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On the mechanism of the cyclopalladation reaction of benzyl-benzylidene-amine with palladium(II) acetate in acetic acid

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Abstract

The reaction of benzyl-benzylidene-amine of formula $C_6H_5CH{=}NCH_2C_6H_5$ (**1**) and palladium(II) acetate in a one-to-one molar ratio in monodeuterated acetic acid (CH_3CO_2D) at 60 °C (reaction **b**) produced deuterium-enriched cyclopalladated compounds of formula (μ-OAc)$_2$[Pd{$C_6H_4CH{=}NCH_2$–2,6-($H_{1-x}D_x$)$_2C_6H_3$}]$_2$ (**2d**), whose deuterium atoms were located at the *ortho* positions of the benzyl groups and whose deuterium content slowly increased with the time of reaction **b**. In addition, treatment of the cyclopalladated compound of formula (μ-OAc)$_2$[Pd($C_6H_4CH{=}NCH_2C_6H_5$)]$_2$ (**2**) in monodeuterated acetic acid at 60 °C for 24 h, led to compound **2d** with a deuterium content [expressed as percentage of occupation by deuterium atoms of the *ortho* positions of its benzyl groups] of ca. 10%. However, reaction **b** after 24 h of reaction yielded a compound **2d** with a deuterium content of ca. 40%. In addition, the solution formed, when **1** and palladium(II) acetate in a one-to-one molar ratio were dissolved in a solution of $CDCl_3$ in perdeuterated acetic acid in a one-to-two volume ratio, contained as major compounds benzaldehyde, $C_6H_5CH_2ND_2$ and Pd(OAc-d_3)$_2$ a few minutes after its formation. However, after 2 weeks at room temperature, its major compounds were benzaldehyde and the cyclopalladated compounds (μ-OAc-d_3)$_2$[Pd($C_6H_4CH_2ND_2$)]$_2$ and (μ-OAc-d_3)$_2$[Pd($C_6H_4CH{=}NCH_2C_6H_5$)]$_2$. These results led to the proposal of a set of reactions that produced **2**, when **1** and palladium(II) acetate reacted in acetic acid.

Keywords: Cyclometallation; Palladium(II) acetate; Benzyl-benzylidene-amine

1. Introduction

In a recent paper [1], we re-examined the cyclopalladation reaction in acetic acid of benzyl-benzylidene-amine of formula $C_6H_5CH{=}NCH_2C_6H_5$ (**1**) with palladium(II) acetate in order to prepare in high yield its acetato bridged *endo*-cyclopalladated dimer of formula (μ-OAc)$_2$[Pd($C_6H_4CH{=}NCH_2C_6H_5$)]$_2$ (**2**). Compound **2** was isolated in 85% yield, when **1** and palladium(II) acetate in a two-to-one molar ratio were treated at reflux of acetic acid for 45 min. We also found that the isolation yields of **2** were moderated (50–60%) when **1** and palladium(II) acetate in a one-to-one molar ratio reacted in acetic acid. In addition, kinetic studies found that the reaction between **1** and palladium(II) acetate in acetic acid was rather complex [2]. These findings led us to undertake a detailed study of the reaction between **1** and palladium(II) acetate in a one-to-one molar ratio in acetic acid, which is presented here.

2. Results and discussion

The structural formula and numbering of the hydrogen and carbon atoms of the aromatic rings of the compounds under discussion are given in Fig. 1.

To explore the reaction of **1** and palladium(II) acetate in a one-to-one molar ratio in acetic acid, we studied the following items: (i) the crude of this reaction after 4 h of reaction at 60 °C (reaction **a**); (ii) the reaction between **1** and palladium(II) acetate in a one-to-one molar ratio in monodeuterated acetic acid (CH_3CO_2D) at 60 °C (reaction **b**); (iii) the reaction of **2** in monodeuterated acetic acid at 60 °C for 24 h (reaction **c**); and (iv) the evolution at room temperature of the solution formed when **1** and palladium(II) acetate in a one-to-one molar ratio were

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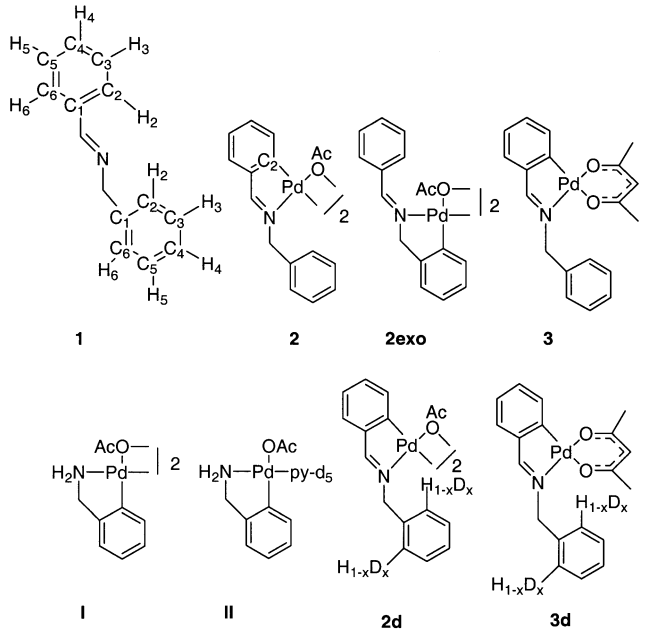


Fig. 1. Structural formula and numbering of the hydrogen and carbon atoms of the aromatic rings of the compounds under discussion.

dissolved in a solution of $CDCl_3$ in perdeuterated acetic acid in a one-to-two volume ratio (solution **d**). The results of these studies are reported below.

(i) The ^{1}H-NMR of solutions of the crude of reaction **a** in $CDCl_3$ and in a solution of Py-d_5 in $CDCl_3$, showed that it consisted of a mixture of benzaldehyde, the acetato bridged cyclopalladated dimer of benzylamine of formula $(\mu\text{-OAc})_2[Pd(C_6H_4CH_2NH_2)]_2$ (**I**) and compound **2**. In addition, these ^{1}H-NMR spectra showed that compound **2** was the major component of the crude of reaction **a**. These results were in accordance with our previous study [1], in which **2** was isolated in 60% yield from reaction **a**. The presence of benzaldehyde and of compound **I** in the crude of reaction **a** was established by comparison between their ^{1}H-NMR spectra in $CDCl_3$ and in a solution of Py-d_5 in $CDCl_3$ and the spectra of the crude of reaction **a** in $CDCl_3$ and in a solution of Py-d_5 in $CDCl_3$. A pure sample of **I** was obtained as previously reported [3]. It was difficult to identify compound **I** in the ^{1}H-NMR in $CDCl_3$ of the crude of reaction **a** since it was, together with benzaldehyde, its minor component and its distinctive NH_2 and CH_2 protons afforded four complex signals [4]. However, the signals of the NH_2 and CH_2 protons of the mononuclear benzylamine cyclopalladated compound of formula *trans*-*N*,*N*′-$[Pd(C_6H_4CH_2NH_2)(OAc)(py\text{-}d_5)]$ (compound **II**) were detected without difficulty in the ^{1}H-NMR spectrum of the solution formed when the crude of reaction **a** was dissolved in a solution of Py-d_5 in $CDCl_3$. It should be noted that a suspension of **I** in $CDCl_3$ reacted with Py-d_5, yielding quantitatively compound **II** [3].

(ii) and (iii) Reaction **b** afforded deuterium-enriched cyclopalladated compounds of formula $(\mu\text{-OAc})_2$-$[Pd\{C_6H_4CH{=}NCH_2\text{–}2,6\text{-}(H_{1-x}D_x)_2C_6H_3\}]_2$ (compounds **2d**), whose deuterium atoms were located at the *ortho* positions of the benzyl groups and whose deuterium content slowly increased with the time of reaction **b** (see Table 1, Entries 1–3). In addition, treatment of **2** in CH_3CO_2D at 60 °C for 24 h (reaction **c**) produced a compound **2d** with a deuterium content [expressed as percentage of occupation by deuterium atoms of the *ortho* positions of its benzyl groups] of ca. 10%. In contrast, reaction **b**, after 24 h of reaction, gave a compound **2d** with a deuterium content of ca. 40% (see Table 1, Entries 1 and 4).

The position at which deuterium was incorporated into compounds **2d** and its deuterium content were established by their transformation into compounds **3d** of formula $[Pd\{C_6H_4CH{=}NCH_2\text{–}2,6\text{-}(H_{1-x}D_x)_2\text{-}C_6H_3\}(acac)]$. This was because the ^{1}H-NMR at 500 MHz of compound **3** of formula $[Pd(C_6H_4CH{=}NCH_2C_6H_5)(acac)]$, afforded clearly separate signals for the non-equivalent aromatic protons and ^{1}H–^{1}H COSY and NOESY experiments at 500 MHz allowed their assignation [1]. Therefore, the relative integrals of the signals of the aromatic protons of compounds **3d** should allow the determination of the aromatic positions that incorporate deuterium and their deuterium content. In fact, in the ^{1}H-NMR spectra at 500 MHz of compounds **3d**, the *ortho* protons of the benzyl group experienced a decrease in their integral in relation to those of the other aromatic protons. In addition, the ^{2}H-NMR of compounds **3d** afforded a broad signal centred at 7.50 ppm, which coincided with the chemical shift of the *ortho* protons of the benzyl group of compound **3** [1]. Thus, these results showed that deuterium was incorporated at the *ortho* positions of the benzyl group. The deuterium content of compounds **3d** was established from their ^{1}H-NMR spectra at 500 MHz by means of Eq. (1); where y is the percentage of occupation by deuterium atoms of the *ortho* positions of the benzyl group of the compound **3d** under study and r is the ratio between the integral of the *ortho* protons of its benzyl group and the integral of the H_3 proton of its palladated phenyl ring. Thereafter, the deuterium content of the compound **3d** under study was assumed to be the same to that of its precursor compound **2d**. Thus, Table 1 gives the estimated deuterium content of the compounds **2d** isolated from reactions **b** and **c**.

$$y = 100(1 - r/2) \quad (1)$$

(iv) The study by ^{1}H-NMR of solution **d** showed that it contained, as major compounds, benzaldehyde, $C_6H_5CH_2ND_2$ and $Pd(OAc\text{-}d_3)_2$, a few minutes after its formation. However, after 2 weeks at room tempera-

Table 1
Estimated deuterium content [a] for compounds **2d** isolated from reactions **b** [b] and **c** [c]

Entry	Reaction	Time (h)	Temperature (°C)	Deuterium content of the isolated compound **2d** (%)
1	**b**	24	60	≈40
2	**b**	6	60	≈10
3	**b**	1	60	≈0
4	**c**	24	60	≈10

[a] Deuterium content expressed as percentage of occupation by deuterium atoms of the *ortho* positions of the benzyl group of the corresponding compound **3d**.
[b] **b** = **1** + $Pd(OAc)_2$ + CH_3CO_2D (molar ratio **1**–$Pd(OAc)_2$ = 1).
[c] **c** = **2** + CH_3CO_2D.

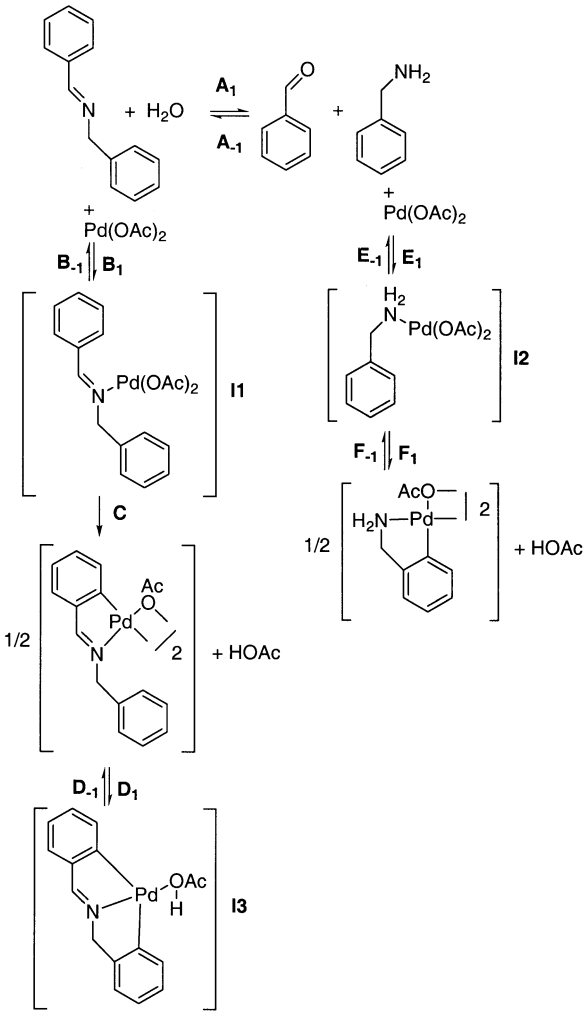
ture, its major compounds were benzaldehyde and the cyclopalladated compounds (μ-OAc-d_3)$_2$[Pd($C_6H_4CH_2$-ND_2)]$_2$ and (μ-OAc-d_3)$_2$[Pd(C_6H_4CH=$NCH_2C_6H_4$)]$_2$. In addition, compound **2exo**, a structural isomer of **2** in which the carbon nitrogen double bond is outside the palladacycle of formula (μ-OAc)$_2$[Pd($C_6H_4CH_2N$=CHC_6H_5)]$_2$, could not be detected during the course of reaction **d**. These results were established by comparison of the ^{1}H-NMR spectra of the solution **d** recorded at different times of reaction with the ^{1}H-NMR spectra of solutions in perdeuterated acetic acid of benzaldehyde, benzylamine, palladium(II) acetate, **I**, **2** and **2exo**. A sample of compound **2exo** was prepared as previously reported by reacting 2-bromobenzyl-benzylidene-amine with tris(dibenzylideneacetone)dipalladium(0) and a subsequent metathesis reaction with silver(I) acetate [5].

The ^{1}H-NMR spectra of palladium(II) acetate, **1**, **I**, **2** and **2exo** in perdeuterated acetic acid merit some comments, which are as follows. (1) The spectra of palladium(II) acetate, **I**, **2** and **2exo** did not show signals corresponding to their acetato ligands. Instead, these ^{1}H-NMR spectra, in the interval of the acetate signals, presented a singlet at 2.05 ppm, which was assigned to the methyl protons of CH_3CO_2D. This was established unambiguously by recording a ^{1}H-NMR of a diluted solution of CH_3CO_2D in perdeuterated acetic acid. Therefore, the quantitative formation of CH_3CO_2D, when palladium(II) acetate, **I**, **2** and **2exo** were dissolved in perdeuterated acetic acid, was the result of a metathesis reaction between the acetato ligands of these latter compounds and perdeuterated acetate anions, which were supplied by the solvent. (2) The spectra of **I**, **2** and **2exo** showed that these compounds presented a non-planar dinuclear structure of low symmetry (C_2 or C_s) in perdeuterated acetic acid. This was established because the NH_2 and CH_2 protons of compound **I** gave broad and complex signals and the CH_2 protons of compounds **2** and **2exo** afforded a broad AB spin system. Thus, compounds **I**, **2** and **2exo** dissolved in perdeuterated acetic acid maintained a dinuclear structure similar to that they present in the solid state or in $CDCl_3$ solution [1,3–5]. (3) The spectrum of **1** gave the signals corresponding to **1**, benzaldehyde and C_6H_5-CH_2ND_2 in an approximate ratio of 1:1:1. Thus, the dissolution of **1** in perdeuterated acetic acid produced its partial hydrolysis. A similar result has been reported for imines of formula 4-ClC_6H_3CH=N–$(CH_2)_n$–NMe_2 (n = 2 or 3) [6].

In relation with the precedent studies, it should be noted that the cyclopalladation reaction of benzylamine with palladium(II) acetate in acetic acid is a reversible process, since the reaction between benzylamine and palladium(II) acetate in monodeuterated acetic acid produces deuterium enriched cyclopalladated compounds of formula (μ-OAc)$_2$[Pd{3-($H_{1-x}D_x$)$C_6H_3CH_2$-NH_2)}]$_2$ with a deuterium content of 70–90% at the 3 position of the palladated phenyl ring [3]. Thus, the precedent results suggest that the set of reactions shown in Scheme 1 are operating when **1** and palladium(II) acetate react in acetic acid.

Intermediate compounds **I1** and **I2** could not be identified during the course of reaction **d** but in favour of their formulation it should be noted that the C–H activation in cyclometallation reactions takes place in a preformed coordination compound [7], such as the proposed intermediate compounds **I1** and **I2**. Furthermore, the results obtained in reaction **c** suggests that the intermediate **I3** is operating in this reaction system. In support of this latter statement, it should be noted that tridentate cycloplatinated compounds of general formula [Pt(Csp^2,Nsp^2,Csp^2)(solvent)] have been prepared in high yield through two consecutive intramolecular C–H bond activations [8,9]. In addition, the fact that deuterium could not be detected at the 6 position of the palladated phenyl ring of compounds **3d** strongly suggested that the C–H bond activation that transforms the intermediate compound **I1** into **2** was an irreversible process. Furthermore, the C–H bond activation which transforms the intermediate compound **I1** into **2**, should proceed with high selectivity since compound **2exo** could not be detected during the course of reaction **d**.

Interestingly, the higher activity of reaction **b** in relation to **c** for the incorporation of deuterium at the *ortho* positions of the benzyl groups of compounds **2d**, together with the facts that: (i) imine **1** was partially



Scheme 1. Reactions operating when **1** and palladium(II) acetate reacts in acetic acid.

hydrolysed in acetic acid; (ii) compound **2exo** could not be detected during the course of reaction **d**; and (iii) the reversibility of the cyclopalladation reaction of benzylamine with palladium(II) acetate in acetic acid [3], suggested that compounds **2d** were formed mainly through the consecutive reactions $\mathbf{F}_{-1}$, $\mathbf{E}_{-1}$, $\mathbf{A}_{-1}$, $\mathbf{B}_1$ and **C**. Finally, the experimental observation that an excess of **1** increases the isolation yield of **2** when **1** and palladium(II) acetate react in acetic acid [1] could be explained by the increase of the concentration of **1** in the medium of reaction and the subsequent acceleration of reactions $\mathbf{B}_1$ and **C**.

3. Experimental

3.1. Instruments and reagents

^{1}H-NMR in $CDCl_3$ were recorded at 200 MHz on a Varian Gemini instrument, using $SiMe_4$ as internal reference. ^{1}H-NMR at 300 MHz in CD_3CO_2D were recorded on a Varian Unity 300 instrument and the residual protons of CD_3CO_2D were used as reference. ^{2}H-NMR at 46.04 MHz were recorded on a Varian Unity 300 instrument, using CD_3COCD_3 as internal reference and $CHCl_3$ as solvent. Solvents were distilled before use as follows: $CHCl_3$ over CaO; C_3H_6O and MeOH over $CaCl_2$ and Et_2O over Na and benzophenone. Chemicals were of commercial grade and used as received. Compounds **1**, **2**, **2exo** and **I** were prepared as reported elsewhere [1,3,5].

3.2. Reactions *b*

3.2.1. Preparation of compounds *2d*

Three suspensions formed by 1.11×10^{-3} mol (0.250 g) of palladium(II) acetate, 1.11×10^{-3} mol (0.217 g) of **1** and 5 cm^3 of CH_3CO_2D were stirred at 60 °C for 24, 6 and 1 h, respectively. The resulting red solutions were concentrated in vacuum and the residues were eluted through silica gel columns with solutions of MeOH in $CHCl_3$ in a 2–100 volume ratio. The orange bands were collected and concentrated under vacuum. Addition of Et_2O (3 cm^3) to the residues produced the precipitation of compounds **2d** as orange powders, which were filtered and dried under vacuum. Yields ranged between 40 and 50%.

3.2.2. Preparation of compounds *3d*

A suspension formed by 1.39×10^{-4} mol (0.100 g) of the corresponding compound **2d**, 5.56×10^{-4} mol (0.078 g) of Na(acac)·H_2O and 20 cm^3 of C_3H_6O was stirred at room temperature (r.t.) for 30 min. The resulting suspension was concentrated in vacuum and the residue was eluted through a silica gel column with $CHCl_3$. The pale yellow band was collected and concentrated under vacuum. Addition of Et_2O (3 cm^3) to the residue produced the precipitation of the corresponding compound **3d** as a pale yellow powder, which was filtered and dried under vacuum. Yields ranged between 50 and 60%.

3.3. Reaction *c*

A suspension formed by 3.47×10^{-4} mol (0.250 g) of compound **2** and 5 cm^3 of CH_3CO_2D was stirred at 60 °C for 24 h. The resulting red solution was concentrated in vacuum and the residue was eluted through a silica gel column with a solution of MeOH in $CHCl_3$ in a 2–100 volume ratio. The orange band was collected and concentrated in vacuum. The residue was treated with 1.39×10^{-4} mol (0.194 g) of Na(acac)·H_2O and 20 cm^3 of C_3H_6O and the mixture was stirred at r.t. for 30 min. The resulting suspension was concentrated in vacuum and the residue was eluted through a silica gel column with $CHCl_3$. The pale yellow band was collected and

concentrated under vacuum. Addition of Et_2O (3 cm^3) to the residue produced the precipitation of the corresponding compound **3d**, which was filtered and dried under vacuum. Yield [relative to compound **2**]: 52% (0.146 g).

3.4. Characterization data

^{1}H-NMR data in $CDCl_3$ of compounds **1**, **2**, **2exo**, **I** and **II** have been previously reported [1,3–5]. The ^{1}H-NMR data in perdeuterated AcOH of compounds **1**, **2**, **2exo** and **I** were as follows. **1**: ^{1}H-NMR (300 MHz, CD_3CO_2D, 298 K) (selected data): 9.97 s (CHO, C_6H_5CHO), 8.90 s (CH=N, **1**), 5.11 s (CH_2, **1**), 4.22 s (CH_2, $C_6H_5CH_2ND_2$). **2**: ^{1}H-NMR (300 MHz, CD_3CO_2D, 298 K) (selected data): 6.81 br signal (H_2 and H_6 benzyl groups), 4.58 br d and 4.09 br d (CH_2). **2exo**: ^{1}H-NMR (300 MHz, CD_3CO_2D, 298 K) (selected data): 8.26 d $^3J_{HH} = 6.5$ Hz, 7.49 d $^3J_{HH} = 6.5$ Hz (H_2 and H_6 protons of the non-palladated phenyl rings), 4.30 br signal, 3.80 br signal (CH_2). **I**: ^{1}H-NMR (300 MHz, CD_3CO_2D, 298 K): 7.25–6.72 br signals (aromatic protons), 5.00–3.00 br signals (NH_2 and CH_2). Compounds **3d** in $CHCl_3$ solution afforded a broad signal centred at 7.50 ppm in their ^{2}H-NMR at 46.04 MHz.

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