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FULL PAPER

Solution behaviour, kinetics and mechanism of the acid-catalysed cyclopalladation of imines *

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The cyclometallation reactions of *N*-benzylidene-benzylamines, -anilines and -propylamine with palladium acetate have been studied in acetic acid solution. Carbon–hydrogen electrophilic bond activation occurs to produce different types of metallacycles, given the polyfunctional nature of the ligands selected. The cyclometallated compounds formed indicate that the stability of the final species is, with respect to the activated C–H bond, in the order: five-membered aromatic *endo* > six-membered aliphatic *endo* > five-membered aromatic *exo*, >>> five-membered *exo*, four-membered. The nature of the final cyclometallated compounds in acetic acid solution has been ascertained *via* ^{1}H NMR spectroscopy; as a whole the spectra are complex, indicating that the nature of the cyclometallated species in solution is not simple, and that a wide variety of compounds is present depending on the imine used. The metallation reactions have been monitored kinetically *via* UV/VIS spectroscopy at different temperatures and pressures in order to establish the mechanism through which these acid-assisted reactions occur. Although the thermal activation parameters cover a wide range of values ($\Delta H^{\ddagger}$ = 49 to 73 kJ mol^{-1}, $\Delta S^{\ddagger}$ = −52 to −138 J K^{-1} mol^{-1}), the activation volume is in a very narrow range, −15 ± 3 cm^3 mol^{-1}. The results are interpreted as the formation of a highly ordered four-centred transition state, involving the C–H and Pd–O (acetato) bonds, which is found to be very sensitive to the presence of any protons that could enhance the leaving-group characteristics of the $MeCO_2H$ ligand, converting it into its protonated $MeCO_2H_2^+$ form.

Although cyclometallation reactions on palladium(II) complexes have been thoroughly studied by a number of research groups in view of their interest in organic synthesis,[1] design of new metallomesogens[2] and antitumoral drugs,[3] usage for enantiomeric excess determination,[4] *etc.*, the number of these studies dealing with kinetic and mechanistic information is very limited.[5] Very little information is available about the nature of the species existing in the reaction solutions.[6] Although it is generally assumed that cyclopalladated compounds maintain their dimeric structure in solution, it is difficult to think in these terms when the reactions are carried out in acetic acid, one of the standard solvents for such cyclopalladation reactions. In this respect, especially enlightening is the characterization of a number of intermediate species arising from the cyclometallation reaction on primary amines in non-protic solvents.[7]

Our interests have been centred on this type of reaction on imine ligands as well as in the mechanisms operating in organometallic reactions involving the activation of C–X bonds on platinum(II) and dinuclear rhodium(II) complexes.[8,9] The final goal of all these investigations is the study of the importance of the relative influences of steric and electronic factors that could tune the reactivity and thermodynamic preferences of the reactions involved in different processes.[10,11]

In this paper we report a kinetic study of the influence of temperature and pressure on the cyclometallation of a wide variety of imines, **X** (Scheme 1), by palladium acetate in acetic acid as solvent. These imines have been selected to allow comparison of the metallation of aromatic *versus* aliphatic carbon atoms, formation of *endo* (**1x**) *versus exo* (**2x**) metallacycles, and formation of five- or six-membered metallacycles (Scheme 2). By doing so, the electronic and steric influence of the substituents in these processes has been examined. A complete study of the nature of the final cyclometallated compounds in acetic acid solution has also been carried out; our findings indicate that important differences exist in the final species in solution, depending on the imine ligand.

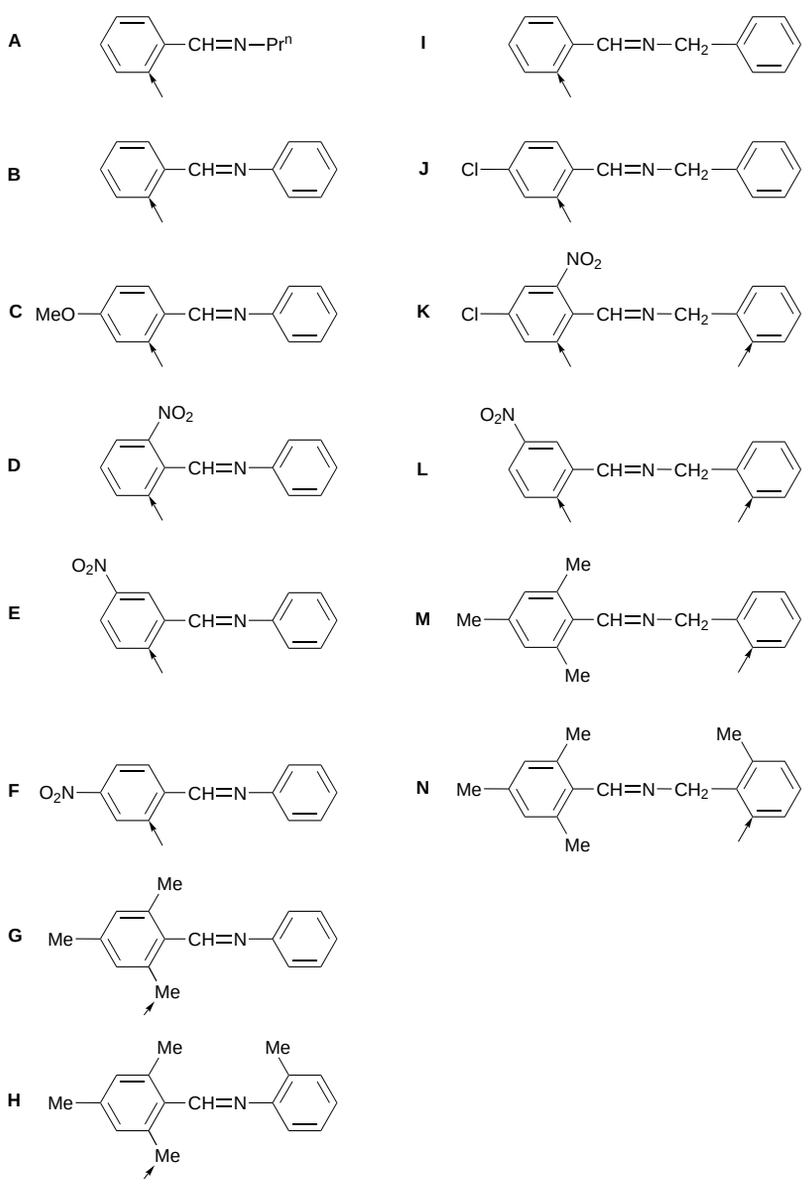
Results and Discussion

Compounds

The reaction of palladium acetate with imines **A**–**N** in acetic acid has been studied. With **A**–**J** and **L**, dinuclear, acetato-bridged, complexes **1x** are obtained. Despite the fact that some of the ligands can undergo metallation at different carbon atoms, *endo*-metallacycles (Scheme 2) were selectively formed in all these cases (Schemes 3 and 4). It should be noted that, although imines **E** and **L**, those containing a nitro substituent in *meta* position, could afford two different five-membered *endo*-metallacycles, only the metallation of the less hindered $C_{aromatic}$–H bond was observed. When the cyclopalladation reaction was performed with imine **K** a mixture of *endo*- and *exo*-palladacycles was obtained, as found in toluene solution. The formation of the *exo*-cyclic compound with this imine can be explained by steric effects. The presence of a nitro group in the *ortho* position of the aromatic ring undergoing metallation (if an *endo*-metallacycle is formed) prevents the adoption of a planar conformation between the imine moiety and this aromatic ring, somehow hindering the formation of the proposed four-centered transition state (see below), in consequence the *exo*-metallacycle is also obtained.

Imines **M** and **N** could afford both five-membered *exo*-metallacycles, by activation of a $C_{aromatic}$–H bond, and six-membered *endo*-metallacycles, by activation of a $C_{aliphatic}$–H bond. Although, in general, a strong tendency to form five-membered metallacycles and preferential activation of aromatic over aliphatic C–H bonds is widely accepted,[12] some exceptions to these rules are known.[13] In this case and for the reactions performed under mild conditions (40 °C, 3 h), the five-membered *exo*-metallacycles, **2x**, were selectively obtained; nevertheless, when the same reactions were carried out under

* *Supplementary data available*: observed pseudo-first order rate constants. For direct electronic access see http://www.rsc.org/suppdata/dt/1998/37/, otherwise available from BLDSC (No. SUP 57315, 5 pp.) or the RSC Library. See Instructions for Authors, 1998, Issue 1 (http://www.rsc.org/dalton).



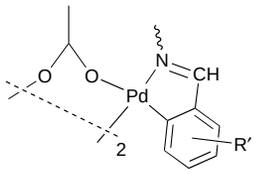
Scheme 1 Arrows indicate the activated position

more energetic conditions (80 °C, 1 h), the six-membered *endo*-metallacycles **1x** were obtained *via* activation of $C_{aliphatic}$–H bonds.

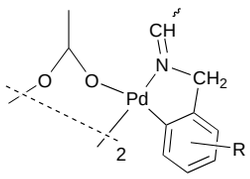
All the final isolated compounds have been previously described, and characterized by comparison with their ^{1}H NMR spectra already published.[8b,e,11,13c,14] Nevertheless, as regards the structure in solution of the acetate- or halide-bridged cyclopalladated compounds, very little data are available. It has been generally assumed, by analysis of the NMR spectra, that these compounds maintain their dimeric structure in solution, but they are usually recorded only in poorly coordinating, non-protic, solvents such as $CDCl_3$. Recently, it has been shown by ^{1}H NMR spectroscopy that even acetone is able to break the bromo bridge of the cyclopalladated complex $[\{PdBr[C_6H_4CH(Me)NH_2]\}_2]$ leading to mononuclear species.[15] In this respect, ^{1}H NMR spectra of acetato-bridged complexes derived from imines similar to those used in this study indicate the existence, in solution, of two isomeric forms. When C_5D_5N is added to these solutions, only the mononuclear complex *trans*-$[Pd(O_2CMe)L(C_5D_5N)]$ (L = metallated imine) is observed, indicating that the two isomeric forms of these compounds are solely related by their dinuclear core.[8c] In view of these data, we have studied the structure of the cyclopalladated compounds in solution by ^{1}H NMR spectroscopy both in non-protic solvents and in acetic acid.

From the NMR data in different deuteriated solvents of the five-membered metallacycles containing a $C_{aromatic}$–Pd bond (Table 1, compounds **1i** and **1l**–**1n**) the following conclusions can be drawn: (*i*) in solution only one isomer can be observed; (*ii*) the acetate CH_3 signal appears as a singlet, which indicates a *trans* arrangement of the C,N chelate around the $\{Pd_2(\mu\text{-}O_2CMe_2)_2\}$ core; (*iii*) the two methylenic protons (CH_2N) are different chemically in all the studied solvents, two doublets, AB spin system, in accordance with a folded open-book dimeric structure, which has been previously found by X-ray diffraction studies of related compounds;[16] (*iv*) the chemical shift of the imine proton indicates that the imine conformation is *E* (upfield from the free imine) in all the *endo*-cyclic compounds and *Z* (downfield from the free imine) in the *exo*-cyclic derivatives.[8a]

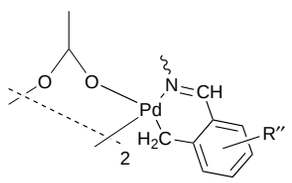
In contrast, the six-membered derivatives, those containing CH_2–Pd bonds, have different structures in solution depending on the nature of the solvent (Table 1, compounds **1g**, **1m** and **1n**). In aprotic solvents, such as $CDCl_3$, [$^2H_8$]toluene or $(CD_3)_2CO$, broad signals for the methylenic protons (those bonded to palladium and nitrogen) are observed. This is characteristic of the hampered movement of the six-membered metallacycles, as a consequence of their folded structure; in some cases even two isomers can be observed. When C_5D_5N is added the NMR spectra show only one compound in solution, obviously the mononuclear complex *trans*-$[Pd(O_2CMe)L(py)]$,



five-membered endocycle

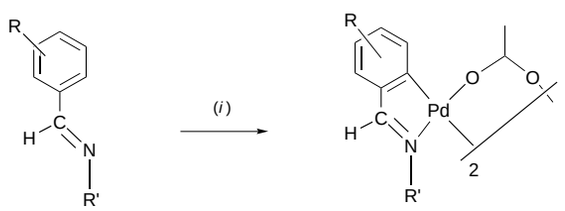


five-membered exocycle



six-membered endocycle

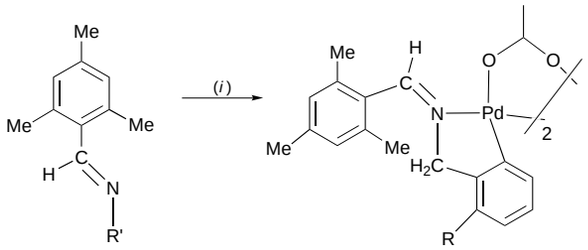
Scheme 2



A R= H, R'= Pr^n
B R= H, R'= Ph
C R= 4-MeO, R'= Ph
D R= 2-NO_2,R'= Ph
E R= 3-NO_2, R'= Ph
F R= 4-NO_2, R'= Ph
I R= H, R'= CH_2Ph
J R= 4-Cl, R'= CH_2Ph
K R= 2-NO_2, R'= CH_2Ph
L R= 3-NO_2, R'= CH_2Ph

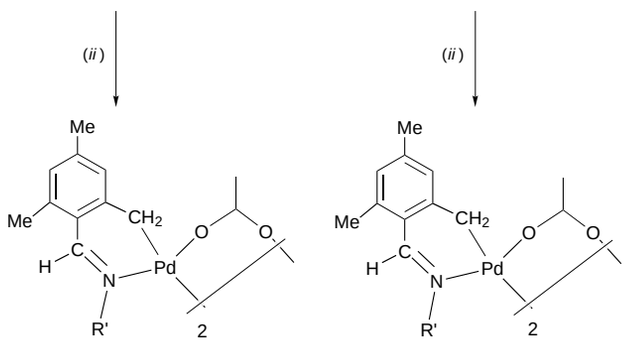
1a R= H, R'= Pr^n
1b R= H, R'= Ph
1c R= 5-MeO, R'= Ph
1d R= 3-NO_2, R'= Ph
1e R= 4-NO_2, R'= Ph
1f R= 5-NO_2, R'= Ph
1i R= H, R'= CH_2Ph
1j R= 5-Cl, R'= CH_2Ph
1k R= 3-NO_2, R'= CH_2Ph
1l R= 4-NO_2, R'= CH_2Ph

Scheme 3 (*i*) Palladium acetate, $MeCO_2H$, 80 °C, 1 h. The exocyclic compound **2k** is also formed with imine **K**



G R'= Ph
H R'= 2-MeC_6H_4
M R'= CH_2Ph
N R'= $CH_2C_6H_4Me$-2

2m R= H
2n R= Me



1g R'= Ph
1h R'= 2-MeC_6H_4

1m R= H
1n R= Me

Scheme 4 (*i*) $Pd(O_2CMe_2)_2$, $MeCO_2H$, 40 °C, 3 h; (*ii*) $Pd(O_2CMe_2)_2$, $MeCO_2H$, 80 °C, 1 h

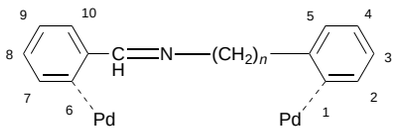
and all the signals became narrow. These results indicate that the different isomers found are directly related with the dinuclear core of these complexes in solution. When the ^1H NMR spectra of these compounds are recorded in deuteriated acetic acid or in the presence of CF_3CO_2H they are very similar to those of the pyridine derivatives; in acidic media the acetato-bridged core seems to be completely broken and the mononuclear complexes *trans*-[$Pd(O_2CMe)L(solv)$] (where solv is a solvent molecule) are formed. Moreover, the substitution of the acetate, assisted by the acidic medium, by the poorly coordinating $CF_3CO_2^-$ group in the six-membered metallacycles is very fast; showing the important bridge lability of the dinuclear compounds. This behaviour of the six-membered metallacycles in solution can be explained by their structural features; in these compounds the six-membered metallacycle is non-planar, adopting a half-skew-chair conformation, as has been shown by crystal structure determination of [$Pd\{1\text{-}CH_2\text{-}2\text{-}(HC{=}NPh)\text{-}3,5\text{-}Me_2C_6H_2\}Br(PPh_3)$].[13c] This important distortion of the metallacycle increases the steric congestion between both moieties of the molecule so decreasing the stability of the dinuclear core.

In the same context we have also studied the ^1H NMR spectra of palladium acetate in acetic acid solution at different concentrations in order to establish the nature of the starting material of the cyclometallation reaction in solution. Although palladium acetate is a trinuclear compound in the solid state, with all the acetato groups acting as bridging ligands,[17] in solution mixtures of trinuclear closed compounds (only with acetato bridges) and open complexes (containing terminal and bridging acetate ligands) have been observed.[6,11] Only one signal at δ 2.05 is observed for a saturated solution of palladium acetate in CD_3CO_2D, but when the spectra are recorded at lower concentrations new signals of low intensity appear, their number increasing with dilution of the sample. Some of the signals appeared at high fields, δ 1.3–1.1, which could be assigned to terminal acetato groups.[8c] All these results suggest that the formation of solvato complexes with palladium acetate have occurred in solution, affording polynuclear species with both bridging and terminal acetate ligands. In this respect cyclopalladation of primary amines has, recently been proposed to occur *via* [$Pd(O_2CMe)_2L'_2$] and [{$Pd(O_2CMe)(\mu\text{-}O_2CMe)L'\}_2$] ($L'$ = primary amine) intermediates, both isolated in the solid state; the crystal structure of the latter has been determined.[7]

Mechanism

The reaction of palladium acetate with imines **A**–**N** in acetic acid has been studied kinetically by means of UV/VIS spectroscopy. The reactions were followed *via* ^1H NMR spectroscopy under the same kinetic conditions in order to establish the presence of the cyclometallated compound as the product of the absorbance change monitored. The products isolated from the reaction mixture once C–H activation is achieved are in excellent agreement with those obtained when the reaction was carried out in toluene solution at 60 °C.[11]

Table 1 Proton NMR data[a] of selected cyclometallated compounds in different deuteriated solvents



Compound	CH_3	CH_2	Aromatic	HC=N
1g (CD_3CO_2D)	2.46 (s, 3 H, Me^{10}) 2.39 (s, 3 H, Me^{8}) $MeCO_2$ [b]	3.35 (s, 2 H)	7.60–7.25 (br m, 5 H) 7.20 (s, 1 H, H^9) 6.90 (s, 1 H, H^7)	8.20 (s, 1 H)
1g + C_5D_5N ($CDCl_3$)	2.30 (s, 3 H, Me^{10}) 2.20 (s, 3 H, Me^{8}) 1.40 (s, 3 H, $MeCO_2$)	2.85 (s, 2 H)	7.50–7.16 (m, 5 H) 6.85 (s, 1 H, H^9) 6.72 (s, 1 H, H^7)	7.97 (s, 1 H)
1i (CD_3CO_2D)	$MeCO_2$ [b]	4.65 [br d, 2 H, ^2J(HH) = 15.8] 4.16 [br d, 2 H, ^2J(HH) = 15.8]	7.60–7.0 (br m, 20 H)	[c]
($CDCl_3$)	2.18 (s, 6 H, $MeCO_2$)	4.58 [d, 2 H, ^2J(HH) = 15.2] 4.04 [d, 2 H, ^2J(HH) = 15.2]	7.30–6.80 (br m, 20 H)	[c]
1i + C_5D_5N ($CDCl_3$)	1.85 (s, 3 H, $MeCO_2$)	4.80 (s, 2 H)	7.33–7.20 (m, 5 H) 7.09 [d, 1 H, ^3J(HH) = 7.2, H^{10}] 6.90–6.80 (m, 2 H, H^9, H^8) 6.17 [d, 1 H, ^3J(HH) = 7.2, H^7]	7.62 (s, 1 H)
1l (CD_3CO_2D)	$MeCO_2$ [b]	4.65 (br d, 2 H) 4.14 (br d, 2 H)	8.10–7.00 (br m, 18 H)	[c]
($CDCl_3$)	2.20 (s, 6 H, $MeCO_2$)	4.58 [d, 2 H, ^2J(HH) = 15.2] 4.04 [d, 2 H, ^2J(HH) = 15.2]	7.30–6.80 (br m, 18 H)	[c]
1m (CD_3CO_2D)	2.28 (s, 3 H, Me^{10}) 2.23 (s, 3 H, Me^{8}) $MeCO_2$ [b]	3.05 (s, 2 H) Pd–CH_2 4.93 (s, 2 H) CH_2N	7.30–7.20 (br m, 5 H) 7.07 (s, 1 H, H^9) 6.80 (s, 1 H, H^7)	7.96 (s, 1 H)
1m + C_5D_5N ($CDCl_3$)	2.24 (s, 6 H, Me^{10}, Me^{8}) 1.94 (s, 3 H, $MeCO_2$)	2.51 (s, 2 H) Pd–CH_2 5.05 (s, 2 H) CH_2N	7.65 [d, ^3J(HH) = 7.2, 2 H] 7.40–7.32 (m, 3 H) 6.72 (s, 1 H, H^9) 6.61 (s, 1 H, H^7)	7.50 (s, 1 H)
1m + CF_3CO_2H ($[^2H_8]$toluene)	2.03 (s, 3 H, Me^{10}) 1.87 (s, 3 H, Me^{8})	2.92 (s, 2 H) Pd–CH_2 4.49 (s, 2 H) CH_2N	7.25–7.05 (br m, 5 H) 6.81 (s, 1 H, H^9) 6.50 (s, 1 H, H^7)	7.36 (s, 1 H)
1n (CD_3CO_2D)	2.32 (s, 3 H, Me^{10}) 2.28 (s, 3 H, Me^{8}) 2.11 (s, 3 H, $MeCO_2$) 2.06 (s, 3 H, Me^{5})	3.20 (s, 2 H) Pd–CH_2 4.96 (s, 2 H) CH_2N	7.26 (br m, 4 H) 7.10 (s, 1 H, H^9) 6.77 (s, 1 H, H^7)	7.70 (s, 1 H)
1n + C_5D_5N ($CDCl_3$)	2.37 (s, 3 H, Me^{10}) 2.27 (s, 3 H, Me^{8}) 2.08 (s, 3 H, Me^{5}) 1.91 (s, 3 H, $MeCO_2$)	2.77 (s, 2 H) Pd–CH_2 5.15 (s, 2 H) CH_2N	7.34–7.25 (br m, 4 H) 6.90 (s, 1 H, H^9) 6.72 (s, 1 H, H^7)	7.60 (s, 1 H)
2m ($CDCl_3$)	2.24 (s, 6 H, $MeCO_2$) 2.14 (s, 6 H, Me^{8}) 2.09 (br s, 6 H, Me^{10}) 1.48 (br s, 6 H, Me^{6})	4.22 [br d, 2 H, ^2J(HH) = 17.5] 3.94 [br d, 2 H, ^2J(HH) = 17.5]	6.6–6.9 (m, 12 H)	8.53 (s, 2 H)
($[^2H_8]$toluene)	2.20 (s, 6 H, $MeCO_2$) 2.04 (s, 6 H, Me^{8}) 1.75 (br s, 6 H, Me^{10}) 1.44 (br s, 6 H, Me^{6})	4.18 [br d, 2 H, ^2J(HH) = 18.0] 4.05 [br d, 2 H, ^2J(HH) = 18.0]	7.2–7.1 (m, 2 H) 6.90–6.80 (m, 4 H) 6.6–6.4 (m, 6 H)	8.65 (s, 2 H)
(CD_3CO_2D)	2.23 (s, 6 H, Me^{8}) 2.10 (br s, 6 H, Me^{10}) 2.06 (s, 6 H, $MeCO_2$) 1.49 (br s, 6 H, Me^{6})	4.37 [br d, 2 H, ^2J(HH) = 18.0] 3.98 [br d, 2 H, ^2J(HH) = 18.0]	7.0–6.6 (m, 12 H)	8.61 (s, 2 H)
2m + C_5D_5N ($CDCl_3$)	2.29 (s, 3 H, Me^{8}) 2.20 (s, 6 H, Me^{6}, Me^{10}) 1.88 (s, 3 H, $MeCO_2$)	4.56 (s, 2 H)	6.92 [t, 1 H, ^3J(HH) = 7.5, H^3] 6.89 (s, 2 H, H^7, H^9) 6.79 [d, 1 H, ^3J(HH) = 7.5, H^5] 6.74 [t, 1 H, ^3J(HH) = 7.5, H^4] 6.11 [t, 1 H, ^3J(HH) = 7.5, H^2]	8.84 (s, 1 H)
2n ($CDCl_3$)	2.26 (s, 6 H, Me^{8}) 2.15 (s, 6 H, $MeCO_2$) 2.07 (br s, 6 H, Me^{10}) 1.84 (s, 6 H, Me^{5}) 1.69 (br s, 6 H, Me^{6})	4.15 [br d, 2 H, ^2J(HH) = 18.0] 3.45 [dd, 2 H, ^2J(HH) = 18.0]	6.9–6.6 (m, 10 H)	8.55 (s, 2 H)
(CD_3CO_2D)	2.24 (s, 6 H, Me^{8}) 2.10 (br s, 6 H, Me^{10}) 2.06 (s, 6 H, $MeCO_2$) 1.84 (s, 6 H, Me^{5}) 1.64 (br s, 6 H, Me^{6})	4.25 [br d, 2 H, ^2J(HH) = 17.5] 3.57 [br d, 2 H, ^2J(HH) = 17.5]	7.0–6.6 (m, 5 H)	8.61 (s, 1 H)
(CD_3COCD_3)	2.25 (s, 3 H, Me^{8}) 2.12 (br s, 3 H, Me^{10}) 2.06 (s, 3 H, $MeCO_2$) 1.86 (s, 3 H, Me^{5}) 1.69 (br s, 3 H, Me^{6})	4.27 [br d, 2 H, ^2J(HH) = 18.0] 3.73 [br d, 2 H, ^2J(HH) = 18.0]	7.0–6.6 (m, 5 H)	8.60 (s, 1 H)
($[^2H_8]$toluene)	2.22 (s, 6 H, $MeCO_2$) 1.96 (s, 6 H, Me^{8}) 1.74 (br s, 6 H, Me^{10}) 1.66 (s, 6 H, Me^{5}) 1.64 (br, s, 6 H, Me^{6})	4.22 [br d, 2 H, ^2J(HH) = 18.0] 4.19 [br d, 2 H, ^2J(HH) = 18.0]	7.2–7.0 [d, 2 H, ^2J(HH) = 18.0] 6.90–6.45 (m, 8 H)	8.68 (s, 1 H)

[a] δ in ppm with respect to internal $SiMe_4$; coupling in Hz; see figure for hydrogen labels. Abbreviations: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. [b] Resonance obscured by solvent. [c] Obscured by aromatic.

Table 2 Kinetic and activation parameters for the cyclometallation reaction of palladium acetate with the imines in Scheme 1 in neat acetic acid solution

Imine	Metallated compound	$10^3k^{298}/s^{-1}$	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	$\Delta V^{\ddagger}$/cm^3 mol^{-1} (T/K)
A	**1a**	1.2	65 ± 7	−87 ± 21	−17 ± 1 (298)
B	**1b**	1.1	73 ± 6	−60 ± 8	−18 ± 1 (298)
C	**1c**	1.5	73 ± 1	−56 ± 4	−15 ± 2 (293)
D	**1d**	3.0[a]	73 ± 4	−52 ± 12	−12 ± 1 (293)
E	**1e**	2.6[a]	73 ± 5	−55 ± 5	−16 ± 3 (293)
F	**1f**	2.3	66 ± 1	−75 ± 3	−17 ± 3 (293)
G	**1g**	1.3	58 ± 3	−108 ± 10	−17 ± 2 (298)
H	**1h**	2.7	65 ± 12	−75 ± 30	−11 ± 1 (293)
I	**1i**	0.15	69 ± 6	−90 ± 18	−15 ± 1 (308)
					−16 ± 2 (318)
J	**1j**	1.5	59 ± 5	−99 ± 17	−17 ± 2 (293)
K	**1k** + **2k**	0.16[b]	60 ± 7	−123 ± 22	−17 ± 1 (318)
L	**1l**	0.47[a]	65 ± 13	−99 ± 40	−16 ± 3 (318)
M	**2m**	1.3	49 ± 5	−138 ± 16	−15 ± 4 (303)
					−11 ± 1 (293)
N	**2n**	0.22[a]	69 ± 6	−91 ± 18	−13 ± 2 (303)

[a] A statistical factor of 2 has been applied. [b] A statistical factor of 1.1 has been applied according to the ratio [**1k**]:[**2k**] = 2.5:1 determined under these conditions in toluene solution.

Blank experiments run in the absence of palladium acetate demonstrated the stability of the selected imines under the monitoring conditions. Imines **A**–**F**, **I**, **J** and **L** produce the *endo* five-membered metallacycles (**1x**) by metallation of the $C_{aromatic}$–H bond; the cyclopalladation reaction of imine **K** produced a mixture of the five-membered *endo*- and *exo*-metallacycles **1k**, **2k** as in toluene solution. Imines **G** and **H** produce also *endo* (**1g**, **1h**) six-membered metallacycles *via* activation of a $C_{aliphatic}$–H bond, while **M** and **N** produce five-membered *exo* (**2m**, **2n**) compounds (Schemes 3 and 4).

Further reaction of all the series of *exo*-metallacycles **2k**, **2m** and **2n** in acetic acid rapidly produces a deep red solution that further evolves to produce the corresponding *endo* (**1k**, **1m** and **1n**) metallacycles in quantitative yield. This reaction, which has not been detected in toluene solution, is currently under study. Parallel ^{1}H NMR monitoring of the kinetically studied reaction mixtures enabled us to insure that under the conditions described in this paper only the first reaction has been followed; by doing so a clear comparison with the previously studied cyclometallation reactions in toluene solution has been achieved.[11]

Two reaction steps are involved in the overall reaction studied: first co-ordination of the imine to the palladium acetate, and secondly C–H bond activation leading to the formation of the final cyclometallated product. The formation of the co-ordination complex is believed to be fast and not detectable under the monitoring condition used in the cyclometallation kinetic study,[18] consequently all the values of the pseudo-first-order rate constants, k_{obs}, correspond to the bond-activation step (SUP 57315). From these observed rate constants, the first-order constants at 298 K, thermal activation parameters, and activation volumes collected in Table 2 were derived. Both the enthalpy and entropy of activation are within the range of values observed for other C–H bond activation *via* electrophilic substitution in the presence or absence of protic solvents.[9c–e,11,12e] The values determined for $\Delta V^{\ddagger}$ (Fig. 1) are in perfect agreement with those found for acid-assisted electrophilic C–H bond-activation reactions on rhodium(II) dimers,[9c–e] indicative of a compressed arrangement in the transition state. All the results obtained are consistent with the presence of a highly ordered transition state as that shown in Scheme 5; in this transition state the neighbouring terminal acetato group, protonated by the acidic medium, accepts a proton from the imine to produce the $MeCO_2H_2^+$ species that acts as an excellent leaving group.

In good agreement with the mechanism here proposed are the recently found intermediates for the cyclopalladation

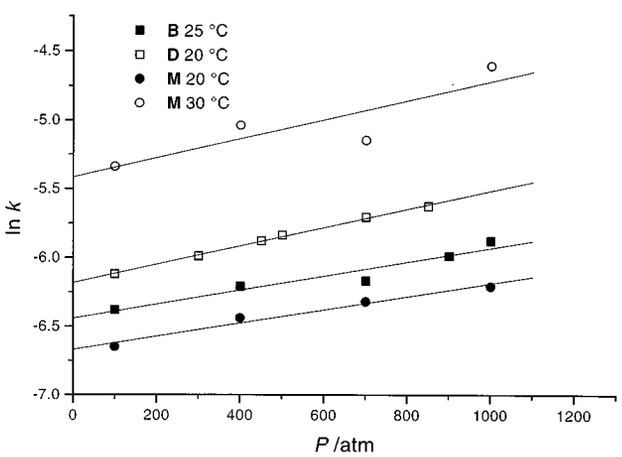
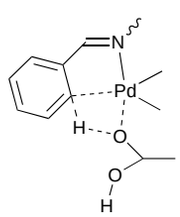


Fig. 1 Plots of the variation with pressure of the cyclometallation rate constants for some of the systems studied



Scheme 5

of primary amines, $[Pd(O_2CMe)_2L'_2]$ and $[\{Pd(O_2CMe)(\mu\text{-}O_2CMe)L'\}_2]$ (L′ = primary amine), both isolated in the solid state.[7] The crystal structure of the latter has also been determined and the distance between the oxygen atom of the monodentate acetate and the *o*-hydrogen of the aromatic ring of the amine is shorter than the sum of their van der Waals radii. This suggests that cyclopalladation reactions could occur through an intramolecular process involving interactions between the monodentate acetate ligand and the *o*-hydrogen atom of the N-donor ligand.

Table 3 collects all the relevant previously published data from the same cyclometallation reactions carried out in toluene, that is in the absence of protons, in order clearly to establish the extreme difference found for the same systems depending on the reaction media. First of all a dramatic acceleration of the reaction rate in acetic acid medium is observed in all cases indicating that the transition state must have a structure with much lower energy than in the case of the spontaneous reac-

Table 3 Kinetic and activation parameters for the cyclometallation reaction of palladium acetate with the imines in Scheme 1 in toluene solution (from ref. 11)

Imine	Metallated compound	$10^4 k^{323}/s^{-1}$	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	$\Delta V^{\ddagger}$/cm^3 mol^{-1} (T/K)
A	**1a**	4.7	63 ± 5	−115 ± 16	−12 ± 3 (318)
B	**1b**	1.4	71 ± 6	−102 ± 18	−23 ± 3 (343)
C	**1c**	1.2	73 ± 10	−97 ± 30	−24 ± 5 (323)
D	**1d**	1.3[a]	66 ± 10	−123 ± 33	−23 ± 4 (343)
E	**1e**	1.6[a]	67 ± 12	−113 ± 36	−21 ± 2 (343)
F	**1f**	0.58	75 ± 18	−96 ± 50	−25 ± 2 (343)
G	**1g**	4.7	48 ± 3	−167 ± 9	−24 ± 3 (333)
H	**1h**	0.59	49 ± 11	−177 ± 33	−20 ± 1 (343)
I	**1i**	5.9	52 ± 3	−150 ± 10	−15 ± 2 (323)
J	**1j**	3.8	65 ± 1	−110 ± 2	−12 ± 1 (333)
K	**1k** + **2k**	5.5[b]	46 ± 4	−168 ± 13	−11 ± 1 (323)
L	**1l**	3.3[a]	45 ± 2	−180 ± 6	−15 ± 4 (323)
M	**2m**	7.0	67 ± 5	−100 ± 15	−12 ± 1 (323)
N	**2n**	9.2[a]	62 ± 2	−120 ± 9	−17 ± 1 (323)

[a] A statistical factor of 2 has been applied. [b] A statistical factor of 1.1 has been applied according to the ratio [**1k**]:[**2k**] = 2.5:1 determined under these conditions.

tion. According to Scheme 5 this fact has to be related to the extremely good leaving ligand characteristics of the $MeCO_2H_2^+$ group; consequently the bond regime in the transition state has to be much more similar to that in the final cyclometallated complex than is the case for the non-H^+-assisted reaction. Such observations have also been made for a large number of electrophilic substitution activations of C–H bonds in Rh^{II}_2 core compounds.[9c–e]

As for the thermal activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, they are both spread over a large range. In this case, though, no important differences can be found between the activation of C–H bonds corresponding to imine ligands with large differences in the N-centred cone angle. Even so, a certain grouping for the aniline derivatives exists with high values ($\Delta H^{\ddagger}$ = 66–73 kJ mol^{-1}, $\Delta S^{\ddagger} = -52$ to -75 J K^{-1} mol^{-1}), while for the *endo* benzylamine and propylamine derivatives the values are lower ($\Delta H^{\ddagger}$ = 59–69 kJ mol^{-1}, $\Delta S^{\ddagger} = -87$ to -123 J K^{-1} mol^{-1}). Given the wide range of the values determined and the lack of a trend for the reactions in toluene solution, it seems clear that the thermal activation parameters follow a uniform trend not observed for the reaction carried out in toluene solution.

Finally, with reference to the volumes of activation, $\Delta V^{\ddagger}$, extracted from the slope of ln k *versus* P plots (Fig. 1), all fall in a rather narrow range around -15 ± 3 cm^3 mol^{-1}. This is the most dramatic difference with respect to the available data for the reactions carried out in toluene solution. In acetic acid solution (*i.e.* acid-assisted process) no differences are detected between the sets of imines that could be separated according to the steric demands of the substituents on the central N, while for the spontaneous reactions (*i.e.* in toluene solution) the values of $\Delta V^{\ddagger}$ fall in two ranges, -23 ± 2 and -14 ± 3 cm^3 mol^{-1} for the large (imines **B** to **H**) and small (imines **A** and **I** to **N**) nitrogen cone angles respectively (Table 3). Somehow, it seems clear that for the acid-assisted reaction the compression to form the transition state is practically independent of the activated imine ligand. The fact that the transition state for this path is more advanced along the reaction co-ordinate (see above) has to be somehow matched by a lesser degree of organization and contraction from the starting materials. That is, the transition state, being more advanced, already involves significant release of the $MeCO_2H_2^+$ group, with consequently a smaller degree of overall compression. Furthermore, given the fact that the transition state is a late one, the influence of the imine steric backbone has to be much less important once the right positioning has taken place for the C–H activation to occur.

Conclusion

The mechanism for the cyclopalladation of imines in acetic acid can be proposed to take place *via* a first fast step, the formation of an imine–palladium co-ordination compound containing terminal and bridging acetate ligands, followed by a second rate-determining step. The formation of a highly ordered transition state in which there is a four-centred interaction between the carbon and the hydrogen atoms of the C–H bond to be activated, the oxygen atom of the monodentate acetate ligand and the metal atom, explains the experimental data both from a synthetic and a kinetic point of view. The evolution of this transition state to the formation of the final Pd–C bond is favoured in protic media, the leaving acetic acid being able to afford the poorly co-ordinating $MeCO_2H_2^+$ group, thus favouring the formation of the final cyclopalladated species.

Experimental

Instruments and materials

Proton NMR spectra were recorded on Varian XL-200 (200), VXR-500 (500) and Bruker DRX-250 (250 MHz) spectrometers, UV/VIS spectra on a HP8452A diode-array instrument and on a Beckmann UV5420 instrument equipped with a high-pressure cell.[19] All the acetato-bridged cyclometallated compounds have been characterized previously.[8b,e,11,13c,14]

Kinetic measurements

The reactions at atmospheric pressure were followed by UV/VIS spectroscopy in the full 750–300 nm range on a HP8452A instrument equipped with a multicell transport, thermostatted (±0.1 °C) with a circulation bath. Observed rate constants were derived from the absorbance *versus* time traces at wavelengths where a maximum increase and/or decrease of absorbance was observed. No dependence of the values on the selected wavelengths was detected, as expected for reactions where a good retention of isosbestic points is observed. The general kinetic technique was that previously described.[19] Solutions for the kinetic runs were prepared by dissolving calculated amounts of the compounds (palladium acetate and imine) in acetic acid. In all cases no dependence on the concentration of palladium acetate or imine was detected, and a [Pd]:[imine] ratio within the range 0.7–1.3:1 was maintained to insure the non-appearance of the insoluble well known $[Pd(O_2CMe)_2(imine)_2]$ species.

For runs at elevated pressure a previously described pressurizing system and high-pressure cell were used.[19] In these cases the absorbance *versus* time traces were recorded on a Beckmann UV5420 instrument at a fixed wavelength chosen from the atmospheric pressure experiments. Rate constants were derived from exponential least-squares fitting by standard routines.

Least-squares errors for the rate constants were always in the range 10–15% of the calculated value. All post-run fitting by rate laws were done by standard fitting programs commercially available.

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