DFT Studies on the Effect of the Nature of the Aryl Halide Y−C_6H_4−X on the Mechanism of Its Oxidative Addition to Pd^0L versus Pd^0L_2

King Chung Lam,[†] Todd B. Marder,*[,‡] and Zhenyang Lin*[,†]

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, and Department of Chemistry, Durham University, South Road, Durham DH1 3LE, U.K.

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Summary: The influence of the nature of the para substituent (Y) and halide (X = Cl, Br, I) of an aryl halide on the preferred reaction pathway and the number of ligands bound to Pd during the oxidative addition of p-Y−C_6H_4−X to Pd(0), which is critical to many Pd-catalyzed cross-coupling reactions, has been examined theoretically with the aid of DFT calculations.

Oxidative addition of aryl halides to Pd(0) complexes is a fundamental step of many Pd-catalyzed cross-coupling reactions, such as the Heck, Stille, Sonogashira, Suzuki−Miyaura, and Buchwald−Hartwig amination reactions, and as such, it has attracted considerable study.[1−2] Many reports suggest that the active species in the fundamental step are either coordinatively unsaturated Pd(0) species having one (PdL) or two donor ligands (PdL_2).[3−8] In 1990, Amatore et al. studied the oxidative addition of substituted iodobenzenes to $Pd(PPh_3)_4$ and found that PhI was oxidatively added to the $Pd(PPh_3)_2$ metal fragment having two phosphine ligands.[4] They have subsequently suggested the importance of anionic species such as $[Pd(PR_3)_2X]^-$ (X = halide, OAc) in the oxidative addition step.[5] In 1994, Hartwig et al. studied the reactions of aryl bromides with Pd(0) complexes having bulkier phosphine ligands, e.g., $P(o\text{-}MeC_6H_4)_3$, and found that $Pd\{P(o\text{-}MeC_6H_4)_3\}$, a highly unsaturated 12e monophosphine Pd(0) complex, is the active species.[3f,6] This was supported by the catalytic studies of Fu et al.[1h] Clearly, whether the active species is PdL or PdL_2 could depend on the bulk of the ligand and whether is it monodentate or bidentate. Less bulky or bidentate ligands are likely to promote oxidative addition via PdL_2, while bulkier monodentate ligands favor oxidative addition via PdL.[7]

Recently, Hartwig et al. reported mechanistic studies of the oxidative addition of chloro-, bromo-, and iodobenzene to [Pd(Q-phos-tol)$_2$] (Q-phos-tol = (di-*tert*-butylphosphino)penta-*p*-tolylferrocene) containing the sterically demanding Q-phos ligands.[8] For PhCl, they observed reversible phosphine dissociation followed by a rate-limiting oxidative addition, and for PhBr, they found rate-limiting phosphine dissociation prior to oxidative addition. For PhI, rate-limiting associative replacement of phosphine in Pd(Q-phos-tol)$_2$ by PhI was observed. In each case, the oxidative addition step proceeds via the monophosphine Pd(0) complex [Pd(Q-phos-tol)(ArX)]. Clearly, the intimate mechanism of oxidative addition is sensitive to the nature of the halide and it could also be sensitive to the electronic properties of the aryl group.

A detailed DFT study of oxidative addition of PhX (X = Cl, Br, I) to [(dmpe)Pd] (dmpe = $Me_2PCH_2CH_2PMe_2$) was carried out by Senn and Ziegler[2a] which suggested a concerted oxidative addition to the *cis*-L_2Pd moiety in the gas phase but a transition state reminiscent of S_N2(Ar) in "solution", using a COSMO model to simulate solvation in THF. Goossen, Thiel, and coworkers[9] have recently reported DFT calculations on the mechanism of oxidative addition of ArX to $[Pd(PMe_3)_2(OAc)]^-$ modeling the routes proposed by Amatore and Jutand.[5] More recently, Norrby et al.[10] studied the oxidative addition of PhI

* To whom correspondence should be addressed. E-mail: todd.marder@durham.ac.uk (T.B.M.); chzlin@ust.hk (Z.L.).

[†] The Hong Kong University of Science and Technology.

[‡] Durham University.

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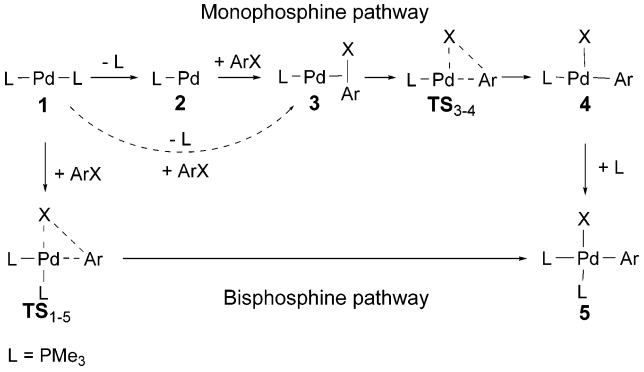
Scheme 1



to Pd(0) and concluded that the preferred number of ligands on Pd is lower than expected.

In this note, we present the results of a DFT investigation into the effect of the nature of the aryl halide on its oxidative addition to Pd(0) complexes containing monodentate phosphines.[11] Despite the extensive theoretical studies,[2,9,10] the question of how the nature of the aryl halide influences the preferred reaction pathway and the number of ligands bound to Pd in the oxidative addition step has not been addressed to date. While the calculated transition states and intermediates we obtained do not differ much from those reported in the literature,[2,9,10] the main purpose of this note is to demonstrate, for the first time, how the electronic properties of different aryl halides, Y−C_6H_4−X, affect the reaction pathways. The detailed structures of the calculated transition states and intermediates can be found in the Supporting Information.

Full geometry optimizations were performed using the B3LYP functional (see the Supporting Information for the computational details). Scheme 1 shows two reaction pathways[12] for the oxidative addition of an aryl halide to [Pd(PMe_3)$_2$] (**1**). While [Pd(PMe_3)$_2$] itself is not isolable and has not been demonstrated as an active species in cross-couplings, we note here that PMe_3 was simply used as a model for a strongly donating monodentate phosphine. In the bisphosphine pathway (Scheme 1), a direct oxidative addition of ArX to [Pd(PMe_3)$_2$], giving the square-planar complex [(PMe_3)$_2$Pd(Ar)(X)] (**5**), is considered. In the monophosphine pathway, **1** first dissociates a phosphine ligand, giving [Pd(PMe_3)] (**2**). Then, **2** coordinates an ArX molecule to give [(PMe_3)Pd(η^2-Ar−X)] (**3**), which undergoes oxidative addition via $\mathbf{TS_{3-4}}$ to afford a three-coordinate Pd(II) complex, [Pd(Ar)(X)(PMe_3)] (**4**). Finally, PMe_3 re-coordinates to give the square-planar complex [(PMe_3)$_2$-Pd(Ar)(X)] (**5**).

To examine how different aryl halides affect the reaction mechanism, we studied first the oxidative addition reactions of the three substrates PhCl, PhBr, and PhI. For each substrate, we calculated the free energy profiles of the two reaction pathways discussed above, shown in Figure 1. Taking into account the effect of entropy, we use the free energies rather than the electronic energies for our discussion because two or more molecules are involved in the reactions studied here.

For PhCl, the monophosphine pathway is favored. $\mathbf{TS_{3-4}}$ is higher in energy than **2**. A rate-limiting oxidative addition is expected. The result is consistent with the experimental finding of Hartwig et al. for reaction of PhCl with [Pd(Q-phos-tol)$_2$] (vide supra).

For PhBr, the reaction also favors the monophosphine pathway. On the basis of the energy profile, we found that the $\mathbf{TS_{3-4}}$ structure has a stability similar to that of **2**. It is not surprising that the experiments by Hartwig and co-workers indicate the dependence of the reaction rate on the ligand dissociation step for this substrate.

For PhI, the calculations still predict that the monophosphine pathway is preferred. However, we can see from the energy profile that the barrier for the bisphosphine pathway is very close to that for the monophosphine pathway. We expect that both pathways may well be competitive in this case.

From Figure 1, we can see that the oxidative addition barriers, i.e., the energy differences between **1** and $\mathbf{TS_{1-5}}$ and between **3** and $\mathbf{TS_{3-4}}$, are closely related to the bond strength of the C−X bonds in the PhX substrates. The stronger C−Cl bond in PhCl gives larger barriers, while the weaker C−I bond in PhI gives smaller barriers. For PhI, **3** → **4** has almost no barrier, reflecting the relatively weak C−I bond in PhI.

It is well-known that aryl halides having electron-withdrawing groups (EWGs) give higher rates of oxidative addition than those containing electron-donating groups (EDGs).[1i,3b,13] EWGs can make the aryl−halide bond more electron deficient and more susceptible to oxidative addition. To examine how different substituents with different electronic properties affect the reaction mechanism, we also calculated the energy profiles (Figure 2) for the oxidative additions of para-substituted aryl halides, Y−C_6H_4−X, having Y = CN, OMe as the EWG and EDG, respectively.

As expected, MeO−C_6H_4−X compounds, which have an electron-donating OMe group, have higher oxidative addition barriers than H−C_6H_4−X, while NC−C_6H_4−X compounds, which have an electron-withdrawing CN group, have smaller oxidative addition barriers than H−C_6H_4−X (Figures 1 and 2). EWGs lower the C−X σ* and π* orbitals in energy (Table 1), stabilizing both complex **3**, in which Ar−X serves as a π-acceptor ligand, and $\mathbf{TS_{1-5}}$ and $\mathbf{TS_{3-4}}$, in which electron density builds up on ArX. EDGs destabilize **3**, $\mathbf{TS_{1-5}}$, and $\mathbf{TS_{3-4}}$, making oxidative addition more difficult. Since Ar−X serves as a π-acceptor ligand, and the C−X σ* and π* orbitals are lower in energy when X becomes heavier (Table 1), the stability of the η^2-ArX complexes **3** (with respect to **1**) increases as X goes from Cl to Br to I (Figures 1 and 2).

For the oxidative additions of the aryl chlorides and bromides, the EDG or EWG, despite being capable of increasing or reducing the reaction barriers, does not alter the preferred monophosphine reaction pathway qualitatively. For the oxidative additions of the aryl iodides, substituents with different electronic properties, however, do play a determining role in choosing the preferred reaction pathway. As mentioned above, for the oxidative addition of the unsubstituted PhI, the monophosphine and bisphosphine pathways are competitive, with a slight preference for the former (Figure 1). The EWG switches the preference in favor of the bisphosphine pathway (Figure

(11) The similarity of charge separation calculated[2a] for the TS for oxidative addition of the substrates PhX (X = Cl, Br, I) to Pd(dmpe) in "solution" and the similarity of solvation energies for the Pd complexes formed from the three substrates implies that the presence or absence of solvent will not affect significantly the relative barrier heights. Thus, in our preliminary study, we do not include solvation effects, as they are not expected to influence our mechanistic conclusions, which specifically address the effects of substrate on the degree of ligation of Pd in the reaction. The effect of solvents of differing polarities and coordinating abilities, as employed in various cross-coupling reactions, as well as the detailed influence of the nature of L, on the intimate mechanism of the oxidative addition, will be addressed in a subsequent report.

(12) We do not consider herein the associative pathway, illustrated with a dashed arrow in Scheme 1, for reaction of **1** with ArX (cf. PhI in ref 8a; vide supra) leading to **3**, as the key step, **3** → **4**, does not depend on how **3** is formed.

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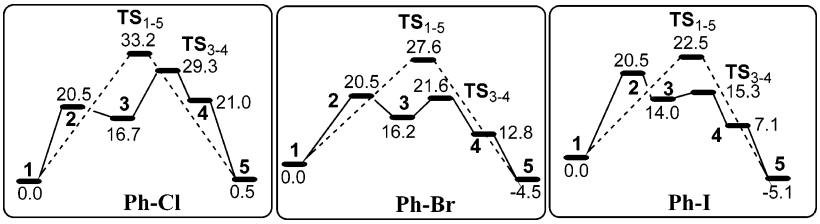

Figure 1. Energy profiles for the oxidative addition of PhX (X = Cl, Br, I) on the basis of the two reaction pathways proposed in Scheme 1. The calculated relative free energies are given in kcal/mol. In calculating the relative free energies, we included the energies of free PhX and PMe_3 whenever necessary in order to make the energies comparable for all of the species.

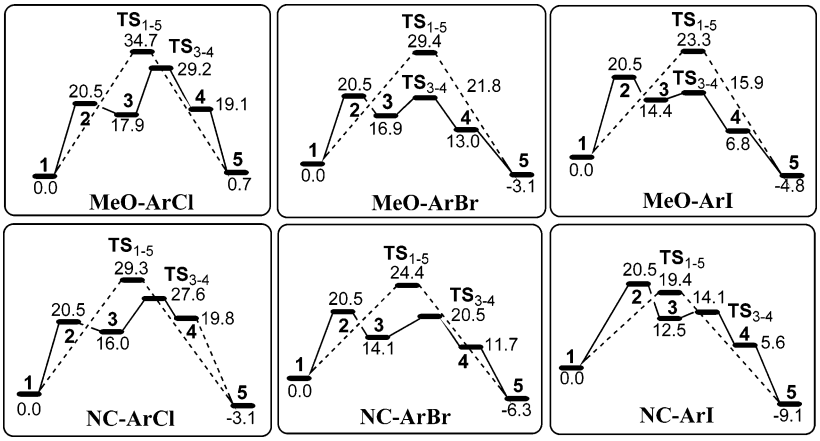

Figure 2. Energy profiles for the oxidative addition of MeO−ArX and NC−ArX (X = Cl, Br, I) on the basis of the two reaction pathways proposed in Scheme 1. The calculated relative free energies are given in kcal/mol. The relative free energies were obtained as in Figure 1.

Table 1. σ^* and π^* Orbital Energies Calculated for Various ArX Substrates

substrate	X	σ^* (eV)	π^* (eV)
p-MeO−C_6H_4−X	Cl	1.15	0.06
	Br	0.13	0.00
	I	−0.75	−0.05
H−C_6H_4−X	Cl	1.06	−0.27
	Br	0.05	−0.33
	I	−0.83	−0.38
p-NC−C_6H_4−X	Cl	0.53	−1.70
	Br	−0.47	−1.73
	I	−1.32	−1.75

2), whereas the EDG further enhances the preference for the monophosphine pathway.

We also note that the reaction free energies calculated for **1** + **ArX** → **5** increase as X goes from Cl to Br to I. The trend reflects the changes in the relative bond strengths of Pd−X vs C−X. The Pd−X and C−X bond strengths both decrease upon going down group 17. However, the C−X bond strength decreases more quickly than that of Pd−X,[14] explaining the trend of the reaction free energies. Substituents also affect the reaction free energies; EWGs give greater reaction free energies, suggesting that they increase the Pd−C(Ar) bond strengths more significantly than the C(Ar)−X bond strengths.

We have demonstrated how the electronic properties of different ArX affect the reaction pathways for their oxidative additions to Pd(0) bisphosphine complexes bearing monodentate ligands. The results explain why ArCl and ArBr are less susceptible to oxidative addition and show that they prefer the dissociative monophosphine pathway. For ArI species which are more susceptible to oxidative addition, the bisphosphine pathway plays a significant role. On the basis of these results, we can make the following important conclusions. The use of bulky and/or hemilabile ligands[15] for the oxidative addition of ArCl and ArBr promotes the reaction because such ligands promote the monoligand pathway. For the oxidative addition of ArI having EWGs, the use of less bulky ligands is suggested. For the oxidative addition of other ArI, the bulk of the ligands may be less important. These insights explain empirical observations leading to the choice of electron-rich, bulky ligands in Pd-catalyzed cross-coupling reactions of ArBr and ArCl, as they should also apply to N-heterocyclic carbenes[16] and other strong donor ligands as well as to phosphines.[1c,h,17] An important component of the energy required for oxidative addition using $(PR_3)_2Pd$ is associated with the bending of the L−Pd−L angle from 180 to 90°.[18] An alternative pathway involves dissociation of one of the ligands. Clearly, the substrate-dependent mechanisms highlighted in the current work are related to a balance between the relative energy of reorganization versus dissociation against the relative energy of the oxidative addition for $(PR_3)_2$-Pd with a P−Pd−P angle of ca. 90° versus $(PR_3)Pd$, the latter being more substrate dependent and the former being related to the specifics of the phosphine ligand, especially its size.

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Supporting Information Available: Text giving computational details and tables giving Cartesian coordinates and electronic energies for all of the calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) While the dependence of the L−Pd−L angle on rates of oxidative addition of aryl halides to chelating (L-L)Pd(0) has been addressed,[9c] the important implications for analogous monodentate PdL and PdL_2 complexes have not been reported.