DFT Study on the Oxidative Addition of 4-Substituted Iodobenzenes on Pd(0)-Phosphine Complexes

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Abstract

The oxidative additon of 4-substituted iodobenzenes on Pd(0)-PMe_3 complexes has been studied at the BP86 level of theory including dispersion correction and solvation effect, with tetrahydrofuran as solvent. The bisphosphine pathway was found to be barrierless, whereas the monophosphine route is hampered by the high dissociation energy of trimethylphosphine. The reaction free energy of this step shows linear correlation with the Hammett constants of the *para* substituents with the most electron withdrawing groups being the most exergonic.

Keywords: Hammett constant; Pd(0); Oxidative addition; DFT; SMD

1. Introduction

Palladium-catalyzed cross-coupling reactions are the most prominent examples in the family of carbon–carbon bond-forming reactions, which have gained enormous popularity in the last few decades [1, 2] and are found in all areas of chemistry, from polymers to pharmaceuticals and agrochemicals [3]. The Suzuki-Miyaura reaction is one of the most frequently used methods to form C–C bond in a catalytic way [4], but the number of applications employing Sonogashira coupling is drastically increased in the recent years as well [5]. Other Pd-catalyzed cross-coupling reactions, such as Stille [6, 7], Kumada [8], and Negishi [9] couplings have their important role in organic synthesis as well.

In general, the initial step in the catalytic cycle is the oxidative addition of an aryl halide to palladium(0) with cleavage of the C–X bond [10], which is followed by transmetallation and reductive elimination. The oxidative addition step has been the subject of several experimental [11–14] and computational [15–22] studies. Investigations regarding the entire catalytic cycle of Heck [23, 24] and Suzuki [25, 26] have been also reported.

In general, the barriers of oxidative addition of aryl halides increase in the order of ArI < ArBr < ArCl consistent with the reactivity order reported by Fitton and Rick [27]. Aryl halides with electron-withdrawing

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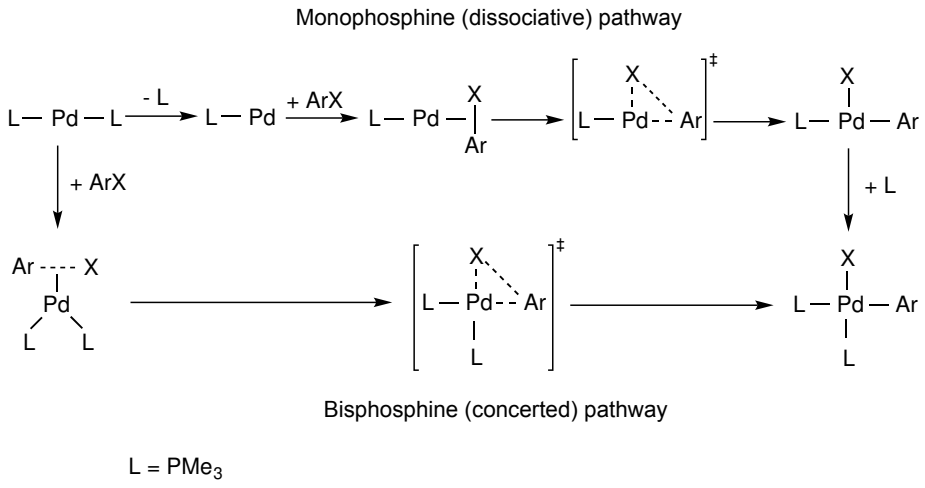
groups give smaller barriers than those having electron-donating groups [10]. As catalytically active complex, $Pd(0)L_2$ is usually considered as reference point due to its relative stability. The $Pd(0)L_2$ complex then reacts with the aryl halide in a concerted manner affording the complex $Pd(II)X_2L_2$ (X=halide). Depending on the basicity, and the bulk of the phosphine, PdL complexes, formed after the dissociation of one phosphine ligand, should be considered as viable alternatives for active catalysts in some specific cases [18, 19]. The bisphosphine and monophosphine pathways are illustrated in Scheme 1.



Scheme 1: Comparison of the bisphosphine and monophosphine pathways

The goal of this study is to explore how the substituents in *para* position influence the energetics of the oxidative addition of iodobenzenes on $Pd(0)$-PMe_3 complexes taking into consideration both the bisphosphine and monophosphine pathways. Our objective is also to get some insight about the electronic structure of Pd-PhI adducts which occur in both pathways.

2. Computational Details

All structures were fully optimized at the DFT/BP86 level of theory [28, 29] with ultrafine grids, assuming THF as solvent, employing the Gaussian 09 suite of programs [30]. The dispersion-correction developed by Grimme has been employed with Becke-Johnson damping, and denoted as BP86-D3 [31]. For palladium and iodine the def2-TZVP, whereas for the other atoms the def2-SVP basis sets were used [32]. Local minima were identified by the absence of the negative eigenvalues in the vibrational frequency analyses, whereas the Hessian matrix of transition states has only one negative eigenvalue. Gibbs free energies were calculated at 298.15 K. Intrinsic reaction coordinate (IRC) analyses [33] were carried out at the same level as the geometry optimizations in order to make sure that the corresponding local minima and transition states are smoothly connected to each other.

The effect of the solvent was taken into account utilizing the SMD solvation model [34], introduced by Marenich, Cramer, and Truhlar, with the dielectric constant of ϵ=7.4257 for tetrahydrofuran. The SMD method is based on the charge density of a solute molecule interacting with the solvent represented as continuum. The full solute electron density is employed without the definition of partial atomic charges, therefore the "D" stands for "density" in the abbreviation of the model. As in the previous SMx solvation models (x=1-8) developed by the Minnesota group the solvent is represented as a dielectric medium with surface tension at the solute–solvent boundary.

For the QTAIM (Quantum Theory of Atoms In Molecules) calculations the AIMAll software package was utilized [35].

3. Results and Discussion

It is known that increasing the phosphine basicity is advantageous to the activity of the catalytic system. It was also shown that sterically more demanding phosphines tend to turn the monoligated pathway as the preferred one. For this study the less bulky, yet strongly basic trimethylphosphine has been selected. For catalytically active complexes both $Pd(PMe_3)_2$ (**1**) and $Pd(PMe_3)$ (**2**) have been taken into consideration in order to decide whether the monoligated or the bisligated pathways are dominating for the various substituted iodobenzenes at the BP86/SMD level of theory including dispersion correction.

The dissociation of one PMe_3 from complex (**1**) undergoes with a free energy of 31.2 kcal/mol, which is notably higher, than that obtained by Lam and co-workers (20.5 kcal/mol) at B3LYP level with double-ζ basis set, without solvation corrections [19]. As expected, the remaining PMe_3 is bound stronger to Pd, which is reflected in the shorter Pd–P bond distance (2.163 Å) as opposed to that in complex **1** (2.282 Å) (Figure 1).

In order to unravel the strong dependence of the dissociation free energy (ΔG_{diss}) of trimethylphosphine from **1** the reaction free energy for the **1** $\rightarrow$**2** + PMe_3 process has been recomputed with the BP86 functional investigating the effect of solvation and dispersion corrections. Surprisingly, the neglect of solvent effects resulted in a ΔG_{diss} being only slightly higher than the original value (32.2 kcal/mol), whereas at the BP86/SMD level (without D3 correction) 24.7 kcal/mol has been obtained, being fairly close to ΔG_{diss}=20.5 kcal/mol achieved with the B3LYP functional [19].

For the pathway involving complex (**1**) iodobenzene coordinates to the palladium center in a η^2-like manner (Figure 2) resulting in the adduct **4a**. The coordination causes a slight increase in Pd–P bond length, as well as in the distance of the coordinating carbon atoms going from 1.407 Å to 1.462 Å. The coordination is exergonic by -7.3 kcal/mol.

The oxidative additon step itself is very facile. The free energy difference between **4a** and transition state **5TSa** is 6.7 kcal/mol, meaning that the overall activation free energy is -0.6 kcal/mol, thus it is below

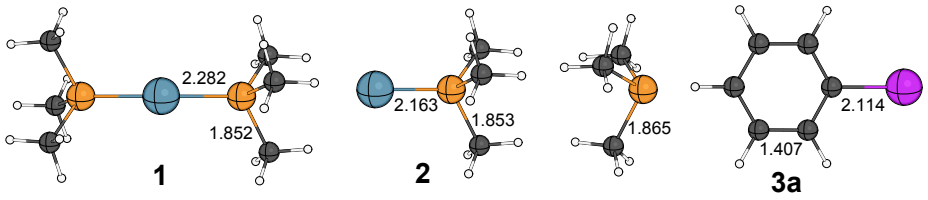


Figure 1: Computed structures of the initial compounds for the oxidative addition step: $Pd(PMe_3)_2$ (**1**), $Pd(PMe_3)$ (**2**), PMe_3, and iodobenzene (**3a**). Bond distances are given in Å.

the sum of the free energies of the separated reactants. As a result of this process a somewhat distorted square planar Pd(II)-iodo-phenyl complex is formed (**6a**) where the phenyl group is perpendicular to the plane spanned by the phosphines and the iodo ligand. The formation of **6a** is exergonic by -36.7 kcal/mol with respect to the summed free energies of **1** and **3a**.

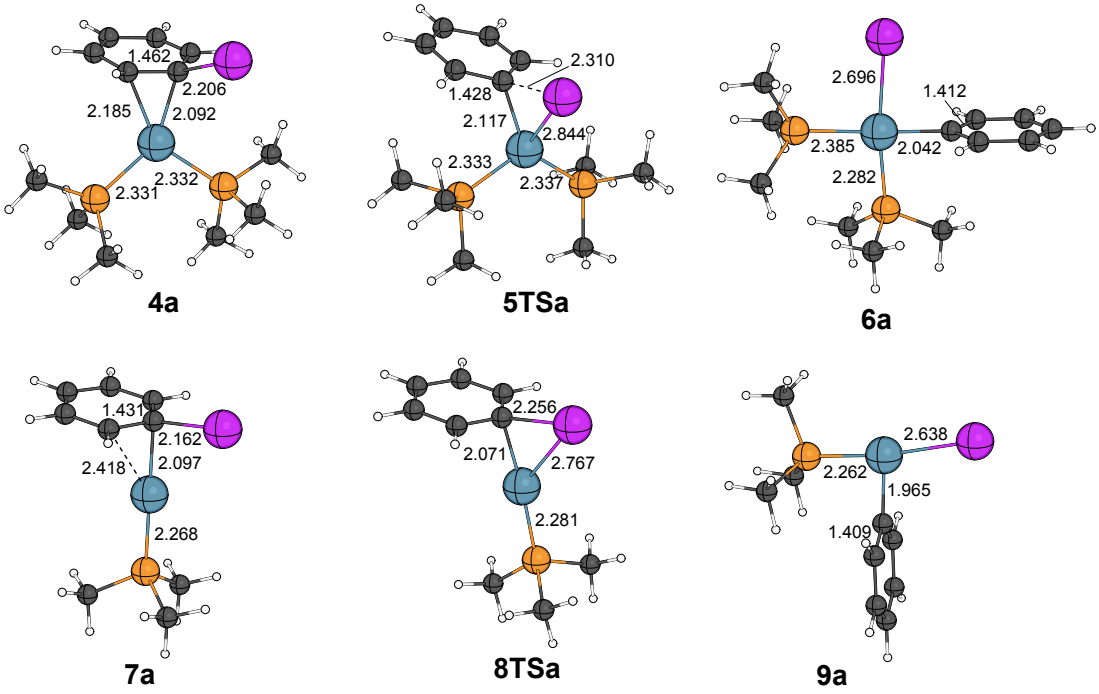


Figure 2: Computed structures of the intermediates and transition states associated with the oxidative addition step. Bond distances are given in Å.

The dissociative pathway starts with the dissociation of one PMe_3 with a bond dissociation free energy of 31.2 kcal/mol (*vide supra*) giving rise to the monoligated complex $Pd(PMe_3)$ (**2**). The coordination of iodobenzene (**3a**) is notably more exergonic (-17.8 kcal/mol) in comparison to that to the more saturated complex (**1**). The coordination type is, however, more like η^1–C, than η^2–(C,C) according to the significant difference in bond lengths between palladium and the coordinating carbon atoms. The oxidative addition

step then proceeds via transition state **8TSa** with a barrier of 0.8 kcal. The formation of the T-shaped Pd(II) complex **9a** is endergonic by 27.3 kcal/mol. The closing step of the dissociative oxidative addition pathway is the coordination of PMe_3 to the vacant site on Pd resulting in **6a**. The free energy associated to this process is -13.1 kcal/mol, meaning that trimethylphosphine is much less weakly bound in **6a**, than in **1**.

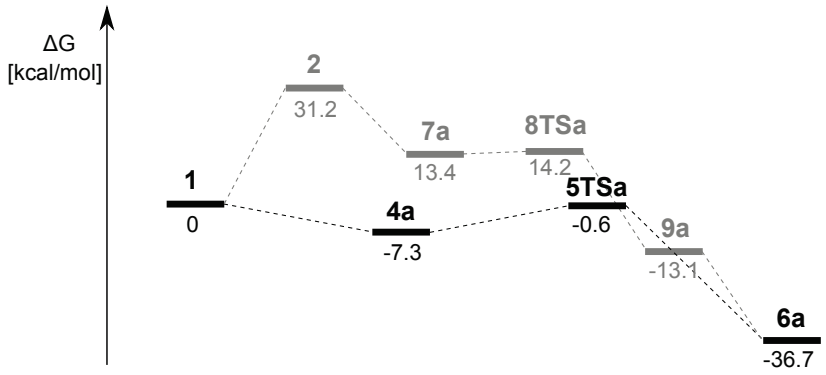


Figure 3: Gibbs free energy diagram of the oxidative addition for the concerted (black) and the dissociative (grey) pathways.

The concerted and the dissociative pathways are compared in Figure 3. A clear preference for the former one is predicted at the BP86-D3 level of theory with virtually no barrier due to the relatively high stability of the transition state **5TSa**.

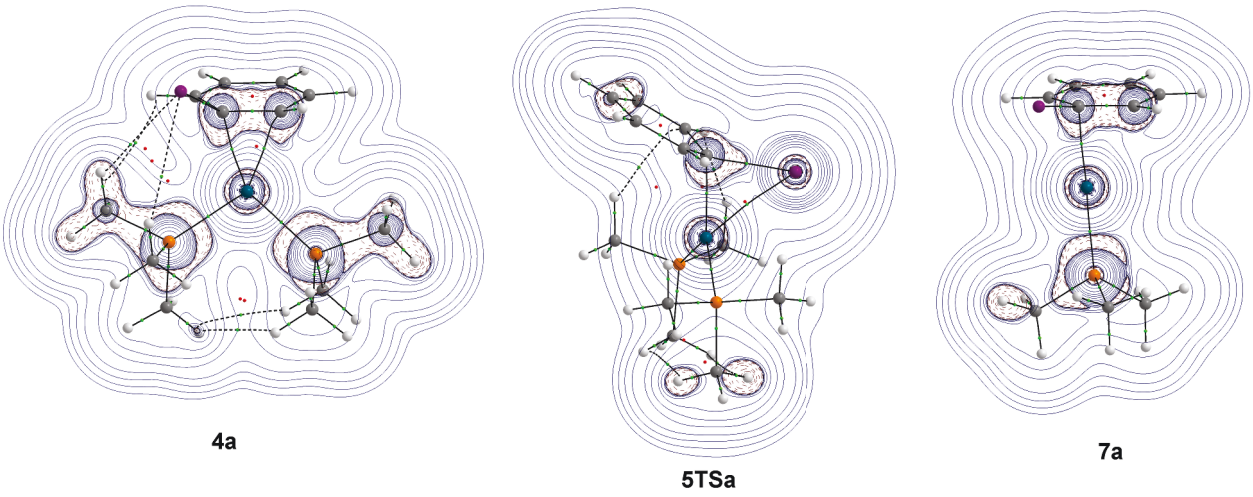


Figure 4: Laplacian ($\nabla^2\rho(\mathbf{r})$) of the electron density of iodobenzene adducts **4a** and **7a** as well as that of transition state **5TSa**. The charge concentration regions ($\nabla^2\rho(\mathbf{r}) < 0$) are designated with dashed lines.

In order to get more insight about the electronic structure of iodobenzene adducts and the oxidative addition transition state, QTAIM calculations [36] have been performed and the Laplacians of the electron

Table 1: Computed activation free energies and reaction free energies (in kcal/mol) for the oxidative addition of 4-substituted iodobenzenes following the bisphosphine pathway.

Substituent	σ_p	Pathway	ΔG_1	$\Delta G^{\ddagger}$	ΔG_2
NMe_2	-0.83	**1**+**3b** →**4b** →**5TSb** →**6b**	-0.1	1.6	-31.7
OMe	-0.37	**1**+**3c** →**4c** →**5TSc** →**6c**	-2.7	-0.7	-32.9
Me	-0.17	**1**+**3d** →**4d** →**5TSd** →**6d**	-4.0	1.0	-35.5
H	0	**1**+**3a** →**4a** →**5TSa** →**6a**	-7.3	-0.6	-36.7
Cl	0.23	**1**+**3e** →**4e** →**5TSe** →**6e**	-6.0	-0.1	-37.7
CF_3	0.54	**1**+**3f** →**4f** →**5TSf** →**6f**	-8.3	-1.7	-38.1
CN	0.66	**1**+**3g** →**4g** →**5TSg** →**6g**	-11.7	-3.8	-39.5
NO_2	0.78	**1**+**3h** →**4h** →**5TSh** →**6h**	-11.4	-5.2	-39.9

densities are depicted in Figure 4. The visual inspection of the Laplacian distribution of **4a** shows a close resemblance to that of olefin complexes, for instance in $W(CO)_5(C_2H_4)$ [37], where the distortion in electron density distribution also emphasizes the presence of a donor interaction. The existence of bond paths between Pd and two carbons in iodobenzene suggests that the coordination mode is indeed η^2-(C,C). On the other hand, the corresponding carbon atoms in **7a** not only show difference in the distance to Pd, but also in the lack of the second Pd–C bond path, and much less distortion in the density distribution of the second carbon. Hence, the coordination mode in the more unsaturated Pd-iodobenzene complex is undoubtedly of η^1-C type.

The Laplacian distribution of transition state **5TSa** reveals the presence of a three-center Pd–C–I bond with bond paths between these three atoms. The electron density distribution around the carbon atom shows significant distortion towards the iodine, which may be responsible for the high relative stability of **5TSa** in terms of free energy.

The substituent effect for the oxidative addition of 4-substituted iodobenzenes was investigated with some representative functional groups spanning the range of Hammett *para* constants between -0.83 and 0.78. The free energies of the iodobenzene coordination, the oxidative additon, as well as the activation free energies were collected in Table 1 for the bisphosphine pathways and in Table 2 for the monophosphine pathways.

In terms of the bond free energy between the iodobenzenes and the palladium containing fragment the substituents show a quite strong dependence on σ_p. For the electron donor groups, such as OMe, and Me the coordination strength is rather weak. Moreover, the iodobenzene coordination and dissociation is almost in equilibrium in the case of the NMe_2 substituent. On the other hand, for the strongly electron withdrawing groups CN and NO_2 the free energy of coordination exceeds -10 kcal/mol.

Interestingly, the free energy difference between the adducts (**4**), and the transition states (**5TS**) shows notable difference only for the most electron donating substituents. For NMe_2, and OMe, this difference is only 1.7, and 2.0 kcal/mol, respectively. On the other hand, it is 5.0 kcal/mol for the methyl group; 6.2 kcal/mol for the nitro group, and difference in free energies fall in this range for all the other substituents. It is important to emphasize, however, that the oxidative addition is very facile in the case of the bisphosphine pathway, regardless of the substituents on iodobenzene, and can be considered as barrierless. This is in contrast with the experimental [13] and theoretical [20] findings with basic, but bulky phosphines, where the free energy barrier for the oxidative addition of PhI was found as 24.6 and 28.4 kcal/mol, respectively, emphasizing the key role of the ligand bulk upon the reaction mechanism.

The reaction free energies for the oxidative addition, following the bisphosphine pathway, however, reveal strong dependence on the Hammett *para* constants. A reasonable linear correlation $r^2 = 0.954$ has been obtained between ΔG and σ_p. The correlation diagram is depicted in Figure 5.

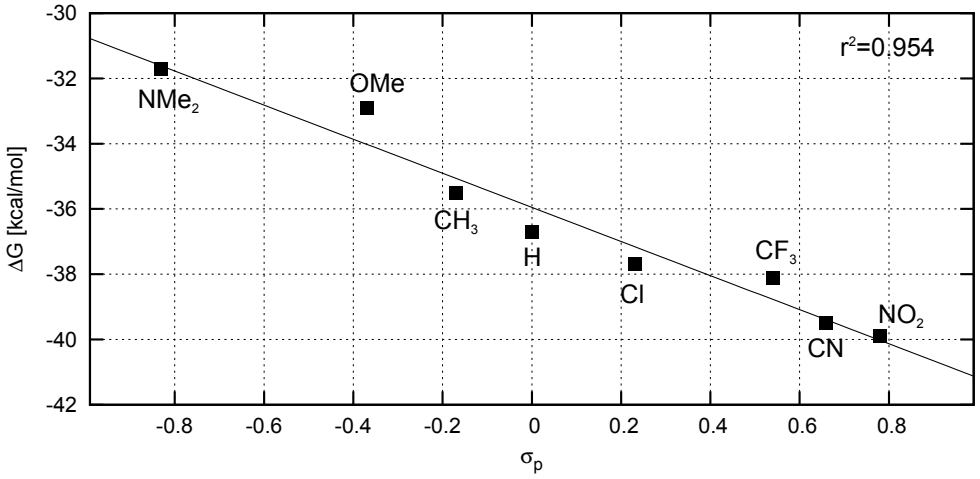


Figure 5: Relationship between the Hammett σ_p constants and the reaction free energy of the oxidative addition of 4-substituted iodobenzenes. Correlation equation: ΔG = -5.224 ($\pm$0.464) $\cdot$ σ_p – 35.952 ($\pm$0.246)

The free energy of coordination of iodobenzenes to the highly unsaturated complex **2** show a peculiar dependence upon the substituent constant (see Table 2). For the electron donating groups, NMe_2, OMe, and CH_3, more stable η^1–C complexes are formed with free energies of only 3.5 – 5.8 kcal/mol above that of the sum of **2** and **3**. Neutral, and electron withdrawing substituents, however, fall into another category with relative free energies over 10 kcal/mol with respect to **2** + **3**. Interestingly, the relative stability of transition states **8TS** show an opposite trend revealing the highest barrier (15.8 kcal/mol) for the methoxy group, and the lowest barrier (11.7 kcal/mol) for the cyano group. On the other hand, the relative free energies of the three-coordinate complexes **9** show no obvious dependence on σ_p. For all substituents the barriers

Table 2: Computed activation free energies and reaction free energies (in kcal/mol) for the oxidative addition of 4-substituted iodobenzenes following the dissociated pathway. The opening step, i.e., the dissociation of one trimethylphosphine needs a free energy of 31.2 kcal/mol. Free energy values are relative to the sum of those of $Pd(PMe_3)_2$ and the corresponding iodobenzenes.

Substituent	σ_p	Pathway	ΔG_1	$\Delta G^{\ddagger}$	ΔG_2
NMe_2	-0.83	(**1** – PMe_3 →) **2**+**3b** →**7b** →**8TSb** →**9b**	3.5	14.6	-10.9
OMe	-0.37	(**1** – PMe_3 →) **2**+**3c** →**7c** →**8TSc** →**9c**	3.0	15.8	-11.3
Me	-0.17	(**1** – PMe_3 →) **2**+**3d** →**7d** →**8TSd** →**9d**	5.8	15.5	-11.2
H	0	(**1** – PMe_3 →) **2**+**3a** →**7a** →**8TSa** →**6a**	13.4	14.2	-13.1
Cl	0.23	(**1** – PMe_3 →) **2**+**3e** →**7e** →**8TSe** →**9e**	11.8	13.0	-12.0
CF_3	0.54	(**1** – PMe_3 →) **2**+**3f** →**7f** →**8TSf** →**9f**	11.9	12.6	-10.5
CN	0.66	(**1** – PMe_3 →) **2**+**3g** →**7g** →**8TSg** →**9g**	11.0	11.7	-13.0
NO_2	0.78	(**1** – PMe_3 →) **2**+**3h** →**7h** →**8TSh** →**9h**	10.6	12.2	-13.6

exceeds those obtained for the bisphosphine pathway, thus the monophosphine route (i.e., the dissociative mechanism) is disfavored in all cases.

4. Conclusion

A DFT study employing the BP86-D3 theory was carried out utilizing the SMD solvation model with THF as solvent in order to shed some light on the mechanism of the oxidative addition of 4-substituted iodobenzenes on Pd(0)-PMe_3 complexes. The bisphosphine pathway, starting from complex $Pd(PMe_3)_2$ (**1**) is compared with the monophosphine route, where the addition of iodobenzenes is preceded by the dissociation of the PMe_3 ligand resulting in complex **2**, as catalyst.

It can be concluded, that this elementary step, with PMe_3, as ligand, is expected to take place in a very fast reaction. The bisphosphine pathway is predicted to be the viable route regardless of the *para* substituents for two reasons: (i) the very facile addition of **3a-h** to **1**, and (ii) the high dissociation free energy of the PMe_3 ligand, which results in an overall barrier of 31.2 kcal/mol for the monophosphine pathways. The reaction free energy of the oxidative addition shows linear correlation with the Hammett constant of the *para* substituent, with the most electron withdrawing groups being the most exergonic.

These results suggest, that in accord with previous findings, palladium complexes with basic and sterically not demanding phosphines may serve as highly active catalyst for cross-coupling reactions where oxidative addition is rate-determining. The strong preference for the bisphosphine pathway, however, emphasizes that the phosphine should be employed at least in a 2:1 ratio with respect to palladium, when the catalyst is formed 'in situ'.

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