymbol{C}_{ortho},\kappa\boldsymbol{N}\}]_2(\mu\text{-}Cl)_2$ (**2**) and $[Pd\{C_6H_4CH{=}N(C_6H_4\text{-}4\text{-}CO_2Me)\text{-}\kappa\boldsymbol{C}_{ortho},\kappa\boldsymbol{N}\}(py)(X)]$ [**3** (X = OAc); **4** (X = Cl)] were also prepared and isolated in good yields by substitution reactions. ^1H and $^{13}C\{^1H\}$ NMR in $CDCl_3$ solution of compounds **3** and **4** revealed that they consisted of a mixture of *trans*- and *cis*-***N,N*** isomers. Addition of pyridine-d_5 to solutions of **1** and **2** in $CDCl_3$ in a molar ratio pyridine-d_5/**1** or **2** ≈ 50–55 gave solutions **A** and **B**, respectively, which contained compounds **5** and **6** analogous to **3** and **4**, but with pyridine-d_5 rather than pyridine in their structural formula. In these solutions, the *trans*- and *cis*-***N,N*** geometrical isomers of compounds **5** and **6** were interconverting between them in a dynamic equilibrium. In addition, an exchange between free and coordinated pyridine-d_5 was also taking place in solutions **A** and **B**. The NMR data for solution **A** showed that the dynamic equilibrium between the *cis*- and *trans*-***N,N*** isomers of compound **5** was shifted to the *trans*-***N,N*** isomer. However, the NMR data for solution **B** suggested that in this solution the equilibrium between the *cis*- and *trans*-***N,N*** isomers of compound **6** was shifted to the *cis*-***N,N*** isomer. Interconversion between the *trans*- and *cis*-***N,N*** isomers of compounds **5** and **6** in solutions **A** and **B** plausibly proceeded through the intermediate ionic complexes $[Pd\{C_6H_4CH{=}N(C_6H_4\text{-}4\text{-}CO_2Me)\text{-}\kappa\boldsymbol{C}_{ortho},\kappa\boldsymbol{N}\}(py\text{-}d_5)_2]X$ [**7** (X = OAc), **8** (X = Cl)]. Ionic complexes **7** and **8** were not observed in $CDCl_3$ solution but were the major species in D_2O solutions containing compounds **1** and **2** and pyridine-d_5 in a molar ratio pyridine-d_5/**1** or **2** ≈ 50–55. The crystal structure of the adduct **1**·2(CH_3COOH) and that of compound **2** were determined by single crystal X-ray diffraction. A theoretical study on the difference in free Gibbs energy in $CHCl_3$ solution between the *cis*- and *trans*-***N,N*** isomers of compounds **3** and **4** is also included in this work.

1. Introduction

In recent years, it has been shown that some ***N***-donor cyclometallated palladium(II) compounds present anticancer activity, both in *vitro* and *in vivo* in mouse models [1–4]. The anticancer activity of these compounds can be modulated by modifying the substituents at the ***N***-donor cyclometallated ligand or by changing through substitution reactions the co-ligands of the palladium(II)

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center [5,6]. Substitution reactions at palladium(II), in which the entering ligand is a DNA nitrogen base or a thiol function of an enzyme, such as Cathepsin B, or oxidation by palladium(II) of mitochondrial membrane protein thiol functions to disulphide groups, seem to be the starting reactions that could explain the cytotoxicity of this type of compounds towards cancer cells [4,7,8]. In addition, cyclopalladated compounds present application as precatalysts for carbon-carbon and carbon-heteroatom coupling reactions [9,10] and as Lewis acid catalysts for some organic reactions [9,11], between many other applications [12]. Furthermore, in recent years the cyclopalladation reaction has been successfully introduced in catalytic cycles that transform C–H bonds in C–C and C-heteroatom bonds [13–15]. Therefore, the study of the synthesis, reactivity and properties of cyclopalladated compounds is a subject of interest [12].

In this work, we deal with *i*) the synthesis and characterization of the dinuclear *ortho*-cyclopalladated compounds [Pd{C_6H_4CH=$N(C_6H_4$-4-CO_2Me)-κ***C***$_{ortho}$,κ***N***}]$_2$(μ-X)$_2$, compounds **1** (X = OAc) and **2** (X = Cl), derived from methyl (*E*)-4-(benzylideneamino)benzoate C_6H_5CH=$N(C_6H_4$-4-CO_2Me), *ii*) the synthesis and characterization of their pyridine and pyridine-d_5 mononuclear derivatives [Pd{C_6H_4CH=$N(C_6H_4$-4-CO_2Me)-κ***C***$_{ortho}$,κ***N***}(L)(X)], compounds **3** (L = pyridine, X = OAc), **4** (L = pyridine, X = Cl), **5** (L = pyridine-d_5, X = OAc) and **6** (L = pyridine-d_5, X = Cl), *iii*) the study of the stereochemistry and behaviour in solution of compounds **3**–**6**, and *iv*) a computational study related with the difference in free Gibbs energy in $CHCl_3$ solution between the *cis*- and *trans*-***N***,***N*** isomers of compounds **3** and **4**.

2. Results and discussion

Scheme 1 outlines the methods of preparation of the compounds under study and gives their numbering, and that of their hydrogen and carbon atoms for the discussion that follows. Complete assignment of the signals of the ^{1}H and ^{13}C{^{1}H} NMR for methyl (*E*)-4-(benzylideneamino)benzoate C_6H_5CH=$N(C_6H_4$-4-CO_2Me), compound **1** and the *trans*- and *cis*-***N***,***N*** isomers of compounds **3** and **4**, was achieved by two-dimensional ^{1}H–^{1}H and ^{1}H–^{13}C NMR experiments.

Methyl (*E*)-4-(benzylideneamino)benzoate was synthesized by a condensation reaction between equimolecular amounts of benzaldehyde and methyl 4-aminobenzoate. The acetato bridge cyclopalladated compound (**1**) was prepared by a cyclopalladation reaction between equimolecular amounts of $Pd(OAc)_2$ and methyl (*E*)-4-(benzylideneamino)benzoate. A metathesis reaction between compound **1** and an excess of LiCl was carried out to produce the chlorido bridge cyclopalladated complex (**2**). Details on the preparation of these compounds are given in Scheme 1 and in the experimental part.

Methyl (*E*)-4-(benzylideneamino)benzoate was a pale yellow solid soluble in $CDCl_3$, and in solution in this solvent afforded a single set of signals both in the ^{1}H and in the ^{13}C{^{1}H} NMR. These results suggested that methyl (*E*)-4-(benzylideneamino)benzoate consisted of only the *E*-stereoisomer in relation to the imine function [16]. The methinic proton and the methinic carbon atom of methyl (*E*)-4-(benzylideneamino)benzoate appeared at 8.44 and 161.7 ppm, respectively, and the C=N and C=O stretchings of the imine and ester functions produced intense bands at 1628 and 1717 cm^{-1}, respectively. In addition, the ESI (+) mass spectrum of methyl (*E*)-4-(benzylideneamino)benzoate gave an intense signal at 240.1 *m/z*, which corresponded to $[M+H]^+$.

Compounds **1** and **2** were red and yellow solids, and were quite and slightly soluble in $CDCl_3$, respectively. The C=N stretching of compounds **1** and **2** appeared at 1609 and 1605 cm^{-1}, as an intense band shifted to lower wavenumbers in relation to the free imine, which was consistent with the coordination of the iminic nitrogen to the palladium(II) center [17]. The asymmetric and symmetric stretchings of the acetato carboxylic functions of **1** produced broad intense bands at 1574 and 1415 cm^{-1}, indicating that the acetato ligands of **2** presented a bridging coordination mode [18]. The C=O stretching of the ester function for compounds **1** and **2** appeared at 1717 and 1719 cm^{-1}, respectively. In addition, the LDI-TOF (+) mass spectra of compounds **1** and **2** produced intense peaks for the cations $[M-X]^+$, where X was acetate for **1** and chloride for **2**, in agreement with their dinuclear structure with acetato and chlorido bridge ligands [19].

The main features of the ^{1}H NMR of compound **1** in $CDCl_3$ solution were *i*) the high-field shift of the methinic proton in relation to the free imine by 0.72 ppm, *ii*) the high-field shift of the H2 proton (6.58 ppm) in relation to the free ligand (7.53–7.47 ppm), and *iii*) the presence of only one singlet produced by the methyl protons of the acetato ligands and by the protons of the methoxycarbonyl functions, which appeared at 1.86 and 3.95 ppm, respectively. Overall the precedent characterization data for compound **1** were consistent with a κ***C***$_{ortho}$,κ***N*** bidentate chelate coordination mode for its imine ligands and with this compound adopting a *trans*-folded dinuclear structure with acetato ligands bridging the palladium(II) centers [19–22].

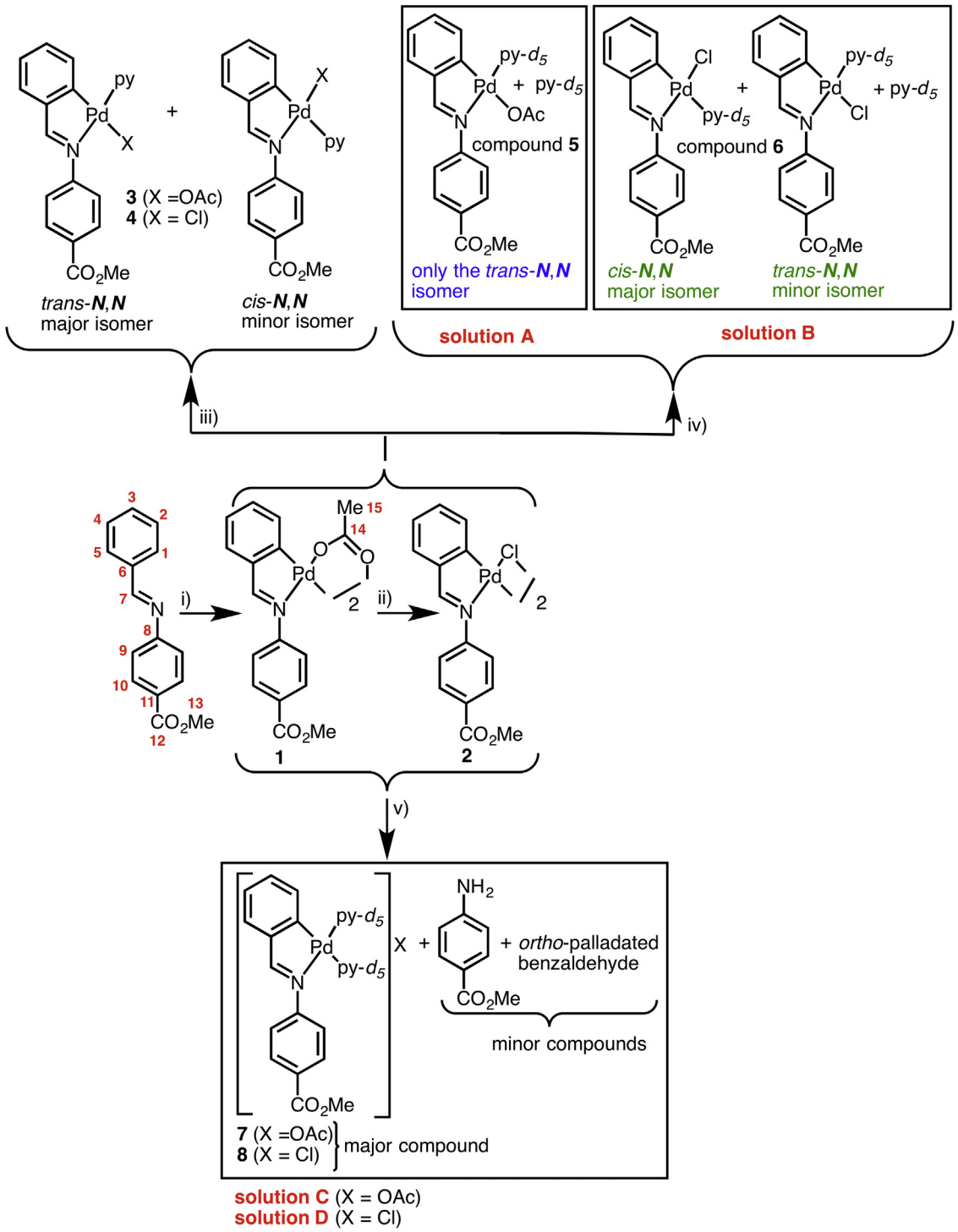
The ^{13}C{^{1}H} NMR in $CDCl_3$ of compound **1** produced a single set of signals, which presented as principal features *i*) the low-field shift of the methinic and the metallated carbon atoms in relation to the free imine by 11.8 and 3.6 ppm, respectively, and *ii*) the single set of signals afforded by the carbon atoms of the acetato ligands, which appeared at 180.6 and 24.2 ppm, and by the carbon atoms of the methoxycarbonyl functions, which resonated at 166.4 and 52.3 ppm. These data were consistent with the κ***C***$_{ortho}$,κ***N*** coordination mode of the imine ligands in compound **1** and with its *trans* stereochemistry [19].

The ^{1}H NMR of compound **2** in $CDCl_3$ at 298 K produced one set of signals, most of them broad, except the methinic protons, which afforded a singlet at 8.01 ppm, 0.43 ppm high-field shifted in relation to the free imine, and the protons of the methoxycarbonyl functions, which produced a singlet at 3.96 ppm. The broadening of the proton NMR signals of dinuclear cyclopalladated compounds with chlorido bridge ligands in $CDCl_3$ has been ascribed to a dynamic equilibrium between their *cis* and *trans* isomers [23].

X-ray quality yellow crystals of the adduct **1**·2(CH_3CO_2H) and of compound **2** were obtained by slow evaporation at room temperature of a solution in acetic acid of **1** and of a solution in chloroform of complex **2**, respectively. Adduct **1**·2(CH_3CO_2H) and compound **2** crystallized in the triclinic P-1 with Z = 2 and in the orthorhombic *Pccn* with Z = 4 space groups, respectively. Details on the X-ray crystallographic structure determinations are given in the Supplementary Material.

Figs. 1 and 2 show ball and stick models for the XRD molecules of compounds **1** and **2**, respectively, together with some distances and angles for them. In the crystal of **1**·2(CH_3CO_2H), the two halves of the molecule of **1** were not equivalent and differed between them only in small differences in distances and angles. On the other hand, in the crystal of **2**, both halves of the molecule of **2** were equivalent since the molecule was situated over a crystallographic center of inversion.

Bond distances and angles around of the palladium(II) centers for the molecules of **1** and **2** were between the normal intervals [5,19,24–26]. The chelate bite angles at palladium(II) showed the largest deviations from the ideal angle of 90°, being 80.0(2)° and 80.7(2)° for **1** and 81.6 (4)° for **2**. The five-membered metallacycles were planar and maximum deviated atoms from the five-membered planar metallacycles were N(1) [0.008(5) Å] and N(2) [−0.022(5) Å] for **1** and C(3) [0.054(13) Å] for **2**. In **1** and **2**, the Pd–O



Scheme 1. i) $Pd(OAc)_2$, HOAc, 60 °C, molecular ratio methyl (*E*)-4-(benzylideneamino)benzoate/$Pd(OAc)_2$ = 1; ii) LiCl excess, acetone, room temperature; iii) pyridine, CH_2Cl_2, room temperature, molar ratio pyridine/**1** or **2** ≈ 3; iv) pyridine-d_5, $CDCl_3$, room temperature, molar ratio pyridine-d_5/**1** or **2** ≈ 50–55, v) pyridine-d_5, D_2O, room temperature, molar ratio pyridine-d_5/**1** or **2** ≈ 50–55. Reactions in deuterated solvent were performed treating *ca.* 6 mg of compound **1** or **2** with 1 cm^3 of the corresponding deuterated solvent and *ca.* 30 mg (30 μL) of pyridine-d_5.

and Pd–Cl bonds *trans* to the metallated carbon atoms were longer than the corresponding bonds *trans* to the iminic nitrogen atom [Pd(1)–O(1) = 2.161(4) Å and Pd(2)–O(4) = 2.156(4) Å but Pd(1)–O(3) = 2.041(4) Å and Pd(2)–O(2) = 2.050(4) Å for **1**, and Pd1–Cl2i = 2.464 (3) Å but Pd1–Cl2 = 2.337 (3) Å for **2**]. These results were in agreement with the greater *trans* influence of the palladated carbon atom in relation to the iminic nitrogen atom [27].

The angle between the palladacycles in compound **1** was 30.8(2)° and the distance between palladium atoms was 2.9175(13) Å. This distance was too long for being considered a palladium–palladium single bond [28]. In compound **2**, the palladacycles and the chlorido bridging ligands defined a plane (plane **1**). For compound **1**, the angles between the phenyls bonded to the iminic nitrogen atoms and the metallacycles were 50.8(3) and

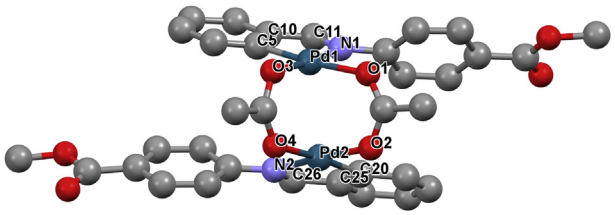


Fig. 1. XRD molecular structure of compound **1**. Hydrogen atoms and solvent molecules have been omitted for clarity. Selected bond distances (Å) and angles (°): Pd(1)–C(5) 1.993(6), Pd(1)–O(3) 2.041(4), Pd(1)–N(1) 2.052(4), Pd(1)–O(1) 2.161(4), Pd(1)–Pd(2) 2.9175(13), Pd(2)–C(20) 1.982(5), Pd(2)–O(2) 2.050(4), Pd(2)–N(2) 2.054(5), Pd(2)–O(4) 2.156(4), N(1)–C(11) 1.298(7), N(2)–C(26) 1.299(7), C(25)–C(26) 1.444(7), C(10)–C(11) 1.425(7), C(20)–C(25) 1.364(7), C(5)–C(10) 1.411(8), C(5)–Pd(1)–O(3) 92.4(2), C(5)–Pd(1)–N(1) 81.0(2), O(3)–Pd(1)–N(1) 173.13(17), C(5)–Pd(1)–O(1) 175.28(18), O(3)–Pd(1)–O(1) 88.60(17), N(1)–Pd(1)–O(1) 97.84(17), C(20)–Pd(2)–O(2) 91.8(2), C(20)–Pd(2)–N(2) 80.7(2), O(2)–Pd(2)–N(2) 172.53(17), C(20)–Pd(2)–O(4) 175.24(18), O(2)–Pd(2)–O(4) 88.15(16), N(2)–Pd(2)–O(4) 99.25(17), C(10)–C(5)–Pd(1) 112.4(4), C(5)–C(10)–C(11) 115.4(5), N(1)–C(11)–C(10) 117.2(5), C(11)–N(1)–Pd(1) 113.9(4), C(26)–N(2)–Pd(2) 112.7(4), N(2)–C(26)–C(25) 117.6(5), C(20)–C(25)–C(26) 114.5(5), C(25)–C(20)–Pd(2) 114.3(4).

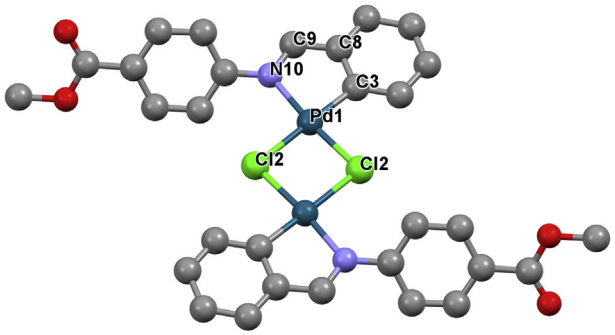


Fig. 2. XRD molecular structure of compound **2**. Hydrogen atoms have been omitted for clarity. Selected bond distances and angles: Pd1–C3 1.980 (13), Pd1–N10 2.089 (9), Pd1–Cl2 2.337 (3), Pd1–Cl2i 2.464 (3), C9–N10 1.304 (15), C8–C9 1.414 (17), C3–C8 1.428 (16), C3–Pd1–N10 81.6 (4), C3–Pd1–Cl2 93.7 (3), N10–Pd1–Cl2 174.6 (3), C3–Pd1–Cl2i 177.1 (4), N10–Pd1–Cl2i 100.5 (3), Cl2–Pd1–Cl2i 84.08 (10), Pd1–⊜Cl2–Pd1i 95.92 (10), C11–N10–Pd1 127.9 (7), N10–C9–C8 119.6 (10), C9–C8–C3 114.6 (11), C8–C3–Pd1 112.4 (9).

41.0(3)°, and for compound **2**, the angle between the phenyls bonded to the iminic nitrogen atoms and plane **1** was 5.89(13)°. For compounds **1** and **2**, the methoxycarbonyl functions and the phenyl groups bonded to the methoxycarbonyl functions were coplanar.

Compounds **3**–**8** were prepared by splitting reactions between the corresponding compound **1** or **2** and pyridine (compounds **3**–**4**) or pyridine-d_5 (compounds **5**–**8**). Compounds **3** and **4** were isolated and fully characterized, whereas compounds **5**–**8** were studied by NMR in $CDCl_3$ solution (compounds **5** and **6**) or in D_2O solution (compounds **7** and **8**) in both cases in presence of free pyridine-d_5.

Compounds **3** and **4** were isolated, as yellow and pale-yellow solids in 82 and 97% yield, respectively. These compounds produced satisfactory elemental analyses, IR and MALDI-TOF-(+) mass spectra. In the IR spectrum of compound **3**, bands at 1720, 1604 and 1586 cm^{-1} were assigned to the C=O stretching of the ester function, the C=N stretching of the imine function and the C=O stretching of the carboxylate function of the terminal acetato ligand, respectively. The C=N stretching of the pyridine ligand of compound **3** was obscured by the strong band corresponding to the C=O stretching of the carboxylate function of the terminal acetato ligand. In the IR spectrum of compound **4**, bands at 1715, 1604 and 1586 cm^{-1} were assigned to the C=O stretching of the ester function, the C=N stretching of the imine function and the C=N stretching of the pyridine ligand, respectively. The MALDI-TOF (+) for compound **3** and **4** produced an intense signal for the cation $[M-X]^+$, where X was acetate for compound **3** and chloride for compound **4**. In addition, compound **4** produced also intense signals for the cations $[2M-Cl]^+$ and $[2M-Cl-py]^+$.

Interestingly, compounds **3** and **4** isolated from the solution resulting from the reaction in CH_2Cl_2 of compounds **1** and **2** with pyridine in a molar ratio pyridine/**1** or **2** ≈ 3 consisted of a mixture of *trans*- and *cis*-***N,N*** isomers (Scheme 1). The relative integral of the signals of the *ortho* protons of the coordinated pyridine allowed to establish the ratio between the *trans* and *cis* isomers of compounds **3** and **4** in $CDCl_3$, which were 1.0:0.8 for compound **3** and 1.0:0.6 for compound **4**. The ratio between the geometrical isomers of **3** and **4** in $CDCl_3$ solution was unaltered after maintaining the precedent solutions at room temperature for two days. Interestingly, the *cis*-***N,N*** isomer of compounds **3** and **4** produced somewhat broad signals for the *ortho* protons of the coordinated pyridine, suggesting that an exchange between the coordinated pyridine *trans* to the palladated carbon atom and an adventitious free L ligand (water or pyridine) was taking place in these solutions. The strong *trans* effect produced by the metallated carbon atom into the coordinated pyridine in the *cis*-***N,N*** isomer of compounds **3** and **4** should favour this exchange [29].

Addition of pyridine-d_5 to a solution of compound **1** in $CDCl_3$ (*ca.* 6 mg of compound **1** in 1 cm^3 of $CDCl_3$) in a molar ratio pyridine-d_5/**1** ≈ 50–55 gave solution **A**. Solution **A** contained as observable palladium(II) compound by ^1H NMR at 400 MHz and at room temperature, compound **5**, which was analogous to compound **3** but with a pyridine-d_5 ligand rather than a pyridine ligand in its structural formula. Doublet signals at 7.83 and 6.63 ppm and a singlet at 3.89 ppm were assigned to methyl 4-aminobenzoate (4-$H_2NC_6H_4CO_2Me$). The molar ratio between compound **5** and methyl 4-aminobenzoate was *ca.* 20. Noteworthy, compound **5** in solution **A** consisted of only the *trans*-***N,N*** geometrical isomer by ^1H NMR at 400 MHz and at room temperature. Thus, a large excess of pyridine-d_5 promoted the *cis* → *trans* isomerization of compound **5**. The precedent results indicated that the *cis*- and *trans*-***N,N*** isomers of compound **5** (or **3**) were the kinetic and thermodynamic control products, respectively, for the reaction **1** + 2 py-d_5 (or 2 py) → **5** (or **3**) (reaction *α*). For reaction *α*, the *cis*-***N,N*** isomer should be the kinetic control product of the reaction due to the strong *trans* effect produced by the metallated carbon atoms into the acetato ***O***-donor atoms *trans* to them in the initial compound **1** [29].

The signals of the aromatic protons of compound **6** in solution **B** at 500 MHz and at 298 K were broad but only one palladium(II) species was observed. Solution **B** was analogous to solution **A** but contained *ca.* 6 mg of compound **2** rather than 6 mg of compound **1**. In the ^1H NMR of solution **B** at 500 MHz and at 298 K, the H10 and H9 protons of compound **6** produced broad signals at 7.97 and 7.12 ppm. These chemical shifts were between the chemical shifts of the H10 and H9 protons of the *cis*-***N,N*** (7.76 and 7.00 ppm) and the *trans*-***N,N*** (8.09 and 7.51 ppm) isomers of compound **4**. These results indicated that the *cis*- and *trans*-isomers of compound **6** were in a fast dynamic equilibrium between them in solution **B**. The lack of a signal of an aromatic proton in the interval between 7.00 and 6.00 ppm and the fact that the chemical shift of the H9 protons (7.12 ppm) was closer to the chemical shift of the H9 protons of the *cis*-***N,N*** isomer (7.00 ppm) than that for the H9 protons of the *trans*-***N,N*** isomer (7.51 ppm) suggested that the *cis*-***N,N*** isomer of compound **6** was the major species in solution **B**. It should be noted that the exchange between coordinated and free pyridine-d_5 in the *cis*-***N,N*** isomer of compound **6** in solution **B** could also be contributing to the broadening of the signals. The strong *trans* effect produced by

the palladated carbon atom on the coordinated pyridine-d_5 in the *cis*-***N,N*** isomer of compound **6** should favour this latter exchange [29].

Interestingly, the ^{1}H NMR of a solution of *ca.* 6 mg of compound **2** in 1 cm^3 of $CDCl_3$ and containing a molar ratio between pyridine-d_5 and compound **2** of *ca.* 4 (solution **B**′) or by reducing the temperature of solution **B** to 223 K (solution **B**″), produced separated signals for the *cis*- and *trans*-***N,N*** isomers of compound **6**, as established by ^{1}H NMR at 400 MHz in the first case, and at 500 MHz in the second. Diagnostic signals for the *cis*- and the *trans*-***N,N*** isomers of compound **6** were the broad signals at 7.80 ppm (H10 protons of the *cis*-***N,N*** isomer) and at 6.12 ppm (H2 proton of the *trans*-***N,N*** isomer). From the ratio between the integral of the H2 proton at 6.12 ppm of the *trans*-***N,N*** isomer of compound **6** and the integral of the protons of the methoxycarbonyl function of compound **6**, which afforded only one sharp signal for the *cis*- and *trans*-isomers of compound **6** at 3.90 ppm in all solutions **B**, it was established that in solutions **B**′ and **B**″ the ratio between the *cis*- and *trans*-***N,N*** isomers of compound **6** was *ca.* 1.

A ^{1}H – ^{1}H COSY recorded on solution **B**″ at 500 MHz, confirmed the assignment of the proton at 6.12 ppm to the H2 proton of the *trans*-***N,N*** isomer of compound **6**, since this proton in the COSY experiment showed a sequential correlation with three more aromatic protons, the last identified as the H5 proton of the *ortho*-palladated phenyl ring of the *trans*-***N,N*** isomer of compound **6**. The H2 proton of the *trans*-***N,N*** isomer of compound **6** was shifted at high-field because it was located in the shielding zone of the coordinated pyridine-d_5 [19,25,30,31]. Fig. 3 gives an expansion of the aromatic region of the ^{1}H–^{1}H COSY experiment of solution **B**″ at 500 MHz showing the COSY signals between the protons of the *ortho*-palladated ring of the *trans*-***N,N*** isomer of compound **6**.

NMR data for solutions **B**, **B**′ and **B**″ indicated that a large excess of pyridine-d_5 promoted the geometrical isomerization of compound **6** and, noteworthy, suggested that the *cis*-***N,N*** isomer of compound **6** (or **4**) was simultaneously the kinetic and thermodynamic control product for the reaction **2** + 2 py-d_5 (or 2py) → **6** (or **4**) (reaction β). For reaction β, the *cis*-***N,N*** isomer should be the kinetic control product of the reaction due to the strong *trans* effect produced by the metallated carbon atoms into the chlorido bridge ligands *trans* to them in the initial compound **2** [29].

In the ^{13}C{^{1}H} NMR at 101 MHz of solution **B** and at room temperature, the carbon signals of the coordinated pyridine-d_5, the carbon bonded to the palladium atom, and the carbons of the phenyl bonded to the iminic nitrogen atom of compound **6** were not observed. On the other hand, the ^{1}H NMR of solution **A** at 400 MHz and at room temperature produced narrow signals for the *trans*-***N,N*** isomer of compound **5**, and in its ^{13}C{^{1}H} NMR at 101 MHz and at room temperature, all the ^{13}C signals were observed, except those of the coordinated pyridine-d_5. Thus, an exchange between free and coordinated pyridine-d_5 was also taking place in solutions **A** and **B**, but this exchange was taking place at a slower rate in solution **A** [19]. The weaker *trans* effect produced by the iminic nitrogen on the coordinated pyridine-d_5 on the *trans*-***N,N*** isomer of compound **5**, in relation to the *trans* effect produced by the palladated carbon atom on the coordinated pyridine-d_5 on the *cis*-***N,N*** isomer of compound **6** should explain this result [29]. In addition, the bulkier acetato terminal ligand in compound **5** in relation to the chlorido terminal ligand in compound **6**, could also decrease the rate of the exchange in solution **A** in relation to solution **B**.

In order to obtain more information on the relative stability of the *cis*- and *trans*-***N,N*** isomers of compounds **3** and **4**, the difference between their electronic energy, absolute enthalpy and absolute

Table 1
Energy differences calculated at the DFT/B3LYP level between the *cis*- and *trans*-***N,N*** isomers for compounds **3** and **4** in kcal mol^{-1}. Positive values indicate that the *trans*-***N,N*** isomer is more stable than the *cis*-***N,N*** isomer. ΔE = electronic energy(*cis*-***N,N***) – electronic energy(*trans*-***N,N***). ΔH = absolute enthalpy(*cis*-***N,N***) – absolute enthalpy(*trans*-***N,N***). ΔG = absolute Gibbs free energy(*cis*-***N,N***) – absolute Gibbs free energy(*trans*-***N,N***). v = vacuum. $CHCl_3$ = chloroform solution.

Compound	ΔE(v)	ΔE($CHCl_3$)	ΔH(v)	ΔH($CHCl_3$)	ΔG(v)	ΔG($CHCl_3$)
3	−0.66	0.05	−0.74	−0.03	−1.57	−0.87
4	−2.31	−0.78	−2.40	−0.87	−2.88	−1.35

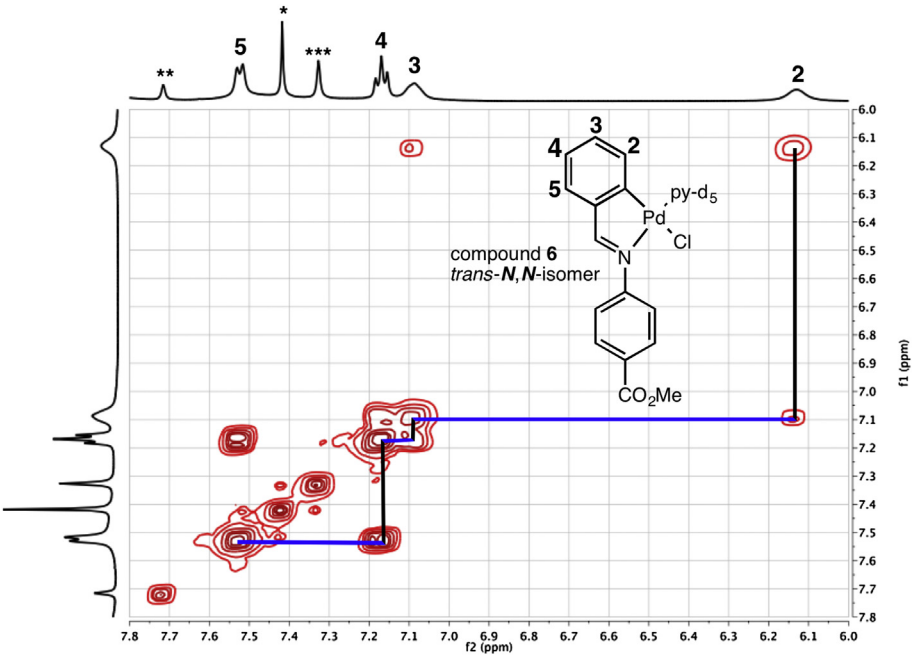


Fig. 3. Expansion of the aromatic region of the ^{1}H–^{1}H COSY experiment at 500 MHz of solution **B**″ (solution **B** at 223 K). * Residual $CHCl_3$ in $CDCl_3$. ** Residual p-C_5HD_4N in pyridine-d_5. *** Residual m-C_5HD_4N in pyridine-d_5.

Gibbs free energy in vacuum and in $CHCl_3$ solution were calculated. Table 1 summarizes the results. Mol files for the optimized geometries for the *trans*- and *cis*-isomers of compounds **3** and **4** and the details of the computational calculations are given in the Supplementary Material. Only the difference of absolute Gibbs free energy in chloroform solution between the *cis*- and *trans*-***N,N*** isomers of compounds **3** and **4** (the last column in Table 1) is discussed because the experimental studies were performed in $CDCl_3$ solution. It should be noted that although the computational study predicted that for both compounds the *cis*-***N,N*** isomer was the most stable one, experimentally the more stable isomer for compound **5** was the *trans*-***N,N*** isomer. However, the computational study predicted in agreement with what was suggested by the experimental work that *i*) the thermodynamic preference for the *cis*-***N,N*** isomer for compound **4** (with a terminal chlorido ligand) was higher than for compound **3** (with a terminal acetato ligand), and *ii*) the difference between the absolute Gibbs free energy in $CHCl_3$ solution for the *cis* and *trans* isomers of compounds **3** and **4** was small.

Relevant to understand the mechanism of the geometrical isomerization of compounds **5** and **6**, compounds **1** and **2** (*ca.* 6 mg), reacted with pyridine-d_5 in D_2O (1 cm^3) in a molar ratio pyridine-d_5/**1** or **2** ≈ 50–55 to form solutions **C** and **D**, which contained as major compounds, the ionic mononuclear cyclopalladated complexes **7** (X = OAc) and **8** (X = Cl) of formula [Pd{C_6H_4CH=N(C_6H_4-4-CO_2Me)-κ***C***$_{ortho}$,κ***N***}(py-d_5)$_2$]X (Scheme 1). The ionic complexes **7** and **8** were not isolated but were characterized in D_2O solution by mono- and bidimensional NMR experiments. *Ortho*-palladated benzaldehyde and methyl 4-aminobenzoate were also observed by NMR in solutions **C** and **D**. The molar ratio between compounds **7** or **8**, *ortho*-palladated benzaldehyde and methyl 4-aminobenzoate in solutions **C** and **D** was *ca.* 1.0: 0.2: 0.2. For the ionic complexes **7** and **8**, the H2 and H9 protons were shifted at high-field (6.19 and 7.02 ppm for compound **7** in solution **C** and at 6.12 and 6.96 ppm for compound **8** in solution **D**) because both type of protons were located in the shielding zone of a pyridine-d_5 ligand [19,25,30,31].

In solutions, **C** and **D**, the *ortho*-palladated benzaldehyde afforded a singlet signal for the proton of the aldehyde function at *ca.* 10.5 ppm and an aromatic system corresponding to a 1,2-disubstituted phenyl ring. On the other hand, methyl 4-aminobenzoate produced signals at *ca.* 7.7 and 6.7 for the aromatic protons and at 3.8 ppm for the methoxycarbonyl protons. The exchangeable amino protons of methyl 4-aminobenzoate were not observed in D_2O.

The κ***C***$_{ortho}$,κ***N*** bidentate chelate coordination mode of the imine ligand in compounds **3** and **4** and compounds **5**–**8** in solutions **A** – **D** was consistent with the high-field shift of the methinic proton of these compounds *ca.* 0.30–0.40 ppm in relation to the free imine ligand [5,6,19,21,22,25] and with the fact that the metallated and the methinic carbon atoms appeared low-field shifted *ca.* 10–20 ppm relative to the free imine ligand [19].

The detection in solutions **C** and **D** of the ionic complexes **7** and **8** suggested that the geometrical isomerization experimented by compounds **5** and **6** in solutions **A** and **B** proceed through the reversible consecutive displacement mechanism given in Fig. 4. The ionic complex **7** or **8** would not be an observable intermediate in $CDCl_3$ by ^1H NMR but at a high concentration of pyridine-d_5 the thermodynamic equilibrium between the geometrical isomers of compounds **5** and **6** in solutions **A** and **B** would be attained through the intermediate ionic complexes **7** and **8**. The reversible character of the reactions **I** and **II** (Fig. 4) was in agreement with the fact that when compound **1** reacted with pyridine in dichloromethane at room temperature for one day in a molar ratio pyridine/**1** ≈ 50–55, the isolated compound **3** from this reaction consisted of a mixture of *trans*- and *cis*-***N,N*** isomers.

It should be noted that the proposed mechanism for the geometrical isomerization of the discussed square planar palladium(II) is the most usual mechanism for the geometrical isomerization of square planar complexes of formula [ML_2X_2] (M = Pt(II) or Pd(II), L = neutral monodentate ligand, X = monoanionic monodentate ligand), and it is termed the consecutive displacement mechanism [32].

In summary, the experimental data indicated that in solutions **A** and **B** the *trans*- and *cis*-***N,N*** isomers of compounds **5** and **6** were interconverting between them in a dynamic equilibrium. In addition, an exchange between free and coordinated pyridine-d_5 was also taking place in these solutions. In solution **A**, the dynamic equilibrium between the *cis*- and *trans*-***N,N*** isomers of compound **5** was shifted to the *trans*-***N,N*** isomer. However, NMR data for solution **B** suggested that in this solution the dynamic equilibrium between the *cis*- and *trans*-***N,N*** isomers of compound **6** was shifted to the *cis*-***N,N*** isomer. Interconversion between the *trans*- and *cis*-***N,N*** isomers of compounds **5** and **6** in solutions **A** and **B** could proceed through the intermediate ionic complexes of formula [Pd{C_6H_4CH=N(C_6H_4-4-CO_2Me)-κ***C***$_{ortho}$,κ***N***}(py-d_5)$_2$]X, **7** (X = OAc) and **8** (X = Cl). Ionic complexes **7** and **8** were not observed in $CDCl_3$ solution but were the major species detected by NMR in D_2O solutions containing compounds **1** and **2** (*ca.* 6 mg of **1** or **2** in 1 cm^3 of D_2O) and pyridine-d_5 in a molar ratio pyridine-d_5/**1** or **2** ≈ 50–55.

A reviewer suggested that a π-stacking interaction between the aryl ring bonded to the iminic nitrogen and the pyridine could stabilize the *cis*-***N,N*** isomers of compounds **3** and **4**. We have found five crystal structures of an sp^2 ***N***-donor cyclopalladated compound containing an aryl group attached to the sp^2 ***N***-donor nitrogen and a pyridine ligand *trans* to the palladated carbon atom [33–36]. In these crystal structures, the aryl ring attached to the sp^2 ***N***-donor atom and the pyridine are in a face-to-face conformation. Table 2 gives the distances between the centroids of the aryl ring attached to the sp^2 ***N***-donor nitrogen (aromatic ring **X**) and that of the pyridine (aromatic ring **Y**) in these crystal structures. Table 2 shows that only two of these distances are in the range expected for a significant π-stacking interaction (CCDC numbers 732584 and 848290).

2.1. Experimental part

^1H and $^{13}C\{^1H\}$ NMR spectra and bidimensional ^1H–^1H and ^1H–^{13}C NMR experiments were recorded in a Varian Mercury 400. The ^1H NMR at 223 K and the ^1H–^1H COSY experiment at 223 K were registered at 500 MHz in a Bruker DMX 500 instrument. Chemical shifts were measured relative to $SiMe_4$ for ^1H and to residual solvent peaks for ^{13}C. Chemical shifts are reported in ppm and coupling constants in Hz. C, H, N microanalyses were performed with a Carlo-Erba EA 1108 instrument. IR spectra were collected with a Nicolet Avatar 300 FT-IR spectrometers using KBr discs. MALDI-TOF(+) mass spectra were registered with a VOYAGER-DE-RP spectrometer using dithranol (DTH), 2,5-dihydroxybenzoic acid (DHB) or *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as matrix. ESI(+) mass spectra were acquired with a LC/MSD-TOF mass spectrometer using H_2O/CH_3CN (1:1) as eluent. Chemical compounds were commercial and were used as received.

2.1.1. Preparation of C_6H_5CH=N(C_6H_4-4-CO_2Me)

Methyl (*E*)-4-(benzylideneamino)benzoate was synthesized by dissolving methyl 4-aminobenzoate (1465 mg, 9.69 mmol) in methanol (60 cm^3) followed by addition of benzaldehyde (1038 mg, 9.78 mmol). The resultant mixture was maintained under reflux for two hours, after which time the crude was allowed to cool down to room temperature. The solution was concentrated in vacuum (to

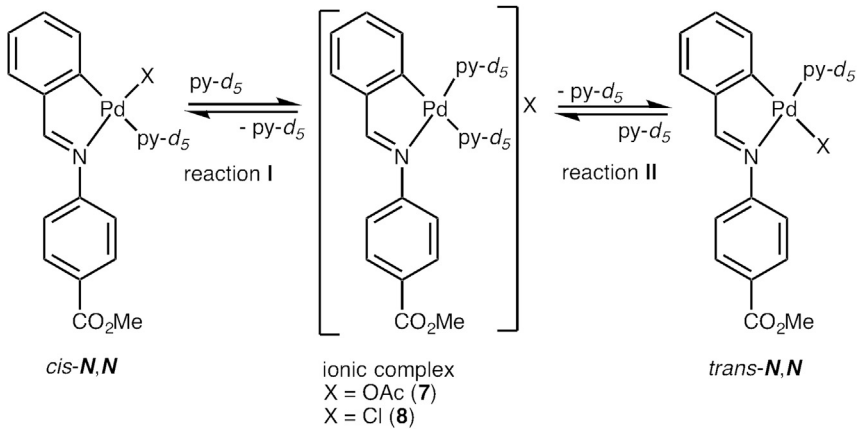


Fig. 4. Consecutive reversible reactions between the species present in solutions **A** and **B**, which could explain the geometrical isomerization taking place in these solutions.

Table 2
Distances in Å between the centroids of the aromatic rings **X** and **Y** (see the text for the definition of the aromatic rings **X** and **Y**).

CCDC number	Cg(X)-Cg(Y)
1299836	4.003(2)
621235	4.703(4)
603386	4.161(5)
732584	3.733(4)
848290	3.777(2)

about 20 cm^3) until precipitation was observed. The pale yellow solid obtained was filtered off and air-dried (1530 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 8.44 (s, 1H, 7), 8.08 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 10), 7.92 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.8 Hz, 2H, 1), 7.53–7.47 (m, 3H, 2, 3 and 5), 7.21 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 9), 3.93 (s, 3H, 13). ^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K), δ (ppm): 166.8 (12), 161.7 (7), 156.2 (8), 135.7 (6), 131.9 (3), 130.9 (10), 129.1 (1), 128.9 (2), 127.4 (11), 120.7 (9), 52.0 (13). IR (KBr, selected data), υ (cm^{-1}): 1717 (C═O st), 1628 (C═N st), 1275 (C–C–O as st), 1114 (C–C–O sym st). MS-ESI (+) {H_2O:CH_3CN (1:1)}, *m/z*: 240.1 (calcd. 240.1) $[M+H]^+$. Anal. Calcd. for $C_{15}H_{13}NO_2$: C 75.30%, H 5.48%, N 5.85%. Found: C 74.6%, H 5.3%, N 5.9%.

2.1.2. Preparation of compound **1**

A solution formed by palladium(II) acetate (226 mg, 1.01 mmol), methyl (*E*)-4-(benzylideneamino)benzoate (241 mg, 1.01 mmol) and 10 cm^3 of glacial acetic acid was heated to 60 °C for 24 h. Afterwards, the solvent of the orange suspension formed was removed under vacuum and the residue subjected to column chromatography (silica gel-60) using a 100: 4 chloroform: methanol mixture as eluent. The red coloured band was collected and evaporated. Addition of the minimum amount of diethyl ether (*ca.* 4 cm^3) gave the target complex as a yellow orangey solid (195 mg, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 7.86 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 10), 7.72 (s, 1H, 7), 7.28 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.4 Hz, 1H, 5), 7.11 (td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, 4), 6.94 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, 3), 6.86 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 9), 6.58 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, 2), 3.95 (s, 3H, 13), 1.86 (s, 3H, 15). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 298 K), δ (ppm): 180.6 (14), 173.5 (7), 166.4 (12), 155.7 (1), 150.9 (8), 145.3 (6), 132.5 (2), 131.2 (3), 131.1 (10), 129.6 (11), 128.9 (5), 128.2 (4), 124.2 (9), 52.3 (13), 24.2 (15). IR (KBr, selected data), υ (cm^{-1}): 1717 (C═O st, ester), 1609 (C═N st), 1574 (COO as st, bridging carboxylato), 1415 (COO sym st, bridging carboxylato), 1282 (C–C–O as st), 1114 (C–C–O sym st). MS-LDI TOF (+) ($CHCl_3$), *m/z*: 746.9 (calcd. 747.0) $[M - OAc]^+$. Anal. Calcd. for $C_{34}H_{30}N_2O_8Pd_2$: C 50.57%, H 3.74%, N 3.47%. Found: C 50.4%, H 3.8%, N 3.5%.

2.1.3. Preparation of compound **2**

A mixture formed by acetato-bridge complex **1** (200 mg, 0.25 mmol), lithium chloride (42 mg, 1 mmol) and acetone (10 cm^3) was stirred at room temperature for 2 h. Afterwards, the solvent of the orange mixture formed was eliminated under vacuum, and the residue eluted through a silica gel-60 column chromatography using dichloromethane:methanol (100:2) as eluent. The yellowish band was collected and concentrated in vacuum. Addition of diethylether (5 cm^3) to the residue produced the precipitation of compound **2** as a yellow solid, which was filtered and dried in vacuum (99 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 8.11 (br d, $^3J_{HH}$ = 7.6 Hz, 2H, 10), 8.01 (s, 1H, 7), 7.44 (br d, $^3J_{HH}$ = 7.3 Hz, 2H, 9), 7.35–7.33 (m, 2H, metallated ring), 7.10 (br s, 2H, metallated ring), 3.96 (s, 3H, 13). Solubility in chloroform was insufficient to obtain carbon NMR data. IR (KBr, selected data), υ (cm^{-1}): 1719 (C═O st), 1605 (C═N st), 1284 (C–C–O as st), 1116 (C–C–O sym st). MS-LDI TOF (+) (acetone), *m/z*: 722.8 (calcd. 722.9) $[M - Cl]^+$. Anal. Calcd. for $C_{30}H_{24}Cl_2N_2O_4Pd_2$: C 47.39%, H 3.18%, N 3.68%. Found: C 47.6%, H 3.3%, N 3.6%.

2.1.4. Preparation of compound **3**

100 mg of complex **1** (0.124 mmol) were treated with 6 cm^3 of a solution of pyridine in CH_2Cl_2 0.064 M (0.384 mmol of pyridine). The solution was allowed to stir at room temperature for 2 h, and thereafter volatiles were evaporated under reduced pressure. Upon addition of diethyl ether (4 cm^3) a light yellow precipitate formed, which was collected by filtration and air-dried (98 mg, 82% yield). Compound **3** consists of a mixture of *trans*-***N***,***N*** and *cis*-***N***,***N*** isomers in a 1.0 : 0.8 ratio. A similar result was obtained reacting 100 mg (0.124 mmol) of compound **1** with 399 mg (*ca.* 5 mmol) of pyridine in10 cm^3 of CH_2Cl_2 stirring at room temperature for 24 h. In this case, the ^{1}H NMR in $CDCl_3$ solution of the isolated compound **3** showed that it consisted of a mixture of *trans*- and *cis*-***N***,***N*** isomers in 1 : 0.56 ratio. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): [*trans*-***N***,***N***] 9.04 (d, $^3J_{HH}$ = 8.0 Hz, 2H, o-py), 8.09 (s, 1H, 7), 8.08 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 10), 7.88 (tt, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, p-py), 7.49 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 9), 7.47–7.44 (m, 2H, m-py), 7.42 (dd, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, 5), 7.12–7.07 (m, overlapped with 4 of *cis*-***N***,***N***, 1H, 4), 7.01 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, 3), 6.29 (d, $^3J_{HH}$ = 7.6 Hz, 1H, 2), 3.93 (s, 3H, 13), 1.55 (s, 3H, 15); [*cis*-***N***,***N***] 8.60 (br d, 2H, o-py), 7.86 (d, $^3J_{HH}$ = 8.6 Hz, partially overlapped with p-py of *trans*-***N***,***N***, 2H, 10), 7.72 (s, 1H, 7), 7.67 (tt, $^3J_{HH}$ = 7.8 Hz,

$^4J_{HH}$ = 1.7 Hz, 1H, p-py), 7.29–7.26 (m, partially overlapped with $CHCl_3$, 3H, 5 + m-py), 7.12–7.07 (m, overlapped with 4 of *trans*-***N,N***, 1H, 4), 6.94 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, 3), 6.86 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 9), 6.58 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 0.7 Hz, 1H, 2), 3.95 (s, 3H, 13), 1.86 (s, 3H, 15). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 298 K), δ (ppm): [*trans*-***N,N***] 177.6 (14), 175.9 (7), 166.4 (12), 157.4 (1), 153.4 (o-py), 151.9 (8), 146.7 (6), 138.1 (p-py), 133.0 (2), 131.5 (3), 130.2 (10), 129.2 (11), 129.1 (5), 125.4 (m-py), 124.6 (4), 123.1 (9), 52.2 (13), 24.5 (15); [*cis*-***N,N***] 180.6 (14), 173.5 (7), 166.4 (12), 155.7 (1), 150.9 (8), 149.9 (br s, o-py), 145.3 (6), 136.0 (br s, p-py), 132.5 (2), 131.1 (3), 129.6 (10), 128.9 (11), 128.1 (5), 124.2 (4), 123.8 (br s, m-py), 123.2 (9), 52.3 (13), 24.2 (15). IR (KBr, selected data), υ (cm^{-1}): 1720 (C═O st, ester), 1604 (C═N st), 1586 (C═O st, terminal acetato), 1378 (C–O st, terminal acetato), 1271 (C–C–O as st), 1108 (C–C–O sym st). MS-MALDI TOF (+) (DHB), *m/z*: 422.9 (calcd. 423.0) $[M - OAc]^+$. Anal. Calcd. for $C_{22}H_{20}N_2O_4Pd$: C 54.73%, H 4.18%, N 5.80%. Found: C 54.7%, H 4.3%, N 6.1%.

2.1.5. Preparation of compound 4

0.100 g (0.132 mmol) of compound **2** were treated with 6 cm^3 of a solution pyridine in CH_2Cl_2 0.064 M (0.384 mmol of pyridine). The solution was allowed to stir at room temperature for 2 h, and thereafter volatiles were evaporated under reduced pressure. Upon addition of diethyl ether (4 cm^3) a light yellow precipitate formed, which was collected by filtration and air-dried (107 mg, 97% yield). Compound **4** consists of a mixture of *trans*-***N,N*** and *cis*-***N,N*** isomers in a 1.0 : 0.5 ratio. A similar result was obtained reacting 100 mg (0.132 mmol) of compound **2** with 417 mg (*ca.* 5.3 mmol) of pyridine in 10 cm^3 of CH_2Cl_2 stirring at room temperature for 24 h. In this case, the ^1H NMR in $CDCl_3$ solution of the isolated compound **2** showed that it consisted of a mixture of *trans*- and *cis*-***N,N*** isomers in 1.0 : 0.6 ratio. ^1H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): [*trans*-***N,N***] 8.93 (d, $^3J_{HH}$ = 5.0 Hz, 2H, o-py), 8.12 (s, 1H, 7), 8.09 (d, $^3J_{HH}$ = 9.2 Hz, 2H, 10), 7.88 (t, $^3J_{HH}$ = 7.5 Hz, 1H, p-py), 7.51 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 9), 7.60–7.41 (m, overlapped with 5 of *cis*-***N,N***, 3H, m-py + 5), 7.15–7.11 (m, overlapped with m-py, 9 and 4 of *cis*-***N,N***, 1H, 4), 7.05 (t, $^3J_{HH}$ = 7.6 Hz, 1H, 3), 6.20 (d, $^3J_{HH}$ = 7.6 Hz, 1H, 2), 3.92 (s, 3H, 13); [*cis*-***N,N***] 8.36 (br d, 2H, o-py), 8.16 (s, 1H, 7), 7.76 (br d, 10), 7.60 (br t, $^3J_{HH}$ = 7.4 Hz, 1H, p-py), 7.52–7.41 (m, overlapped with m-py, 10 and 5 of *trans*-***N,N***, 1H, 5), 7.24 (t, $^3J_{HH}$ = 7.6 Hz, 1H, 3), 7.15–7.11 (m, overlapped with 4 of *trans*-***N,N***, 3H, m-py + 4 and 2), 7.00 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 9), 3.89 (s, 3H, 13). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 298 K), δ (ppm): [*trans*-***N,N***] 176.9 (7), 166.4 (12), 158.7 (1), 153.2 (o-py), 152.5 (8), 146.4 (overlapped with 6 of *cis*-***N,N***, 6), 138.2 (p-py), 132.2 (2), 131.8 (3), 130.0 (10), 129.3 (11), 129.1 (overlapped with 5 of *cis*-***N,N***, 5), 125.6 (m-py), 124.9 (overlapped with m-py of *cis*-***N,N***, 4), 123.8 (9), 52.1 (13); [*cis*-***N,N***] 176.8 (7), 165.9 (12), 157.0 (1), 152.2 (8), 150.6 (o-py), 146.4 (overlapped with 6 of *trans*-***N,N***, 6), 137.5 (br s, p-py), 136.7 (2), 131.7 (3), 130.4 (10), 129.1 (overlapped with 5 of *trans*-***N,N***, 5), 128.9 (11), 124.9 (overlapped with 4 of *trans*-***N,N***, m-py), 124.6 (4), 122.5 (9), 52.3 (13). IR (KBr, selected data), υ (cm^{-1}): 1715 (C═O st), 1604 (C═N st), 1587 (C═N st pyridine), 1277 (C–C–O as st), 1113 (C–C–O sym st). MS-ESI (+) {H_2O:CH_3OH (1:1)}, *m/z*: 881.0 (calcd. 881.0) $[2\ M-Cl]^+$, 802.0 (calcd. 802.0) $[2\ M-Cl-py]^+$, 423.0 (calcd. 423.0) $[M-Cl]^+$. Anal. Calcd. for $C_{20}H_{17}ClN_2O_2Pd$: C 52.31%, H 3.73%, N 6.10%. Found: C 51.9%, H 3.8%, N 6.3%.

2.1.6. Preparation of solution A

Solution **A** was prepared by adding *ca.* 30 mg (30 μL) of pyridine-d_5 to a suspension of compound **1** (*ca.* 6 mg) in 1 cm^3 of $CDCl_3$ (molar ratio pyridine-d_5/compound **1** ≈ 50–55). ^1H NMR (400 MHz, $CDCl_3$ + py-d_5, 298 K), δ (ppm) (compound **5**): 8.12 (s, 1H, 7), 8.08 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 10), 7.50 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 9), 7.42 (dd, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, 5), 7.09 (td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 0.9 Hz, 1H, 4), 7.01 (td, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 1.5 Hz, 1H, 3), 6.29 (d, $^3J_{HH}$ = 7.5 Hz, 1H, 2), 3.93 (s, 3H, 13), 1.56 (s, 3H, 15). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$ + py-d_5, 298 K), δ (ppm) (compound **5**): 177.6 (s, 14), 175.9 (s, 7), 166.4 (s, 12), 157.3 (s, 1), 151.9 (s, 8), 146.7 (s, 6), 133.0 (s, 2), 131.5 (s, 3), 130.2 (s, 10), 129.2 (s, 11), 129.1 (s, 5), 124.5 (s, 4), 123.1 (s, 9), 52.2 (s, 13), 24.5 (s, 15). Due to the rapid exchange between coordinated and free pyridine-d_5, carbon NMR signals of coordinated pyridine-d_5 were not observed.

2.1.7. Preparation of solution B

Solution **B** was prepared by adding *ca.* 30 mg (30 μL) of pyridine-d_5 to a suspension of compound **2** (*ca.* 6 mg) in 1 cm^3 of $CDCl_3$ (molar ratio pyridine-d_5/compound **2** ≈ 50–55). ^1H NMR (400 MHz, $CDCl_3$ + py-d_5, 298 K), δ (ppm) (compound **6**): 8.12 (s, 1H, 7), 7.98 (br d, 2H, 10), 7.43 (m, 1H, 5), 7.31 (br signal, 2H), 7.11 (br d, 2H, 9) 3.89 (s, 3H, 13). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$ + py-d_5, 298 K), δ (ppm) (compound **6**): 176.8 (s, 7), 166.2 (s, 12), 146.4 (s, 6), 131.8 (s, 3), 130.1 (br s, 2), 129.1 (s, 5), 124.9 (s, 4), 52.2 (s, 13). Due to the rapid exchange between coordinated and free pyridine-d_5, carbon NMR signals of coordinated pyridine-d_5 and some carbon peaks of the cyclopalladated ligand could not be observed (C1 and C8 – C11).

2.1.8. Preparation of solution C

Solution **C** was prepared by adding *ca.* 30 mg (30 μL) of pyridine-d_5 to a suspension of acetato-bridge cyclopalladated compound **1** (6 mg, approx.) in deuterated water (*ca.* 1 cm^3) (molar ratio pyridine-d_5/compound **1** ≈ 50–55). ^1H NMR in D_2O revealed the presence of the cationic complex **7**, together with *ortho*-palladated benzaldehyde and methyl 4-aminobenzoate in a 1.0 : 0.2 : 0.2 ratio. ^1H NMR (400 MHz, D_2O + py-d_5, 298 K), δ (ppm); compound **7**: 8.22 (s, 1H, 7), 7.69 (d, $^3J_{HH}$ = 8.8 Hz, 2H, 10), 7.58 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, 5), 7.24 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, 4), 7.11 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, 3), 7.02 (d, $^3J_{HH}$ = 8.8 Hz, 2H, 9), 6.19 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, 2), 3.83 (s, 3H, 13), 1.90 (s, 3H, 15); *ortho*-palladated benzaldehyde: 10.50 (s, 1H, CH═O), 8.02 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.53 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, 1H), 7.30 (td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 7.13–7.06 ($^4J_{HH}$ = 1.1 Hz, partially obscured by 3 of **7**, 1H), 1.90 (s, 3H, 15); methyl 4-aminobenzoate: 7.73 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 6.74 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 3.79 (s, 3H). Signal of exchangeable amino protons was not observed in D_2O.

2.1.9. Preparation of solution D

Solution **D** was prepared by adding *ca.* 30 mg (30 μL) of pyridine-d_5 to a suspension of chlorido-bridge cyclopalladated compound **2** (*ca.* 6 mg) in deuterated water (*ca.* 1 cm^3) (molar ratio pyridine-d_5/compound **2** ≈ 50–55). ^1H NMR in D_2O revealed the presence of the cationic complex **8**, together with *ortho*-palladated benzaldehyde and methyl 4-aminobenzoate in a 1.0 : 0.2 : 0.2 ratio. ^1H NMR (400 MHz, D_2O + py-d_5, 298 K), δ (ppm); compound **8**: 8.16 (s, 1H, 7), 7.64 (d, $^3J_{HH}$ = 8.4 Hz, slightly overlapped with 2H of methyl 4-aminobenzoate, 2H, 10), 7.56 (d, $^3J_{HH}$ = 7.5 Hz, 1H, 5), 7.22 (t, $^3J_{HH}$ = 7.5 Hz, 1H, 4), 7.09–7.04 (m, overlapped with 1H of metallated aldehyde, 1H, 3), 6.96 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 9), 6.12 (d, $^3J_{HH}$ = 7.8 Hz, 1H, 2), 3.80 (s, 3H, 13); *ortho*-palladated benzaldehyde: 10.45 (s, 1H, CH═O), 7.98 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 7.47 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.27 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 7.09–7.04 (m, overlapped with 3 of **8**, 1H); methyl 4-aminobenzoate: 7.68 (d, $^3J_{HH}$ = 8.5 Hz, slightly overlapped with 10 of **8**, 2H), 6.72 (d, $^3J_{HH}$ = 8.5 Hz, 2H, 9), 3.76 (s, 3H, 13). Signal of exchangeable amino protons was not observed in D_2O.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2016.05.003.

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