

Oxidative Addition of Aryl Chlorides to Monoligated Palladium(0): A DFT-SCRF Study

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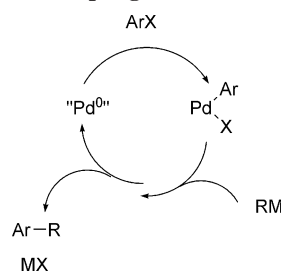
Oxidative addition of aryl chlorides to palladium has been investigated by hybrid density functional theory methods (B3LYP), including a continuum model describing the solvent implicitly. A series of para-substituted aryl chlorides were studied to see the influence of electronic effects on the reaction. It was found that the experimentally observed higher reactivity of the more electron deficient aryl chlorides is due to their ability to accept back-donation from Pd⁰ and form reasonably strong pre-reactive complexes. This effect is less pronounced in the transition state; when it is measured from the pre-reactive complex, the barrier to oxidative addition is actually higher for the electron-deficient aryl chlorides, but the overall reaction barrier is still lower than for the electron-rich aryl chlorides.

Introduction

Palladium-catalyzed reactions have had a major impact on organic chemistry. A myriad of coupling reactions between aryl halides and nucleophiles have been developed over the last few decades.¹ In the prototypic cross-coupling reaction depicted in Scheme 1, the organometallic reagent RM provides the coupling partner,² but similar catalytic cycles are also valid for palladium-catalyzed additions to π systems.³ A major achievement was the development of catalytic systems that are able to couple aryl chlorides rather than the iodo and bromo analogues.⁴ Similar catalyst systems have recently been shown to be able to couple even less reactive substrates such as tosylates and phosphates.⁵

Within this class of reactions, the first step in the catalytic cycle is oxidative addition of an aryl halide to a low-ligated Pd⁰ species. This step, and its microscopic reverse, reductive elimination, has been the subject of much investigation.⁶ In particular, a number of computational studies of the mechanism of oxidative addition of aryl halides have recently appeared.⁷ Of special interest is a study by Senn and Ziegler, demonstrating that the nature of the oxidative addition transition state changes

Scheme 1. Generic Catalytic Cycle for Pd-Catalyzed Coupling Reactions



qualitatively when going from calculations in the gas phase to models incorporating an average influence of the solvent (a continuum model).^{7a}

Herein we report a density functional theory investigation of the effect of the electron density of the aryl chloride on the oxidative addition. All calculations were performed at the B3LYP/LACVP* level of theory, applying a Poisson–Boltzmann self-consistent reaction field to describe the solvent implicitly.⁸

Results and Discussion

Oxidative Addition to Pd(PtBu₃). One of the most commonly employed palladium sources for cross-coupling reactions

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(8) DFT calculations were carried out with the Jaguar 4.2 program package from Schrödinger Inc., Portland, OR (<http://www.schrodinger.com>). All of the calculations were performed at the B3LYP/LACVP* level. The geometries were fully optimized in solvent, simulated with the PB-SCRF model: Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775. The parameters were set to $\epsilon = 38$ probe radius = 2.48 to simulate DMF.

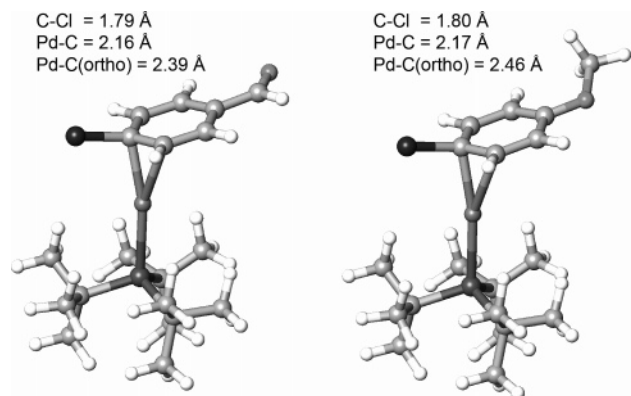


Figure 1. Pre-reactive complexes of Pd(PtBu₃) with *p*-chlorobenzaldehyde and *p*-chloroanisole.

of aryl chlorides is Pd(PtBu₃)₂, a catalytic system originally developed by Fu and co-workers.⁹ The 14-electron complex Pd(PtBu₃)₂ is believed to be the major species in solution and was therefore chosen as the reference complex of our investigation. The calculated geometry of Pd(PtBu₃)₂ is similar to that of the previously reported triphenylphosphine analogue,¹⁰ in that it adopts a linear structure. The Pd–P bond lengths were found to be slightly longer in Pd(PtBu₃)₂ than in Pd(PPh₃)₂: 2.38 Å vs 2.34 Å. We note that this geometry is consistent with the bonding model of Weinhold and Landis: of the 6 *s* and *d* valence orbitals on Pd, 5 are occupied by the 10 valence electrons of Pd⁰. The last valence orbital can accommodate 2 ligands in a trans relationship by a 3-center–4-electron ω -bond.¹¹

Palladium catalysts bearing bulky phosphines have been proposed to react via monocoordinate 12-electron complexes:¹² in the current case, Pd(PtBu₃). A significant decrease of the Pd–P distance is observed in Pd(PtBu₃), by 0.11 Å to 2.27 Å, a consequence of the strong trans influence of the phosphine (similar results were found for PPh₃ complexes in an earlier study¹⁰). Using the Weinhold–Landis bonding model, the bond is now a standard 2e bond, significantly stronger *per ligand* than the ω bond. Frequently these types of reactions are performed in coordinating solvents, e.g., DMF, and in these cases a solvent molecule is likely to coordinate trans to the single phosphine, in an unsymmetrical ω -bond.

Investigation of the influence of para substituents on the aryl chlorides can give valuable information on electronic effects in chemical reactions. In the current study, we have included six different aryl chlorides, with both electron-withdrawing and -donating substituents. For all of these, we have optimized pre-reactive complexes where one aryl chloride and one phosphine coordinate to Pd. Two of the structures are shown in Figure 1, and the energies relative to Pd(PtBu₃)₂ of all the complexes are given in Table 1. From the values of the relative energies it is clear that the electron-poor aryl chlorides form much more stable complexes with Pd⁰ than do the aryl chlorides with higher electron density. A comparison between the aryl chlorides with the strongest and weakest binding, *p*-OHC-PhCl and *p*-MeO-PhCl, respectively, reveals a difference of as much as 17 kJ mol⁻¹. This trend can be rationalized by the high aptitude of Pd⁰ for d– π^* back-bonding. A similar trend has previously been observed for binding of alkynes to Pd⁰.¹³

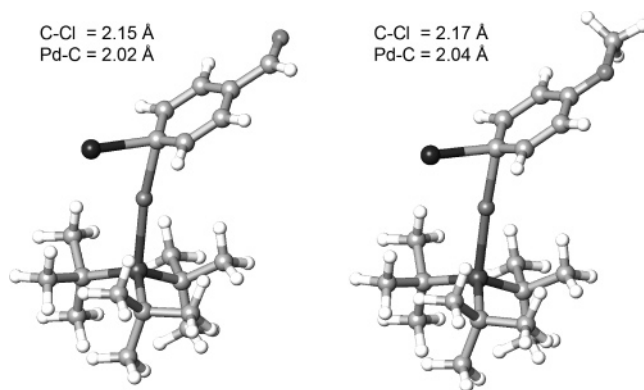


Figure 2. Transition states for the oxidative addition of *p*-chlorobenzaldehyde and *p*-chloroanisole to Pd(PtBu₃).

Table 1. Energies of the Pre-reactive Complexes Pd(ArCl)PtBu₃ and the Subsequent Oxidative Addition Transition States, Relative to Pd(PtBu₃)₂, in kJ mol⁻¹

X in <i>p</i> -Cl-PhX	pre-reactive complex	transition state
–CHO	64.9	104.6
–CN	65.7	104.8
–H	75.8	112.5
–NH ₂	74.2	107.0
–Me	76.8	112.6
–OMe	81.7	114.2

The transition states for the oxidative addition of the aryl chlorides reveal an intriguing feature. Relative to the case for the respective pre-reactive complexes the barrier for oxidative addition is calculated to be lower for electron-rich aryl chlorides. For example, the barrier is only 32 kJ mol⁻¹ for Pd(PtBu₃)(*p*-MeO-PhCl) compared to 40 kJ mol⁻¹ for Pd(PtBu₃)(*p*-OHC-PhCl) (Figure 2). However, the total barrier (as shown in Table 1), obtained as the sum of the activation barrier for the addition step and the energy of the intermediate, is still substantially lower for the electron-deficient aryl chlorides, with a span of 10 kJ mol⁻¹ between the least and most reactive aryl chloride. Thus, the binding advantage of the electron-deficient aryl chlorides is only partially retained in the TS, but this is still sufficient to increase the reactivity.

Oxidative Addition to [PdCl]⁻. [PdX]⁻ has been proposed as the active intermediate when applying certain Pd^{II} complexes, e.g., palladacycle and pincer complexes, as a source of highly active Pd⁰ species.¹⁵ Recently a theoretical study concluded that the oxidative addition in the presence of phosphines could occur at a [PdX]⁻ type complex.¹⁰ The reactivity of [PdCl]⁻ toward the same aryl chlorides as above was therefore investigated. Most of the palladium present is still undoubtedly ligated by at least one phosphine, but as we have shown earlier, loss of the additional ligands before the actual oxidative addition step substantially reduces the free energy barrier.¹⁰ Under some reaction conditions, complexes coordinating one phosphine and an anion have been proposed to be the major species,¹⁴ motivating the choice of [Pd(PtBu₃)Cl]⁻ as the reference complex herein.

Formation of the pre-reactive complexes of the type [Pd(ArCl)Cl]⁻ follows a trend similar to that for the neutral

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Table 2. Energies of Pre-reactive Complexes [Pd(ArCl)Cl]⁻ and the Subsequent Oxidative Addition Transition States Relative to [Pd(PtBu₃)Cl]⁻, in kJ mol⁻¹ ^a

X in <i>p</i> -Cl-PhX	pre-reactive complex	transition state
-CHO	39.6 (35.3)	78.9 (72.3)
-CN	41.0 (37.6)	78.8 (72.8)
-H	58.8 (56.2)	90.7 (84.9)
-NH ₂	52.9 (52.0)	90.6 (87.2)
-Me	58.9 (57.6)	91.7 (87.6)
-OMe	59.3 (57.6)	92.9 (88.2)

^a Given in parentheses are values from single-point calculations including diffuse functions on all heavy elements.

palladium complexes, although a more strongly pronounced electronic effect is observed for the anionic complexes. Also here the relative stability of the pre-reactive complexes with the electron-deficient aryl chlorides is much higher than the stability of the complexes with the electron-rich aryl chlorides, with a difference between the two extremes *p*-OHC-PhCl and *p*-Me-PhCl calculated to be as large as 20 kJ mol⁻¹ in favor of the complex with *p*-OHC-PhCl. Geometrically the anionic complexes differ slightly from the neutral phosphine complexes in that the aryl chloride is more tightly bound to Pd. In [Pd-(OHC-PhCl)Cl]⁻ the Pd-C_{ipso} distance is 2.09 Å and the Pd-C_{ortho} distance is 2.22 Å. The C-Cl distances are almost identical in the anionic and neutral complexes: 1.80 and 1.79 Å, respectively.

The barriers from the respective pre-reactive complexes follow the same trend as for the neutral complexes, with the lowest barrier found for the complexes containing electron-rich aryl chlorides (relative to the respective pre-reactive complexes) (Table 2). However, also for the anionic reaction the overall barrier from the separated reactants is substantially lower for the electron-deficient aryl chlorides. The difference between the highest and lowest barrier in the anionic path is calculated to be 14 kJ mol⁻¹, compared to the 10 kJ mol⁻¹ span for the neutral path. The higher reactivity difference for the anionic palladium species is in agreement with the experimental observations by Herrmann et al. that reactions under phosphine-free conditions show a higher ρ value than for reactions with phosphines present, which was attributed to the formation of the highly active anionic species [Pd(OAc)]⁻.^{15a}

Rationale for the Reactivity. To further understand which factors are responsible for the reactivity difference, the homolytic bond dissociation energies (BDE) of the aryl chlorides were calculated. In Figure 3 the BDE:s are plotted against σ^p , which gave a good fit. The lowest and the highest BDE values were found for NC-PhCl and H₂N-PhCl, respectively, with a 7.65 kJ mol⁻¹ lower value for NC-PhCl. In the oxidative addition a similar trend is observed: i.e., electron-deficient aryl chlorides react more readily than the electron-rich analogues. However, the difference in reactivity is much larger than the difference in BDE; the barrier for oxidative addition of NC-PhCl is 14.1 kJ mol⁻¹ lower than for MeO-PhCl. A Hammett plot of the activation barriers against σ^- gave a good correlation, whereas σ^p correlated poorly. Although the strength of the C-Cl bond could account for some of the difference in the barriers, additional factors must be present that explain the correlation with σ^- rather than σ^p , as well as the high reactivity difference, despite the lower difference in bond strength. The fact that the barriers correlate with σ^- suggests that the mechanism is best described as an S_NAr type mechanism. An even stronger electronic effect (20 kJ mol⁻¹) is observed in the formation of the pre-reactive complexes as compared to that in the transition state (Figure 4). Structurally the pre-reactive complexes resemble π complexes which are known to be favored by electron-

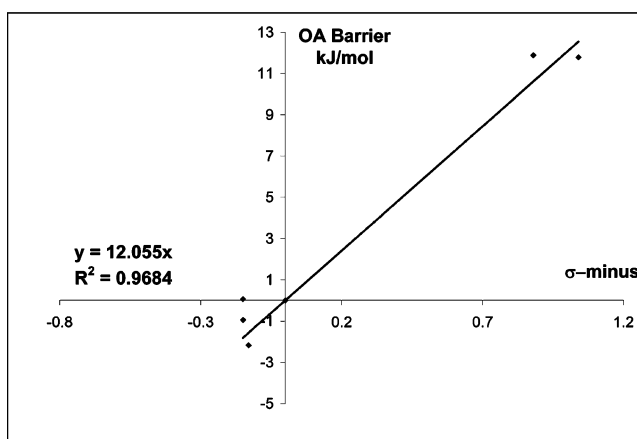
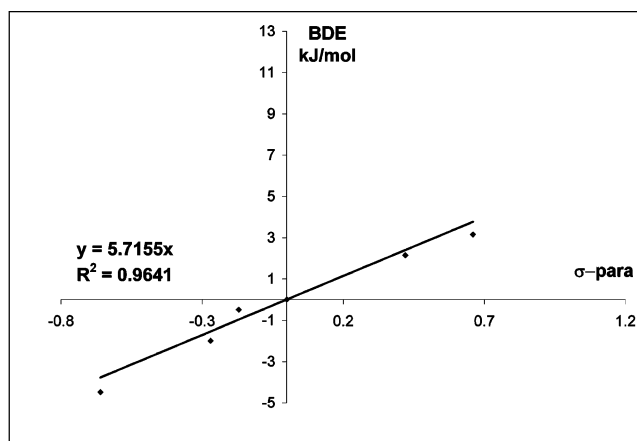


Figure 3. Hammett plots of (top) the C-Cl BDE values of the aryl chlorides and (bottom) the relative potential energies of the transition states for oxidative addition of aryl chlorides to mono-coordinate palladium(0).

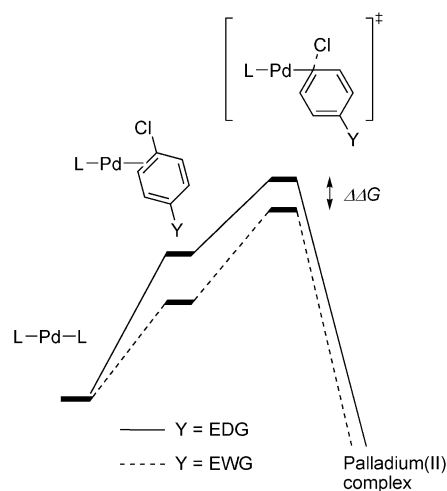


Figure 4. Illustration of the effect of introduction of an electron-withdrawing group in the aryl chloride. The effect of having an electron-deficient aryl chloride is greatest in the pre-reactive complex but remains to a substantial extent in the oxidative addition transition state.

withdrawing substituents that allow for more back-donation from palladium. In the transition states some of the transferred charge is relocalized to the dissociating chloride; hence, the electronic effect remains, but to a lesser extent.

Catalytic Activity. The oxidative addition barriers of the neutral palladium species are calculated to be in the range 106–

114 kJ mol⁻¹ relative to Pd(PtBu₃)₂, where the lower barriers were obtained for addition of electron-deficient aryl chlorides. This is substantially higher than the previously calculated barriers for phenyl iodide,^{7,10} in good agreement with the observation that reactions of aryl chlorides frequently require heating. However, we want to point out that a substantial part of the reaction barrier comes from the necessity to dissociate one of the phosphines from Pd. Reaction conditions allowing formation of monoligated Pd,¹² possibly with a coordinating solvent molecule, would substantially reduce the barrier to oxidative addition.

The anionic path was found to proceed with barriers in the range 79–93 kJ mol⁻¹ relative to the anionic complex [Pd(PtBu₃)Cl]⁻.¹⁶ If we start instead from the solvated anionic palladium species [Pd(DMF)Cl]⁻, the barrier is drastically decreased to 13–27 kJ mol⁻¹. Complexes such as [Pd(DMF)Cl]⁻ are likely to be highly unstable species, yet even if they are present in only minute concentrations, they would be highly active toward oxidative addition. De Vries and co-workers

(16) We have avoided comparing the anionic and neutral paths directly, due to the fact that the solvation of small anions sometimes gives results not accurate enough for such a comparison to be reasonable. Due to the cancellation of errors, a comparison of complexes of the same overall charge should yield more reliable results. Ahlquist, M.; Kozuch, S.; Shaik, S.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *25*, 45.

reported that the anionic Pd(0) complex [Pd(H₂O)OAc]⁻ was detected by ESI-MS under ligand-free conditions, using Pd(OAc)₂ as the source of palladium, which suggests that the anionic solvent complexes described in the current study are possible intermediates.

Conclusions

An investigation of the oxidative addition of aryl chlorides to monoligated Pd(0) species has been presented. It was shown that the reactivity difference between electron-deficient and electron-rich aryl chlorides is due to the higher ligating ability of the electron-deficient aryl chlorides. The actual C–Cl bond-breaking step was shown to proceed with a lower barrier for the electron-rich species than for the electron-deficient analogues, relative to the respective pre-reactive complexes. Overall the energy required for the oxidative addition is less for the electron-poor aryl chlorides, in agreement with earlier experimental observations.^{4a}

Supporting Information Available: Tables giving xyz coordinates and solution-phase energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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