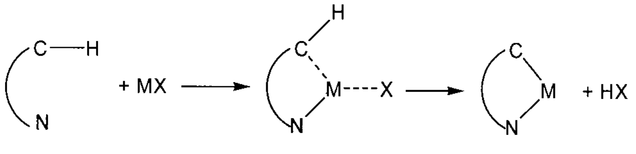
A Theoretical Assessment of the Thermodynamic Preferences in the Cyclopalladation of Amines

Ramón Bosque*[a] **and Feliu Maseras**[b,c]

Keywords: Density functional calculations / Metallacycles / N ligands / Palladium

The factors affecting the cyclopalladation of amines are explored by a comparison of the energy differences between the cyclopalladated amine and the free ligand for a series of compounds. Four factors are considered: the substituents in the nitrogen atom (primary vs. tertiary amines), the hybridization (sp^2 or sp^3) of the metalated carbon atom, the number of members in the metallacycle ring (four, five, or six), and the presence of electron-donor or -acceptor groups. The trends that arise from these calculations, performed at the B3LYP level of theory, are compared with the experimental data available.

Introduction



Scheme 1.

The activation of C–H bonds is among the most important topics in organometallic chemistry. One of the ways that it can be achieved is by means of the so-called cyclometallation reaction, which can be defined as the formation of a bond between a transition metal and a carbon atom of one of its ligands, giving rise to a cycle that contains the metal atom (Scheme 1).[1] The most widely used metal is palladium, and to a lesser extent platinum, gold, manganese, rhodium, and ruthenium. As for the heteroatom E that attaches the ligand to the metal, most of the published work deals with N-donor systems, although there are examples with phosphorus, sulfur, oxygen, and arsenic. The mechanism of this reaction depends on the nature of the metallic atom; for example, cobalt(II) and palladium(II) react through an electrophilic pathway, while other late transition elements follow a nucleophilic pathway, which can also be regarded as an oxidative addition. On the other hand, early transition metals react via a multicentered pathway, which can be formally written as a nucleophilically assisted electrophilic reaction.[2]

There are many examples in the literature of the use of cyclometallated complexes in organic synthesis,[3] catalysis,[4] and medicine;[5] these substances can also be used as liquid crystals[6] or even as nanoscale devices.[7] Due to the importance of this cyclometallation reaction, a large amount of experimental work has been published, both presenting new features of the reaction and trying to elucidate which factors play a dominant role in its mechanism.[8,9] The work from Cope and Friedrich[8] regarding the cyclopalladation of N-donor ligands has achieved a seminal importance. These authors undertook the cyclopalladation of aromatic amines. By comparing the relative ease with which the reaction occurs, the authors postulated some empirical rules (the so-called Cope rules), that can be summarized as follows: (a) the stability of the cyclometallated species is greatest when the cycle has five members; (b) the reaction occurs more easily when the amine nitrogen is tertiary; (c) the mechanism is based on an electrophilic substitution. Although there are some exceptions in the literature,[10] these rules provide a useful guide for the rationalization of the products of the reaction in polyfunctional substracts. More recently, Ryabov[2] has reviewed the most important features of the mechanism based on kinetic measurements.

In contrast with the abundance of experimental results, the theoretical work published is scarce: although some articles about the reactivity of these species have appeared in the literature,[11] to the best of our knowledge the theoretical basis for the Cope rules has not been analyzed. In the bibliography there are several examples of theoretical studies of C–H activation;[12] however, none of them deals with cyclometallation reactions. The aim of this work is to start filling this void by presenting a first approach to the factors

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[a] Department de Química Inorgànica, Universitat de Barcelona,
Martí i Franquès 1–11, 08028 Barcelona, Spain
E-mail: ramon.bosque@qi.ub.es
[b] Institute of Chemical Research of Catalonia (ICIQ),
Av. Països Catalans s/n, 43007 Tarragona, Spain
[c] Unitat de Química Física, Edifici Cn,
Universitat Autònoma de Barcelona,
08193 Bellaterra, Spain

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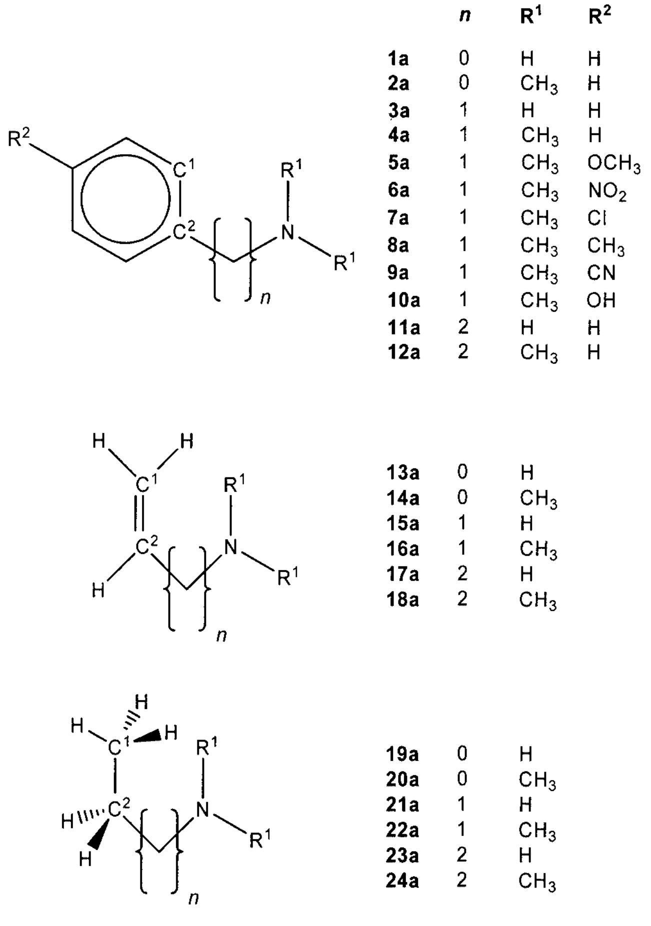
DOI: 10.1002/ejic.200500158

influencing the mechanism of the cyclopalladation reaction from the thermodynamic point of view.

Results and Discussion

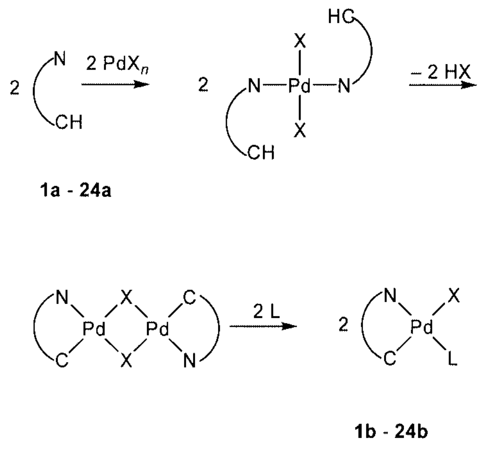
The cyclopalladation reaction is the most important example of cyclometallation that follows an electrophilic pathway.[2] It is also the most widely studied from an experimental point of view, beginning with the work of Cope and Friedrich that resulted in the empirical Cope rules.[8] In order to find the eventual thermodynamic basis for these rules, we have studied the variations in energy between the free amines and the cyclopalladated complexes (**1a**–**24a** and **1b**–**24b** respectively; Scheme 2). In the first stage, we performed the calculations on a series of aromatic amines (**1a**–**12a**). In order to discern the influence of the hybridization of the metalated carbon atom, we also studied a series of alkenylamines (**13a**–**18a**), as well as alkylamines (**19a**–**24a**). The role of the basicity of the nitrogen atom was evaluated by using either hydrogen or methyl as the substituent R^1 on nitrogen. On the other hand, modification of the number *n* of methylene groups allowed us to study the influence of the size of the metallacycle (from four to six members). In the case of five-membered rings derived from tertiary benzylamines, either acceptor or donor groups were added in order to evaluate their effect.

According to the proposed mechanism, the reaction takes place in two stages:[2] first, the palladium coordinates to the nitrogen atom, and then the electrophilic substitution of hydrogen occurs. Usually a dimeric compound, with halogen or acetate bridging ligands, depending on the starting palladium derivative, is obtained; subsequent treatment with a Lewis base affords the corresponding monomer (Scheme 3). It is worth noting that this ligand usually occupies a position *cis* to the metalated carbon; this is the so-called transphobia effect.[13] To simplify the calculations, we only considered the free ligand and the cyclometallated monomer with a phosphane ligand. As all the other species involved in the process are the same for all the reactions, the differences in energy between the metalated complexes and the corresponding free amines allowed us to define a simple scale of relative energies; the energy associated with the cyclopalladation of *N*,*N*-dimethylbenzylamine (**4a**), which features the formation of a five-membered metallacycle with an aromatic metalated carbon, a tertiary nitrogen, and with hydrogen as the only substituent in the remaining carbon atoms, was chosen as reference and assigned the value of 0 kcal mol^{-1}.



	n	R^1	R^2
1a	0	H	H
2a	0	CH_3	H
3a	1	H	H
4a	1	CH_3	H
5a	1	CH_3	OCH_3
6a	1	CH_3	NO_2
7a	1	CH_3	Cl
8a	1	CH_3	CH_3
9a	1	CH_3	CN
10a	1	CH_3	OH
11a	2	H	H
12a	2	CH_3	H
13a	0	H	
14a	0	CH_3	
15a	1	H	
16a	1	CH_3	
17a	2	H	
18a	2	CH_3	
19a	0	H	
20a	0	CH_3	
21a	1	H	
22a	1	CH_3	
23a	2	H	
24a	2	CH_3	

Scheme 2.



1a - 24a

1b - 24b

X= Cl^-, Br^-, AcO^-
L = PR_3

Scheme 3.

Geometry Optimizations

In order to obtain accurate values for the energies corresponding to the different species, the geometries of the free amines and the cyclometallated species were optimized without imposing any symmetry restriction. The most important geometric parameters for the amines that can give rise to four-membered metallacycles are listed in Table 1; the data for all the remaining ligands are included as Supporting Information. In these systems a possible problem of conformation arises from the free rotation around the single bonds. For this reason, several conformations were calculated for the different systems, and in each case only the most stable one was taken into account. In the case of the amines **11a**, **12a**, **17a**, and **18a**, which have larger chains, a systematic search of conformers was performed at the semi-empirical AM1 level;[14] the most stable one for each ligand was then re-optimized at the DFT level.

Table 1. Selected optimized geometric parameters for the amines leading to four-membered metallacycles. Lengths are given in angstroms and angles in degrees.

	C1–C2	C2–N	C1–C2–N
1a	1.405	1.398	120.7
2a	1.413	1.394	121.3
13a	1.339	1.394	126.7
14a	1.330	1.431	122.7
19a	1.526	1.468	110.4
20a	1.529	1.464	113.5

The geometrical parameters corresponding to the cyclopalladated compounds are given in Table 2. The geometric distortions are apparent in the four-membered rings, with C(1)–Pd–N angles (see Scheme 2 for the atom numbering) of less than 70°, rather than the 90° that would correspond to a nonstressed, square-planar geometry. It is also worth mentioning the values of the C–N–Pd angles (87–92°, compared to a range of 105–110° for the five-membered rings and 114–120° for the six-membered metallacycles) and the C(2)–C(1)–Pd angles (93–99°, compared with 106–117° and 108–125° for the five- and six-membered rings); this angle is also smaller in the metallacycles that feature a metalated carbon atom with sp^3 hybridization.

The environment around the palladium atom changes as a function of the substituents in the nitrogen atom. Thus, in the tertiary amines the Pd–P and Pd–Cl distances are larger, while the palladium–carbon bonds are shorter than in the primary ones. On the other hand, the variation in the nitrogen–palladium bond-length also depends on the size of the metallacycle: the bonds in the five- and six-membered rings are much longer for the tertiary amines, while in the four-membered rings the observed trend is the opposite.

The variation in the size of the rings also modifies the environment of the palladium atom. The Pd–P and Pd–Cl distances increase upon incrementing the number of members of the ring. The palladium–carbon bond-length shows a less definite trend: for the non-aromatic sp^2 and sp^3 carbon atoms, the distance is smallest for the five-membered rings and largest for the six-membered systems, whereas for the aromatic derivatives the distance is smallest for the four-membered rings, while for the larger rings it depends also on the nature of the nitrogen atom. Finally, no clear trend arises for the variation of the palladium–nitrogen distances.

The changes of the hybridization of the carbon atom also result in some variations of the distances between the palladium atom and its neighbors. However, the only clear trend arises from the palladium–carbon bond length, which increases in the following order: $d[\mathrm{Pd{-}C(sp^2)}$, non aromatic$] < d[\mathrm{Pd{-}C(sp^2)}$, aromatic$] < d[\mathrm{Pd{-}C(sp^3)}]$. As for the C(1)–Pd–N bite angle, this parameter is larger in nearly all cases for the $C(sp^3)$ systems, as would be expected from the increment in the C(1)–C(2) distance that takes place upon changing the bond between these atoms from double to single; an exception is the six-membered ring with a tertiary nitrogen (**24b** vs. **12b** and **18b**): in this case the angle is nearly constant due to the flexibility of the aliphatic chain. The increment of the bite angle for the four- and five-membered metallacycles involves a decrease of the strain around the palladium atom due to the fact that it is smaller than

Table 2. Optimized geometric parameters for the cyclopalladated systems **1b**–**24b**. Lengths are given in angstroms and angles in degrees.

	C1–C2[a]	C1–Pd	N–Pd	P–Pd	Cl–Pd	P–Pd–N	C–Pd–Cl	Cl–Pd–N	P–Pd–C	C–N–Pd	C2–C1–Pd	C–C–N	C–Pd–N
1b	1.393	2.019	2.214	2.254	2.421	169.7	171.8	105.4	103.4	87.5	97.8	108.4	66.3
2b	1.393	2.015	2.198	2.267	2.423	171.1	168.8	102.0	104.3	87.5	97.3	108.3	66.9
3b	1.416	2.033	2.125	2.280	2.434	177.5	173.9	92.9	100.7	108.4	112.9	108.0	81.1
4b	1.413	2.030	2.177	2.283	2.454	177.4	176.5	96.5	99.7	105.3	113.0	110.0	81.9
5b	1.401	2.031	2.177	2.282	2.456	177.2	176.5	96.6	100.0	105.1	112.8	109.8	81.9
6b	1.415	2.029	2.178	2.285	2.440	178.0	176.5	96.2	99.8	105.8	113.3	110.3	81.9
7b	1.413	2.030	2.177	2.284	2.447	177.6	176.6	96.4	100.0	105.5	113.1	110.0	81.9
8b	1.413	2.030	2.179	2.282	2.456	177.5	176.5	96.5	99.7	105.2	112.8	109.9	81.9
9b	1.414	2.030	2.177	2.286	2.441	177.6	176.5	96.3	100.1	105.6	113.2	110.1	81.9
10b	1.412	2.030	2.177	2.284	2.447	177.6	176.6	96.4	100.0	105.5	113.1	110.0	81.9
11b	1.409	2.031	2.152	2.280	2.449	172.9	176.3	86.5	95.6	119.4	117.4	111.9	90.1
12b	1.408	2.039	2.216	2.287	2.486	170.0	172.7	92.6	94.2	114.7	120.6	113.1	93.2
13b	1.330	2.016	2.198	2.259	2.421	169.2	171.3	106.0	104.0	87.2	99.2	108.4	65.3
14b	1.330	2.015	2.191	2.268	2.426	170.4	169.2	103.6	104.8	87.0	98.6	108.9	65.6
15b	1.342	2.012	2.132	2.272	2.432	178.6	174.4	93.8	98.0	110.5	115.4	108.3	80.7
16b	1.340	2.006	2.180	2.274	2.454	178.2	177.1	96.7	97.1	107.3	115.4	110.0	81.4
17b	1.339	2.017	2.129	2.283	2.451	174.3	177.8	87.1	94.8	117.0	126.0	111.4	90.8
18b	1.336	2.014	2.202	2.282	2.488	174.1	173.4	93.0	92.7	115.8	125.2	115.3	93.0
19b	1.531	2.072	2.140	2.273	2.438	171.2	171.9	103.0	102.3	92.3	94.3	103.4	68.9
20b	1.528	2.070	2.148	2.279	2.442	171.7	169.7	100.9	102.9	90.9	93.4	103.4	68.8
21b	1.536	2.077	2.140	2.272	2.443	179.0	175.1	92.3	96.3	109.7	107.2	107.1	83.1
22b	1.532	2.070	2.183	2.273	2.466	178.9	178.3	94.5	95.4	106.9	106.7	109.8	84.0
23b	1.529	2.081	2.150	2.275	2.459	174.8	176.8	86.9	94.4	114.6	111.3	111.7	90.2
24b	1.528	2.077	2.216	2.276	2.491	175.3	174.4	93.2	93.9	113.4	108.8	115.9	90.3

[a] See Scheme 2 for the atom numbering.

Table 3. Relative energies [kcal mol^{-1}] for the metalation of amines **1a**–**24a**.

		Benzylamines			Alkenylamines		Alkylamines	
Ring size	N substituent	R^2 subst.	Aromatic					
4	H	(H)[a]	**1a**	14.1	**13a**	13.1	**19a**	4.9
4	CH_3	(H)[a]	**2a**	11.7	**14a**	6.7	**20a**	5.7
5	H	(H)[a]	**3a**	–3.3	**15a**	–6.0	**21a**	–4.3
5	CH_3	(H)[a]	**4a**	0.0[b]	**16a**	–2.5	**22a**	–1.9
5	CH_3	OCH_3	**5a**	1.2				
5	CH_3	NO_2	**6a**	1.8				
5	CH_3	Cl	**7a**	–5.6				
5	CH_3	CH_3	**8a**	0.4				
5	CH_3	CN	**9a**	1.5				
5	CH_3	OH	**10a**	–5.4				
6	H	(H)[a]	**11a**	–3.2	**17a**	–7.4	**23a**	–1.1
6	CH_3	(H)[a]	**12a**	0.4	**18a**	–2.2	**24a**	3.6

[a] Only applicable to aromatic amines. [b] Value taken as reference.

90° in all cases. The influence of the presence of donor or acceptor groups upon the environment of the palladium is small.

Factors Affecting the Cyclopalladation Reaction

In order to compare the factors that affect the stability of the palladacycles, the relative increment in energy corresponding to the metalation of the amines was calculated. We took into account the difference of energy between the cyclometallated species and the free amine, and the results were referenced to the formation of compound **4b** (five-membered ring with an aromatic metalated carbon, a tertiary nitrogen and without donor or acceptor groups bonded to the remaining carbon atoms), which was taken as 0.0 kcal mol^{-1}. The results are shown in Table 3.

Hybridization of the Metalated Carbon

The first factor that we took into account was the nature of the metalated carbon: C(sp^2, aromatic), C(sp^2, non-aromatic), or C(sp^3). Cope and Friedrich[8] worked only with benzylamine derivatives, and nearly all the published articles deal with the metalation of aromatic carbons; however, there are examples of the activation of C(sp^3)–H bonds in imines where there are aromatic carbons available.[15] This result is more remarkable considering that, in this case, the reaction yields a six-membered ring, while the activation of the C(sp^2)–H bond would yield a five-membered metallacycle, which is regarded as the most favored ring size. In this case, however, there are other factors that must be considered, especially the position of the C=N double bond: the systems in which this bond is included in the metallacycle (endocyclic) are formed more easily than those with the bond outside the metallacycle (exocyclic).[16] Minghetti and co-workers[17] have compared the aliphatic vs. aromatic C–H activation in the reaction of 6-substituted 2,2′-bipyridines with Na_2PdCl_4 in order to obtain five- or six-membered metallacycles. The reaction depends strongly on the substituent of the 2,2′-bipyridine, often in an unpredictable way. Dunina and co-workers[18] have studied the activation of C(sp^3)–H and C(sp^2)–H bonds in the reaction of *N*-methyl-α-*tert*-butylbenzylamine with palladium(II). In this secondary amine, weak palladating agents such as Li_2PdCl_4 favor the formation of C(sp^3)–Pd bonds, while under more drastic reaction conditions the C(sp^2)–H bond is activated. However, in the related tertiary amine *N*,*N*′-dimethyl-α-*tert*-butylbenzylamine only the palladation of the aromatic carbon is observed. There are other examples of four-[19] and five-membered[20] metallacycles with C(sp^3) metalated atoms, but they are prepared by oxidative addition and not by means of the cyclometallation reaction. A five-membered metallacycle with an aliphatic metalated carbon and a negative charge has also been postulated as an intermediate in the palladium-catalyzed internal phenylation of *N*,*N*-dialkylallylamines,[21] while an intermediate in the intramolecular Heck reaction of a pyrrolidine that features a five-membered aliphatic ring has recently been isolated and characterized.[22]

Finally, there are some examples of five-membered metallacycles where the metalated carbon has sp^2 hybridization although it is not aromatic,[23] and thus they are formally similar to our system **16b**. However, they are not prepared by the cyclopalladation reaction of the corresponding tertiary allylamine, but via the chloropalladation of substituted alkynes.

In view of this experimental evidence, we found it interesting to study the behavior of three different types of carbon center. The first of them was a phenyl, as in benzylamine (systems **1**–**12**), which represents the most usual case of aromatic carbons. The second one was a saturated alkyl (systems **19**–**24**), in line with the more recent results. We also introduced alkenyl in the comparison (systems **13**–**18**), with the idea that, if the energetics were similar, it could be a more computationally accessible model for a phenyl group. The relative energies from the calculations presented in Table 3 allow a series of comparisons between the behaviors of the three types of carbon hybridization. In order for the comparison to be fair, one must take a series of compounds where only the nature of the carbon changes and the rest of characteristics, that is, the substituents R^1 at nitrogen and the number, *n*, of carbons in the chain remain the same. A number of phenyl/alkenyl/alkyl series can be defined following this concept, namely, **1/13/19**, **2/14/20**, **3/15/21**, **4/16/22**, **11/17/23**, and **12/18/24**. The corresponding relative energies are 14.1/13.1/4.9, 11.7/6.7/5.7, –3.3/–6.0/–4.3, 0.0/–2.5/–1.9, –3.2/–7.5/–1.1, and 0.4/–2.2/3.6 kcal mol^{-1}, respectively. It is worth noting that the first number of the series, corresponding to phenyl, is in no case the lowest (or the most negative). Thus, it can be concluded that the abundance of aromatic carbons in cyclopalladated compounds cannot be attributed to a thermodynamic preference because in no case is this the favored reaction. A second observation is that there is no special similarity between the first (phenyl) and the second (alkenyl) number of each series. Finally, concerning the particular numbers being presented, it can be seen that the larger differences (up to 10 kcal mol^{-1}) appear in the first two series (**1/13/19** and **2/14/20**), while for the other four groups the differences are 6 kcal mol^{-1} at most. This can be easily explained by the geometric strain of the four-membered rings in the first two sequences. The C–C–Pd angles are smaller than 100° in **1b**, **13b**, and **19b**, and this is more easily tolerated by sp^3 carbons than by their sp^2 counterparts.

Substituents on the Nitrogen Atom

The second factor considered was the variation in the nitrogen substituents. It is commonly assumed that M–N bonds are weaker in tertiary than in primary or secondary amines.[2] This effect is attributed, among other factors, to the steric hindrance of tertiary amines, as well as to the decrease in the outer-sphere solvation energy induced by N-alkylation;[24] however, it has been found that, in some cases, N-alkylation can stabilize coordination complexes in the gas phase.[25] Cope[8] was able to cyclometallate only tertiary amines, and nearly all the published work about the cyclopalladation of amines deals with tertiary nitrogen. Several explanations have been proposed for this fact: the greater coordinating ability of primary and secondary amines, which makes the subsequent C–H bond cleavage by the palladium atom via an electrophilic attack more difficult,[8] steric factors, which lead to a smaller internal entropy decrease in the cyclometallation of tertiary amines;[26] and, finally, the weaker bond between the palladium and the tertiary nitrogen atoms in the coordination intermediates, which facilitate the formation of unsaturated species that subsequently undergo Pd–C bond formation.[2] However, under carefully controlled experimental conditions, it is possible to prepare cyclopalladated compounds with primary[27] or secondary[27f,28] amines. Recently, the mechanism of the cyclometallation of primary amines has been investigated,[29] and it has been found that the choice of the solvent is critical in order to perform this reaction.

In our calculations we examined two limiting cases: primary amines, with two hydrogen substituents at nitrogen, and tertiary amines, with two methyl substituents. In this case, there are as many as nine primary/tertiary pairs of relative energies in Table 3 that can be compared. These are **1/2**, **3/4**, **11/12**, **13/14**, **15/16**, **17/18**, **19/20**, **21/22**, and **23/24**. The corresponding relative energies are 14.1/11.7, –3.3/0.0, –3.2/0.4, 13.1/6.7, –6.0/–2.5, –7.5/–2.2, 4.9/5.7, –4.3/–1.9, and –1.1/3.6 kcal mol^{-1}. In all but two pairs (**1/2** and **13/14**) the first number is smaller than the second, indicating that the reaction of primary amines is thermodynamically favored. The only two exceptions correspond to four-membered rings, which have their own characteristics associated with the large steric strain. Our calculations therefore indicate that cyclometallation tends to be favored when the nitrogen is primary; the energy differences between the metalation of primary and tertiary amines are between 2 and 5 kcal mol^{-1} for the five- and six-membered rings. The reasons for this can be electronic and/or steric; in this regard, the comparison of the Pd–N distances shows a shortening of the bond in the primary amines as compared to the tertiary ones. Also, we cannot rule out the presence of an interaction between the hydrogen of the primary amine and the chlorine atom. This interaction could lead to a stabilization of those metallacycles that feature primary nitrogen.

The experimental observation that the primary amines are so difficult to cyclopalladate is thus not due to a lack of thermodynamic stability of the product. In fact, it has been proposed from experimental data that an intermediate complex with two amines coordinated is too stable in this case, thus precluding the cyclometallation.[2] However, a definite answer can only be obtained after a thorough computational study of all the intermediates corresponding to the cyclopalladation reaction.

Size of the Metallacyle

The number of members in the formed metallacycle is considered to be a crucial factor in this reaction. In their original work, Cope and Friedrich tried the reaction of lithium tetrachloropalladate with *N*,*N′*-dimethylbenzylamine, *N*,*N′*-dimethyl-1-ethyl-2-phenylamine and *N*,*N′*-dimethyl-3-phenyl-1-propylamine in order to obtain five-, six-, and seven-membered rings, respectively, but they were successful only in the first case.[8] However, there are some recent examples of six-membered rings with primary benzyl-[10,30] and ferrocenylamines,[27e] and also with heterocycles.[31] Five- or six-membered rings can be obtained in the cyclopalladation of imines depending on the reaction conditions;[15,32] however, examples with six-membered metallacycles are less common than their five-membered counterparts.[1]

In order to test the importance of the ring size we performed calculations with four-, five-, and six-membered rings, both for primary and for tertiary amines (Table 3). In this case, we can form six series of relative energies corresponding to four/five/six-membered rings with identical settings for the other variables. The series are **1/3/11**, **2/4/12**, **13/15/17**, **14/16/18**, **19/21/23**, and **20/22/24**, and the corresponding relative energies are 14.1/–3.3/–3.2, 11.7/0.0/0.4, 13.1/–6.0/–7.5, 6.7/–2.5/–2.2, 4.9/–4.3/–1.1, and 5.7/–1.9/3.6 kcal mol^{-1}, respectively. As could be expected, the first number of the triad is always the highest, indicating that the formation of four-membered palladacycles is always the least thermodynamically favored, with differences larger than 10 kcal mol^{-1} in a number of cases. The reason for this is the greater strain associated with four-membered rings, as can be seen in the comparison of the bond angles in the metallacycles (Table 2).

The comparison between five- and six-membered systems shows that the cyclopalladation is more favored for the former in nearly all the cases, with the only exception being the tertiary alkenylamines. Due to the lack of reaction between lithium tetrachloropalladate and *N*,*N*-dimethyl-1-ethyl-2-phenylamine,[8] it could be anticipated that the formation of six-membered rings would be less favored than in the five-membered systems. However, our calculations show that the difference in energy is small, mainly in the case of the aromatic amines, where it is smaller than 0.5 kcal mol^{-1}.

In order to ascertain the transferability of the results of these calculations, we analyzed the combined effect of the nature of the metalated atom and the size of the metallacycle on the 2-methylbenzylamine system depicted in Figure 1, which can produce the two different cyclometallation products shown. The calculation indicates that the isomer on the left-hand side, which features an aromatic metalated carbon atom and a five-membered metallacycle, is 5.9 kcal mol^{-1} more stable than the one on the right-hand side, which contains an aliphatic metalated carbon atom and a six-membered metallacycle. This compares well with the numbers in Table 3, where the reaction associated to an alkyl compound with a tertiary amine leading to a six-membered cyclometallated complex (**24a**) is 3.6 kcal mol^{-1} disfavored with respect to that of an aryl compound with a tertiary amine leading to a five-membered cyclometallated complex (**4a**). The minor difference between both energy differences can be easily explained by the presence of some sp^2 carbons in the six-membered ring of our test compound that are absent in model species **24b**.

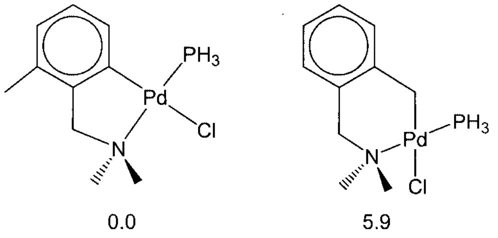


Figure 1. Relative energies [kcal mol^{-1}] of the two possible isomers that arise from the cyclopalladation of *N*,*N*-dimethyl(*o*-tolyl)methylamine.

We thus see that four-membered rings are indeed greatly disfavored from a thermodynamic point of view, and that five-membered rings are slightly more favored than six-membered rings. Therefore, it seems that the Cope rule concerning the size of the rings being formed can be explained by the thermodynamic stability of the product.

Electron-Donor or -Acceptor Groups in the Aromatic Ring

The last factor that was taken into account was the presence of electron-donor or -acceptor groups in the aryl ring. If the reaction has an electrophilic character, donors will favor it, while acceptors will render it more difficult. An example of this is the cyclopalladation of substituted azobenzenes, where the ring with electron-donating groups is preferentially metalated.[33] As for the tertiary benzylamines, Cope and Friedrich[8] metalated the 4-methoxy and 3,5-dimethoxy derivatives, with yields very similar to the unsubstituted tertiary amine, but were unsuccessful with the 4-NO_2 analog; this compound needs stronger palladating agents, such as palladium(II) acetate.[34] Kinetic measurements for the cyclometallation reaction of substituted *N*,*N*-dimethylbenzylamines[9a] or *N*-benzyltriamines[9d] show that there is a linear correlation between the logarithm of the rate constant and the Hammett parameter, σ_m, of the substituents, thus confirming that the reaction takes place through an electrophilic attack of the Pd^{II} center on the carbon atom.

In order to test the importance of the ring substituents we performed calculations on several substituted *N*,*N'*-dimethylbenzylamines of general formula 4-R-$C_6H_4CH_2N(CH_3)_2$, where R = -OCH_3 (**5a**), -NO_2 (**6a**), -Cl (**7a**), -CH_3 (**8a**), -CN (**9a**), and –OH (**10a**). They are depicted in Scheme 2. In addition to **5a** and **6a**, the cyclopalladated derivatives of **7a** and **8a** have been prepared previously,[9a] while, to the best of our knowledge, there are no examples of simple cyclopalladated derivatives of the hydroxy- and cyano-substituted tertiary benzylamines.

The relative energies corresponding to the cyclopalladation reactions, taking the unsubstituted tertiary benzylamine **4a** as reference, are shown in Table 3. There is not a perfect relationship between the electron-donor or -acceptor character of the R groups and the stability of the resulting palladacycles, but some trends are apparent. Acceptor groups, such as NO_2 (+1.8 kcal mol^{-1}) and CN (+1.5 kcal mol^{-1}), seem to render the metallacycles more unstable, whereas donor groups, such as OH (–5.4 kcal mol^{-1}), tend to stabilize the palladacycles, as would be expected from the electrophilic substitution mechanism indicated by the Cope rules. Donor groups making the reaction more difficult, as is the case with OCH_3 (+1.2 kcal mol^{-1}) and CH_3 (+0.4 kcal mol^{-1}), is somehow in disagreement with the rule, but can be attributed to their *meta* arrangement with respect to carbon C1. Finally, the chloro-substituted benzylamine **7a**, with a relative reaction energy of –5.6 kcal mol^{-1}, has a similar behavior to the electron donor OH. However, it has been reported that, at least in azobenzenes, a chloro substituent renders the substrate less reactive towards cyclopalladation than a hydrogen atom,[35] which would be in disagreement with this result.

It seems clear from these results that our simplified analysis fails to reproduce the experimental reactivity trends associated with the effect of electron-donor and electron-acceptor substituents. A subsequent study of the reaction mechanism could shed some light on the effect of these groups on the reaction kinetics.

Conclusions

A comparison of the relative energies of a series of amines and those of the corresponding cyclometallated compounds allows a relatively simple computational evaluation of the correlation between the nature of the amine and the thermodynamic change involved in the cyclopalladation reaction. If these thermodynamic trends reproduced the experimental observations on the easiness of the reaction, this would be an efficient approach for the prediction of the likeliness of cyclometallation for a given compound and for the identification of the preferred product when more than one is possible. Unfortunately, our results indicate that this is not always the case.

The empirical rules proposed initially by Cope, and confirmed by a variety of experimental data afterwards, predict that cyclometallation is favored in the case of five-membered-ring products, tertiary amines, and in the presence of electron donors. Of these three rules, only the first of them, concerning the size of the rings, has an undisputable thermodynamic basis. Four-membered rings are strongly disfavored by the large steric strain, and products with five-membered rings are also preferred over their six-membered counterparts. The second rule, concerning the nature of the substituents at both the nitrogen and the carbon atoms, does not have a thermodynamic origin. It must therefore be associated to kinetics. The third rule, related to the nature of the substituents at the carbon atoms, seems to have a certain thermodynamic basis, but there are exceptions for some substituents, thus suggesting a significant kinetic contribution. The theoretical evaluation of kinetics requires a detailed knowledge of the reaction mechanism, with location of intermediates, transition states, and their associated energies. Further understanding of these empirical rules, as well as computational predictions on cyclometallation, will thus require the performance of a much more elaborate computational study.

Computational Details

All calculations were carried out with the Gaussian 98[36] package of programs at the B3LYP computational level.[37] The basis set was chosen as follows: an effective core potential was used to replace the 36 innermost electrons of Pd and the 10 innermost electrons of P and Cl; for these atoms, the LANL2DZ basis[38] was used, and in the case of phosphorus and chlorine, polarization functions were added. For carbon, hydrogen, oxygen, and nitrogen the 6-31G(d,p) basis including polarization functions[39] was used. Some conformational searches were carried out at the AM1 computational level[14] using the Spartan program.[40]

Acknowledgments

We are indebted to the Spanish Ministerio de Ciencia y Tecnología (grant nos. BQU2003-00906 and BQU2002-04110-CO2-02) and to the Generalitat de Catalunya (grant nos. SGR-2001-00054 and SGR-2001-00179) for financial support. FM thanks DURSI as well as the ICIQ foundation for financial support.

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Received: February 22, 2005