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Suzuki-Miyaura Coupling Revisited: An Integrated Computational Study

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New density functional theory (DFT) computations are reported concerning the mechanism of the Suzuki-Miyaura cross-coupling reaction of aryl halides and aryl boronic acids catalyzed by palladium phosphine complexes. The calculations are aimed at refining the understanding of the overall catalytic mechanism by using state of the art theoretical approaches (including for the first time an attempt to describe the Gibbs energy of the reactant base in a realistic way). New experimental results (Thomas and Denmark, *Science*, 2016, **352**, 329-332) concerning pre-transmetallation intermediates with a Pd—O—B linkage provide an invaluable benchmark to test the accuracy of the calculations. The calculations show that bottlenecks to catalysis associated with oxidative addition, X-to-O substitution at Pd, and transmetallation can lie close in energy.

1. Introduction

Computational techniques based on quantum mechanical description of electronic structure have evolved to become one of the primary sources of information concerning reaction mechanisms in organometallic chemistry. From the point of view of the computational chemist, this is both a welcome recognition of the power of these techniques, and a daunting challenge given the many links in the logical chain that connects *in silico* models and experimental reality. Much of the focus in computational studies has traditionally been placed on obtaining qualitative insights into structure and bonding in different intermediates and transition states. However, in recent years, there has been a progressive shift towards attempting to obtain more quantitative predictions concerning the rates of individual steps or of overall transformations. In the context of cross-coupling catalysis, we have previously shown that it is possible to predict computationally which of the several related mechanisms for oxidative addition should be favoured for given aryl halide substrates and phosphine ligands.¹ For the – computationally relatively tractable – case of cobalt-catalyzed hydroformylation, we have even been able to predict the rate of catalytic turnover with almost quantitative accuracy.² To do this, we have predicted Gibbs energies for all relevant intermediates and TSs, and then predicted the kinetic behaviour of the resulting network of reaction steps. In this paper, we wish to start to carry out a similar process for a much more challenging reaction, namely, one of the most important cases of homogeneous organometallic catalysis, Suzuki-Miyaura coupling of aryl halides and boronic acids.

The Suzuki-Miyaura coupling of boronic acids with aryl and vinyl halides³⁻⁸ is one of the most commonly-used palladium-catalyzed organic transformations, and accordingly its reaction

mechanism has received extensive attention. Early on in the experimental development of this reaction, it was suggested that the key steps involved were precatalyst activation (to form a Pd(0) species), oxidative addition of the aryl halide to form an aryl-Pd(II) species, transmetallation with the boronic acid species RBX_2 to form an aryl—Pd—R species, and reductive elimination. While there is evidence that in some cases, different chemistry involving dimeric palladium species or other oxidation states such as Pd(I) and Pd(IV) may be involved,⁹ it has since become the consensus that this is indeed the general mechanism for the reaction, and that will also be the focus in this study.

Each of the key steps has been the focus of many experimental^{10,11,12} and computational^{13,14,15,16,17} mechanistic studies, which have in turn often led to guidelines for improved reactivity. Briefly, oxidative addition is known to be favoured with aryl iodides and bromides vs. chlorides,¹⁸ with other substrates such as esters also being possible in some cases. Also, lower coordination of the palladium centre by ligands is favourable,¹ as is high electron density at the Pd centre, leading to the development of bulky electron-donating ligands.¹⁹ Most experimental conditions use phosphine ligands, but N-heterocyclic carbenes²⁰ have also been successfully used in some cases.²¹ Careful experimental kinetic studies have played an important role in uncovering these aspects, and there have also been many computational studies. Reductive elimination has also been extensively explored, both experimentally^{22,23} and computationally.^{24,25}

It appears that the transmetallation step can be overall turnover-limiting for some variants of the Suzuki-Miyaura coupling,²⁶ and accordingly there have been large numbers of studies addressing this step.^{27,28} These studies have addressed among other topics the dependence of reactivity on the nature of the boronic acid species, for example, investigating the differences in mechanism arising when using boronic acids

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RB(OH)_2 as substrates compared to using the related trifluoroborate salts $\text{RBF}_3 \cdot \text{M}$ ($\text{M} = \text{K}, \text{Na}$).²⁹

There has been a lot of debate in the literature concerning the precise mechanism by which transmetalation from species **1** occurs, with two widely discussed possibilities being direct substitution by boronate **2**, which is the ‘hydroxyboronate substitution’ route which we will also refer to as “Path α ”, and the indirect ‘hydroxide substitution then boronic acid addition’ route through hydroxide **3** followed by addition of boronic acid **4** or “Path β ” (Scheme 1).^{30,31,32}

Scheme 1: Classical transmetalation pathways

Somewhat surprisingly given their centrality in suggested Suzuki-Miyaura coupling mechanisms, until recently, no pre-transmetalation complexes containing a Pd-O-B connected motif, such as species **5** in Scheme 1, had been isolated experimentally. This state of affairs changed following the careful work by Denmark and co-authors, who were able to characterize a number of such species using low-temperature NMR approaches.^{33,34} This led to a better understanding of the manifold of reactions that can occur during transmetalation, and in particular showed that Scheme 1 underestimates the complexity of the network of reactions that may be involved. Also, Scheme 1 perhaps places too much emphasis on the nature of the nucleophilic substitution step and not enough on the actual transmetalation step.^{33,34}

As well as experimental and computational studies of individual steps in the catalysis, there have been a number of notable attempts to characterize the whole process, and here we especially wish to highlight the through computational study by Kozuch and Martin which attempted to derive general rules for designing a successful catalytic cycle based on the computational insight.³⁵

In this study, we revisit the question of the overall mechanism of Suzuki coupling of boronic acids with aryl bromides catalysed by PdL_n species ($\text{L} = \text{P-}i\text{Pr}_3, \text{PPh}_3$). Compared to our previous work on oxidative addition to Pd(0) ,¹ this study will require that we consider many more possible intermediates and reaction steps. Compared to our previous work on hydroformylation,² we will need to deal with the complexity of a reaction taking place in multiple phases and involving many charged species (ions or ion pairs). We have found recently³⁶ that obtaining accurate calculated Gibbs energies for such polar species remains very challenging, with maximum errors on Gibbs energies remaining of the order of 5 kcal mol⁻¹ even when using highly accurate quantum-chemical methods. Nevertheless, the new experimental data relating to new pre-transmetalation intermediates and the kinetics of their conversion to products

provides a new opportunity to test the accuracy of computational work in the field, and motivates this study.

2. Computational details

All calculations were performed using DFT, with the Gaussian 16 program package.³⁷ All intermediate and transition state geometries were optimized with the B3LYP functional as implemented in Gaussian, together with Grimme's D3-BJ³⁸ dispersion correction and the SMD continuum solvation model³⁹ with parameters appropriate for THF as the solvent. For several species, we found that explicit representation of a THF molecule leads to a lower Gibbs energy than when using only the continuum model of THF. This typically occurs when a metal-coordinated oxygen atom bears a hydrogen atom, which can donate a hydrogen bond to THF. At 293.15 K, this leads to a significantly lower free energy for one species (15 in Fig. 1), and accordingly the Gibbs energy shown below refers to that explicitly solvated structure. For Br, Pd, and I atoms, effective core potentials from the Stuttgart group, and associated triple zeta basis sets were used (with the 'SDD' keyword in Gaussian) as implemented in Gaussian; whereas for all other atoms the 6-31g(d) basis set, also as implemented in Gaussian, was used. Frequency calculations were carried out at the optimized structures at the same level of theory. All transition states were identified by having one negative eigenvalue in the Hessian matrix. Based on the masses, rotational constants and vibrational frequencies obtained in this way for each species, Gibbs energy corrections were calculated using the quasi-harmonic approximation⁴⁰ whereby vibrational frequencies with a magnitude smaller than 100 cm⁻¹ were set to 100 cm⁻¹ for the statistical mechanical treatment. For the translational partition function, a volume corresponding to a standard state concentration of 1 mol dm⁻³ was used for all species, except for gas phase species (1 bar standard state) and THF solvent (12.3 mol dm⁻³). Single point energies at the optimized structures were calculated, also with the B3LYP functional, the D3-BJ dispersion correction and the SMD continuum model for THF, but using a larger basis set. This used for Br, Pd, and I atoms the Ahlrichs Def2TZVPP basis set (which includes an ECP for core electrons for Pd and I), whereas the other atoms were treated with the Ahlrichs Def2TZVP basis set as implemented in Gaussian.

To identify the preferred conformation for all species, a number of different starting structures were used, and the reported results correspond to the structure with the lowest Gibbs energy at the level just described (in some cases structures of alternative conformations are included in the supporting information). This issue is particularly important in the case of species containing the $\text{P-}i\text{Pr}_3$ ligand, which has complicated conformational behaviour, and considerable care has been taken to identify favoured conformers.

3. Results and discussions

One of the major challenges associated with carrying out modelling relating to the mechanism of Suzuki-Miyaura coupling is the sheer diversity of reactions and reaction conditions that fall under this name. As mentioned in the Introduction, we restrict ourselves here to coupling with palladium, to reactions taking place in tetrahydrofuran (THF) solvent, to tris(isopropyl) phosphine ($P\text{-}i\text{Pr}_3$) or triphenyl phosphine (PPh_3) as the ligands, to p -fluorophenyl boronic acid as the nucleophile, to p -fluorophenyl iodide or bromide as the electrophile, and to solid $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$ as the base. For the Gibbs energy calculations, we also need to assign the temperature, and many different values could in principle be chosen with reference to different experiments. For simplicity, we have picked $T = 293 \text{ K}$ (20°C) as the standard temperature for thermodynamic analysis for all species. As many of the target experiments were performed at lower temperature, we also computed thermal corrections at -30°C (243 K) and these values are included in the SI. Reaction with anhydrous Na_2CO_3 in anhydrous THF is not usually possible, and our calculations allow for the presence of a small amount ($1 \text{ M} = 1 \text{ mol dm}^{-3}$) of water in the THF. By and large all these choices reflect common practice when carrying out Suzuki-Miyaura coupling, as well as the conditions used in the new mechanistic work from the Denmark group mentioned in the Introduction.^{33,34}

Quantitative work in mechanistic chemistry requires attention to many aspects concerning the level of electronic structure theory, the treatment of solvation, the calculation of entropic contributions, the exploration of the different conformers for each species in the reaction mechanism, and so on.⁴¹ In this study, we have opted for a relatively straightforward methodology, based on the B3LYP DFT functional, flexible basis sets for optimization and single-point energy evaluation, a continuum model of solvent,⁴² and full inclusion of entropic effects. Based on our previous experience,³⁶ though, it should be remembered that this type of approach can lead to errors in predicted relative Gibbs energies of 5 kcal mol^{-1} or more.

Within this chosen modelling framework, we have considered a number of different mechanistic steps, and now describe our results for these in the following sections. Note that we have not reported any new calculations on the oxidative addition of the electrophile to $\text{Pd}(0)$, as this has already been extensively studied by us¹ and others.⁹⁻¹²

3.1 Speciation of boronic acid

Boronic acid derivatives have been the most commonly used nucleophilic partners in Suzuki-Miyaura coupling,⁴³ and choice of them in addition to the choice of base can play an important role. There are some recent examples of the usage of stable metal tri-hydroxy-boronate complexes⁴⁴ directly without the use of a base.³² We start by taking a closer look at the energetics of the reaction of a neutral boronic acid molecule $\text{ArB}(\text{OH})_2$ reacting with different bases to produce its $\text{ArB}(\text{OH})_3^-$ derivative, with different modelling assumptions (Table 1).

The most common approach in the computational literature has been to model the base directly as an OH^- anion, or an OH^- anion in coordination with water.³² Using the simplest

approach, the reaction $p\text{-FC}_6\text{H}_4\text{B}(\text{OH})_2 + \text{OH}^- \rightarrow p\text{-FC}_6\text{H}_4\text{B}(\text{OH})_3^-$ is calculated to be very favourable in Gibbs energy, which would suggest that under basic conditions typical for Suzuki-Miyaura coupling, boronic acids would always be present as their boronate conjugate bases. However, continuum models underestimate the solvation Gibbs energies of small, high charge-to-radius ratio anions such as hydroxide, and this is particularly true in the case of THF/water mixtures that are commonly used in such reactions. Using our default H_2O concentration of 1 M , we calculate that species $\text{OH}^-(\text{H}_2\text{O})_n$ ($n = 1 - 3$) are lower in Gibbs energy than separate OH^- and $n \text{ H}_2\text{O}$, with the lowest Gibbs energy being returned for $n = 3$. Likewise, the bare boronate $p\text{-FC}_6\text{H}_4\text{B}(\text{OH})_3^-$ is stabilized by hydrogen bonding to three water molecules. This leads to a modified estimate for the relative Gibbs energy of the boronate taking into account the solvation by water molecules, which is less favourable. Our relative Gibbs energy in Table 1 is similar to that reported by Ortuno et al.³²

Table 1: Computed relative Gibbs energies ($/ \text{ kcal mol}^{-1}$) for formation of boronate anion $p\text{-FC}_6\text{H}_4\text{B}(\text{OH})_3^-$ at 293 K in THF (with $1 \text{ M H}_2\text{O}$). Ar denotes $p\text{-FC}_6\text{H}_4-$. The detail of the reaction modelled is shown in each case. Unless otherwise specified, each species is treated in THF continuum solvent.

Base	Boronate Reaction modelled	ΔG°
OH^-	$\text{ArB}(\text{OH})_3^-$ $\text{OH}^- + \text{ArB}(\text{OH})_2 \rightarrow \text{ArB}(\text{OH})_3^-$	-36.2
$\text{OH}^-(\text{H}_2\text{O})_3$	$\text{ArB}(\text{OH})_3^-(\text{H}_2\text{O})_3$ $\text{OH}^-(\text{H}_2\text{O})_3 + \text{ArB}(\text{OH})_2 \rightarrow \text{ArB}(\text{OH})_3^-(\text{H}_2\text{O})_3$	-14.3
$\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}_{(\text{s})}$	$\text{ArB}(\text{OH})_3^- \text{Na}^+(\text{THF})_2$ $\text{ArB}(\text{OH})_2 + \text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}_{(\text{s})} + 2 \text{ THF} \rightarrow \text{NaHCO}_{3(\text{s})} + \text{ArB}(\text{OH})_3^- \text{Na}^+(\text{THF})_2$	+18.5

However, using solution phase hydroxide in any form may not be appropriate, and could lead to an exaggeration in the predicted basicity of the reaction conditions. In many cases the base employed in the Suzuki-Miyaura coupling is a weak base, often solid sodium or potassium carbonate, or these bases dissolved in a separate aqueous phase.^{43,45} Accordingly, we have instead used an approach whereby the base is modelled as solid $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$. This raises the question as to how such a base can be included in a computational thermodynamic scheme based on molecular quantum chemical computations. The approach used here is one that we have used previously on several occasions for other solid reactants or by-products (originally for solid ZnO in ref. 46). Experimental data is obtained for the Gibbs energy of the target solid and of appropriate gas-phase species containing the same elements. This is then combined with computed Gibbs energies for the gas-phase species, and for the desired solution-phase species, which allows a thermodynamic cycle to be closed, and inclusion of the solid species in the calculated Gibbs energy profile.

In the present case, we wish to calculate the Gibbs energy change for formation of the boronate anion, starting from solid $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}_{(\text{s})}$, using the reaction shown. For this purpose, we take the experimental^{47,48} Gibbs energy change for the reaction $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}_{(\text{s})} \rightarrow 2 \text{ Na}_{(\text{g})} + \text{CO}_{2(\text{g})} + 1/2 \text{ O}_{2(\text{g})} + \text{H}_2\text{O}_{(\text{g})}$ ($+197.2 \text{ kcal mol}^{-1}$), and the corresponding value for NaHCO_3 ($\text{NaHCO}_{3(\text{s})} \rightarrow$

$\text{Na}_{(\text{g})} + \text{CO}_{2(\text{g})} + 1/2 \text{O}_{2(\text{g})} + 1/2 \text{H}_{2(\text{g})}$, which is $+128.4 \text{ kcal mol}^{-1}$). Together with DFT-computed values for the gas-phase Gibbs energies of Na, H_2O , O_2 , H_2 , and CO_2 , this allows us to assign quantum-chemical ‘Gibbs energies’ to the solids $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$ and NaHCO_3 , and thereby to obtain the relative Gibbs energy for the conversion described above, as shown in Table 1. This procedure amounts to combining experimental Gibbs energies for the solid bases and a DFT-derived Gibbs energy change for the reaction $\text{ArB}(\text{OH})_2(\text{THF}) + 1/2 \text{O}_{2(\text{g})} + 1/2 \text{H}_{2(\text{g})} + \text{Na}_{(\text{g})} + 2 \text{THF}_{(\text{THF})} \rightarrow \text{ArB}(\text{OH})_3 \cdot \text{Na}^+(\text{THF})_2(\text{THF})$. Note that this reaction is far from being isodesmic, and involves quite large changes in electronic structure, so the procedure used here is subject to errors arising from the DFT treatment of the gaseous species such as the sodium atom. This error is mitigated by the good performance of B3LYP for atomization energies and the use of a large basis for the single-point energies. Nevertheless, this procedure likely leads to additional errors for this reason. A refined procedure could be put in place where additional high-level quantum chemical computations are performed (e.g. CCSD(T) with large basis sets and/or explicit correlation treatment) for the gas-phase species).

The value of this procedure is that it provides a complementary assessment of the relative Gibbs energy of the boronate, which is now significantly *higher* than that of the boronic acid, counter to the estimate where solution phase hydroxide was used as a reference point. This suggests that the equilibrium between boronic acid and boronate could be highly dependent on reaction conditions. It has been shown that boronate and boronic acid are present in roughly equal amounts in presence of potassium carbonate,^{29,30} but these observations relate to dissolved carbonate in roughly 1:1 THF:water and acetone:water mixtures, respectively. The present calculations suggest that in THF solvent with low water concentration, assuming carbonate is not dissolved, the equilibrium should instead be highly on the side of the boronic acid. Given the above caveats about the accuracy of the procedure, the value shown in Table 1 must be understood to be associated with some error, but the trend whereby boronate formation is much less favourable than when modelled with reference to solution-phase hydroxide should be correct.

3.2 X to O substitution

A lot of previous work on the transmetallation step in Suzuki-Miyaura coupling has focussed on this reaction step, namely the replacement of a halide group at palladium by an oxygen-containing nucleophile. As mentioned above, there has been a lot of debate concerning the mechanism of this step.^{29–31} Computationally, the state of affairs seems to be that path 1 in Scheme 1 is predicted to be preferred. In perhaps the most thorough computational study,²⁴ the Gibbs energy barrier for substitution of bromide in $\text{PhPd}(\text{PPh}_3)_2\text{Br}$ by $\text{PhB}(\text{OH})_3^-$ was calculated to be $18.9 \text{ kcal mol}^{-1}$ in a model where the boronate anion was solvated by three explicit water molecules as well as by a continuum model. The Gibbs energy barrier for substitution by hydroxide anion (also treated as being solvated by three water molecules) was lower, at $16.9 \text{ kcal mol}^{-1}$ (and the barrier for substitution by ‘naked’ hydroxide, surrounded only by

continuum model of solvent, was *much* lower, at $8.3 \text{ kcal mol}^{-1}$). However, hydroxide anion was computed – as here in section 3.1 – to bind strongly to boronic acid, and when taking this into account, overall, the ‘direct’ route had a lower Gibbs energy barrier in the computations.²⁴ Our own test calculations show that TS structures and relative energies are very similar with $\text{L} = \text{P}(\text{iPr})_3$ and with $\text{L} = \text{PPh}_3$, and accordingly, we have not explored this issue again in detail, instead relying on the results from ref. 24.

On the other hand, experimental studies have argued that the indirect route for substitution is preferred. Carrow and Hartwig measured the rate for reaction of $\text{PhPd}(\text{PPh}_3)_2\text{Br}$ with *p*-tolylB(OH)₃[−]K⁺ in 50:1 THF:water mixture in presence of 18-crown-6 at several temperatures including -30°C and room temperature (25°C), and found slow conversion at -30°C (10% after 11 h). Analysis of their observed rate constant at room temperature (see SI) yields an estimated Gibbs energy barrier of about $16.1 \text{ kcal mol}^{-1}$, fairly close to the calculated value of $18.9 \text{ kcal mol}^{-1}$ mentioned above. The same authors find that PhPdL_2OH ($\approx 10^{-3} \text{ M}$) and PhPdL_2Br ($\text{L} = \text{PPh}_3, \text{PCy}_3$) interconvert rapidly to reach roughly equimolar concentrations at room temperature in THF:water (50:1 or 25:1) in presence of tetrabutylammonium bromide ($\approx 10^{-3} \text{ M}$; rapid equilibrium is also observed for chloride and iodide species). Specifically, they find that equilibrium is reached during the time needed to carry out ³¹P NMR spectroscopy, i.e. in less than 5 minutes, implying that the reaction of tetrabutylammonium hydroxide with PhPdL_2Br is rapid also. The observed timescale translates into a half-life for reaction of less than roughly 30 seconds, which analysis shows (see SI) corresponds to an upper bound to the Gibbs energy barrier of $12.5 \text{ kcal mol}^{-1}$. This value is somewhere in between the computational estimates of 8.3 and $16.9 \text{ kcal mol}^{-1}$ deriving from models with no microscopic hydration of the hydroxide anion and with three-fold hydration, respectively.³² Given that the experiments are performed in 25:1 THF:water, and that the *n*-butylammonium counterion, neglected in the computations, may play some role, again, this agreement is reasonable. In any case, it is clear that experimentally, a lower Gibbs energy barrier has been found for substitution by hydroxide than by trihydroxyboronate.

It should be pointed out, though, that this does *not* contradict the results from computation. As mentioned above, the computations only predict that the ‘direct’ route is overall favoured once one takes into account the fact that hydroxide binds very strongly to boronic acid.²⁴ This factor is not accounted for in the above experimental comparison of rates.³⁰ Even the computational study²⁴ acknowledges that intrinsically, the ‘indirect’ route is somewhat more favourable, and thereby might be expected to compete under some conditions.

Other experiments³¹ consider turnover for reaction of $\text{ArPd}(\text{PPh}_3)_2\text{X}$ (for $\text{X} = \text{Cl}, \text{Br}$ and I and $\text{Ar} = p$ -substituted phenyl) with $\text{Ar'B}(\text{OH})_2$ (Ar' is Ph or another substituted phenyl group) in the presence of tetrabutylammonium hydroxide, in DMF solution at 25°C . The authors observe conversion to product with a complicated type of dependence on the concentration of hydroxide and boronic acid – increased hydroxide initially leads to faster conversion, but higher concentrations then lead to

slower conversion again. For $X = \text{Br}$ and $\text{PhB}(\text{OH})_2$, the rate peaks for $[\text{OH}]_0 \approx 0.7 [\text{PhB}(\text{OH})_2]_0$. The same authors report³¹ that $\text{PhB}(\text{OH})_3^-$ is completely unreactive towards $(p\text{-CN-Ph})\text{Pd}(\text{PPh}_3)_2\text{Br}$ and thereby rule out the 'direct' mechanism completely. Despite the use of a different solvent, this observation seems hard to reconcile with the observation by Carrow and Hartwig of a rate of reaction of $\text{PhPd}(\text{PPh}_3)_2\text{Br}$ with $p\text{-tolylB}(\text{OH})_3\text{K}^+$ in 50:1 THF:water, that is low at -30°C but quite high at room temperature. The authors also reported³¹ a detailed kinetic analysis of their results, concluding that the indirect route occurs, and that the peculiar inversion of the reactivity trend with increasing hydroxide amounts is due to competition between OH^- substitution of X and trapping of $\text{PhB}(\text{OH})_2$ as unreactive boronate.

As already said, these authors rule out occurrence of the direct route, based on their observed unreactivity of $\text{PhB}(\text{OH})_3^-$ with $(p\text{-CN-Ph})\text{Pd}(\text{PPh}_3)_2\text{Br}$. Given the good agreement between the computational Gibbs energy barrier for this key step in the 'direct' route³¹ and the Gibbs energy barrier extracted from the experiments, as discussed above, it seems likely that this step can in fact occur. The reason why it is not observed in the experimental study by Amatore et al.³¹ may relate to peculiarities of the solvent used (DMF vs. THF) or of the electrochemical detection method, or of the way in which the experimental results were analysed.

In summary for this section, both hydroxide and boronate $\text{ArB}(\text{OH})_3^-$ seem to be able to carry out substitution of Pd-bound X with barriers of the order of 15 kcal mol^{-1} . Computation shows that hydroxide – which is expected to be a better nucleophile – reacts over a slightly lower barrier than boronate, though under some conditions will also be present in much smaller amounts. Indeed, based on the results of the previous section, under many typical conditions for Suzuki-Miyaura coupling, the concentration of *both* hydroxide and boronate will be rather low, which means that the reactant species for the paths shown in Scheme 1 will not be present in large amounts. This will also impact on the overall thermodynamics of halide to hydroxide substitution. Using a similar protocol as in section 3.1 for treating solid sodium bromide, carbonate and bicarbonate, the reaction: $\text{ArPdL}_2\text{Br}(\text{THF}) + \text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}_{(\text{s})} \rightarrow \text{ArPdL}_2\text{OH} + \text{NaHCO}_3_{(\text{s})} + \text{NaBr}_{(\text{s})}$ is predicted to be rather unfavourable in Gibbs energy terms, by $+13.7 \text{ kcal mol}^{-1}$. In more base-rich media, with e.g. mixtures of THF and water or acetone and water, with significant solution-phase concentration of carbonate, however, the step may be less unfavourable thermodynamically.

3.3 Pre-transmetallation species

We next turn to the question of the speciation of compounds formed following the X to O substitution, especially those containing a Pd-O-B linkage. In Scheme 2, we have shown two possible products from this substitution, the hydroxide **3** and the boronate **5**. As already shown by Carrow and Hartwig,³⁰ analogues of **3** react rapidly with boronic acid, presumably to form species such as **5**. However, the new experiments from the Denmark group^{33,34} have shown that **5** is not stable under cross-coupling conditions. Instead, under phosphine-rich

conditions (more than two equivalents of ligand per Pd), species **6** is formed when reacting **3** with boronic acid, as a result of spontaneous dehydration of **5**. The same species **6** can be formed by reacting **3** with boroxine **7**. Under phosphine-poor conditions (one L per Pd), the dimer **8** instead yields the cyclic dipalladium complex **9**. Both **6** and **9** could be identified by NMR, and constitute the first well-characterized pretransmetallation intermediates with Pd-O-B linkages.

Our calculations (Table 2) indeed confirm that **5** is somewhat more stable than **3 + 4**, with the dehydrated **6** lying even lower in Gibbs energy (we find **6** to lie $4.6 \text{ kcal mol}^{-1}$ below **5**, similar to the difference of $10.8 \text{ kcal mol}^{-1}$ reported in ref. 34, bearing in mind the significant changes in computational protocol). The calculations also show that the corresponding reaction with **7** is favourable in Gibbs energy terms. Also, even though the corresponding reactions with PPh_3 have not been performed, our calculations show that the calculated Gibbs energies are rather similar with this ligand. It should be noted here that species **3**, **5**, and **6** can exist as *cis* or *trans* isomers, with the values reported here being for the more stable *trans* isomer. Values for the *cis* isomers can be found in the SI or in the literature for some species.³⁵ Full exploration of the mechanism for the water loss goes beyond the scope of this paper, but a preliminary investigation yielded a TS lying $22.4 \text{ kcal mol}^{-1}$ higher in Gibbs energy than **5**. Our TS structure is for a simple intramolecular water loss with an unfavourable 4-membered-ring structure – lower Gibbs energy pathways involving shuttling of proton and/or intermediate proton transfer will certainly exist.

Scheme 2: Synthetic route for pre-transmetallation intermediates **6** and **9**

Table 2: Computed relative Gibbs energies (kcal mol^{-1} , THF, 293 K) for pre-transmetallation species.

Species	$\Delta G^0 \text{ P}(\text{iPr})_3$	$\Delta G^0 \text{ PPh}_3$
3 + 4	0.0	0.0
5	-2.8	-0.7
6 + H₂O	-7.4	-7.3
3 + 1/3 7 + H₂O	0.3	0.2
2 × 3 + 4	0.0	0.0
8 + 4 + 2 × PR₃	12.0	3.8
9 + 2 × PR₃	11.3	3.7

Calculations and optimization were also carried out on species **8** and **9** that are relevant under low-phosphine conditions. Formation of **8** by loss of phosphine from two equivalents of **3** is found to be unfavourable with both $L = P(iPr)_3$ and PPh_3 , although only just in the latter case. Indeed, in the presence of excess $P(iPr)_3$, **8** is known to convert to **3**.³⁴ Likewise, **9** lies higher in Gibbs energy compared to **6**, and indeed addition of excess phosphine is known to convert **9** to **6** (see Scheme 22 in ref. 34). Species **9** is calculated to be nearly equal in Gibbs energy to **8** at 293 K (-0.7 kcal mol⁻¹). The thermodynamic driving force is larger at lower temperatures (see SI), consistent with the fact that NMR characterization of **9** is feasible only at low temperature. A possible route from hydroxide **8** and boronic acid **4** to the six-membered ring species **9** has been explored computationally, see below in Figure 2.

Our calculations hereby confirm the stability of the key observed species **6** and **9**. Indeed, formation of **6** from the hydroxide species **3** is sufficiently favourable in Gibbs energy terms that even using solid $Na_2CO_3 \cdot H_2O$ as a base, this pretransmetallation species, having a Pd–O–B linkage, should be competitive in terms of Gibbs energy with the $ArPdL_2Br$ oxidative addition species **1**. At room temperature, we calculate that **6** lies just 6.3 kcal mol⁻¹ above **1**.

3.4 Transmetallation and reductive elimination

In this section, we discuss our results relating to the transmetallation itself, which is often described as being the most complex and least understood step.⁴⁹ It leads to formation of a diaryl Pd(II) species, which can then undergo reductive elimination. As for the other steps, there have been many previous computational studies.^{50,51} There has recently developed a consensus that transmetallation starts from species with just one phosphine ligand, such as **10** or **11** in Scheme 3, as reactions starting from bisligated species such as **5** or **6** were calculated to be less favourable.¹⁷ The Gibbs energy needed to lose a phosphine from species **5** or **6** is compensated for by a higher intrinsic reactivity. Most previous studies have presented TSs originating from **10**, however, kinetic data presented in the recent work on isolated Pd–O–B pretransmetallation species³⁴ showed an inhibitory role for excess water which was interpreted as favouring **11** as a direct precursor.

Scheme 3: Possible transmetallation initiator species **10** and **11**

For consistency with our present work, which takes better account of dispersion effects, the corresponding TSs have been considered again here (Figure 1). In both cases, the overall process occurs in two main steps: first, the initial species (**10** or **11**) which involves the organoborate coordinating to Pd through two oxygen atoms converts to an O,C-chelating rotamer **12** or

13, after which the B–C bond converts to a Pd–C bond, and a *cis*-diaryl Pd(II) species **14** or **15** is formed through TSs **TS1** or **TS2**.¹⁸ After loss of boric acid, the biaryl palladium species **16** (and its diphosphine variant **17**) is formed, which can then undergo reductive elimination through **TS3** to form biaryl **18** and $L_2Pd(0)$ **19**, which can then reinitiate the cycle.

In our calculations, **TS1** lies considerably lower, by 10.9 kcal mol⁻¹ in Gibbs energy than **TS2**. **TS2** leads to formation of a complex **15** between the bisaryl palladium species and a dehydrated form of boric acid, $HO-B=O$. The latter is a rather unstable species, with formation of the more usual $B(OH)_3$ from $HBO + H_2O$ calculated to be 33.6 kcal mol⁻¹ favourable in Gibbs energy terms at our level of theory. This means that the step through **TS2** is rather endothermic, and **TS2** is a very late or product-like TS, lying just 3.7 kcal/mol higher in Gibbs energy than **15**. These aspects can also be seen in the earlier computational work,³⁴ where it was however argued that HBO can be significantly stabilized by forming a cyclic trimer. This stabilization is however not possible in **TS2**. The high energy of **TS2** appears to rule it out as a possible funnel for the actual transmetallation step, which must therefore instead proceed through **TS1** or a similar route. The importance of **TS2** was suggested based on the observed kinetic effect of added water on the reaction,³⁴ but the present computational results lead us to suggest that this relatively small effect (adding ten equivalents of water to the reaction depresses the rate or transmetallation from **5** by a factor of two) may be due to other aspects of the chemistry of water in THF, which is known to be complicated.⁴⁵

The reductive elimination **TS3** is similar to that reported in previous studies.³⁵ It lies lower in Gibbs energy than **TS1** by 9.0 kcal mol⁻¹ according to our calculations, suggesting that at least for this ligand and aryl groups, the reductive elimination step is unlikely to be kinetically relevant. Finally for this part the final biaryl product **18** is calculated and its Gibbs energy (together with that of the Pd(0) complex $Pd(PiPr_3)_2$ and $B(OH)_3$) lies 47.9 kcal/mol lower than that of **10**, showing that it is the most stable product of this scheme as very much expected.

Figure 1: Calculated Gibbs energy profile (kcal mol⁻¹, 293 K) for the transmetallation routes via **10** and **11**.

When the reaction is initiated from the dimeric Pd hydroxide species **8** containing just one phosphine ligand per Pd centre, in the absence of added ligand, the transmetallation route followed will be different (Figure 2). As already discussed in relation to Scheme 2, **8** can react with **4** to form **9**. The initial step involves formation of complex **20**, which lies lower in potential energy but higher in Gibbs energy than the separated species. Intramolecular substitution through **TS4** yields **9**. The energy of **TS4** obtained here is a bit high considering the observed³⁴ quite fast conversion of **8** to **9** at 173 K; this discrepancy may be resolved if there are lower-energy TSs involving proton shuffling, but we have not explored these here. Adding a further boronic acid **4** yields (after rearrangement) complex **21**, which can then split to form two equivalents of species **10**, which can then react further as just discussed. Formation of **10** in this way is supported by the observation³⁴ that reaction of **8** with a dimethyl boronic ester leads to an isolable dimethylester variant of **10**. The same species can be formed from reaction of **8** with the normal boronic acid, followed by exposure to methanol.

The calculated Gibbs energies for the transmetallation step can be compared to the results from kinetics experiment starting from either species **6** (Figure 1) or species **8** (Figure 3). In the first case, **6** is formed *in situ* upon mixing **3** with boronic acid **4** (see Scheme 2), and the kinetics of decay of **6** to the final Suzuki-Miyaura coupling product were measured at 293 K, under various conditions including addition of water or various amounts of excess P(*i*Pr)₃. The observed rate of product formation is not very dependent on the conditions, but we compare here specifically to the experiment with no added water and with 2.85 equivalents of P(*i*Pr)₃, where product formation occurred with a rate constant of $4.8 \pm 0.65 \times 10^{-3} \text{ s}^{-1}$, equivalent to a Gibbs energy barrier of 20.3 kcal/mol. The overall Gibbs energy of activation relative to species **6** calculated here is 30.8 kcal/mol, with **TS1** being the bottle-neck. The substantial disagreement with experiment could be due to errors in the computational method, though it is also conceivable that an alternative TS to **TS1** might be involved.

Figure 2: Calculated Gibbs energy profile (kcal mol⁻¹ at 293 K) for the transmetallation mechanism with **8** as the starting material

In the experiments where **8** or **9** is the starting point, it was assumed that the path to formation of the biaryl product is

again through monopalladium species **10**. In experiment, formation of the Suzuki-Miyaura coupling product occurs with a rate constant of $8.09 \pm 0.86 \times 10^{-3} \text{ s}^{-1}$ at 263 K, corresponding to an activation Gibbs energy of 17.9 kcal mol⁻¹. Our calculations return an activation Gibbs energy from **9** to **TS1** of 21.0 kcal mol⁻¹.

3.5 Overall reaction scheme and kinetics

In the previous sections, we have attempted to explore the level of agreement between experiment and theory for the various individual steps in Suzuki-Miyaura cross-coupling of aryl halides with aryl boronic acids. One of the most valuable resources here with which to gauge the accuracy of the calculations is the set of recent stoichiometric experiments concerning the formation and reactivity of novel pre-transmetallation species with Pd—O—B linkages. The thermodynamic and kinetic observations relating to these species provide an excellent challenge for computation. As was discussed in the previous sections, the agreement with experiment is in general fair, indicating that the computational methods used here are able to model the target reactions, but that significant progress is needed in order to obtain quantitative insight. In particular we note the following points of disagreement: first, in Figure 1, our predicted Gibbs energy of activation for reaction of **6** differs by 10 kcal mol⁻¹ from experiment. Next, we find that computation strongly supports the occurrence of transmetallation through **TS1** rather than the experimentally³⁴ suggested **TS2**.

In the present section, however, we wish to instead switch to discussing the level of agreement between experiment and theory concerning reactivity data under *catalytic* conditions. We consider first the overall thermodynamics of the overall reaction. In the presence of solid base, this can be modelled as $\text{ArBr} + \text{ArB}(\text{OH})_2 + \text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}_{(\text{s})} \rightarrow \text{Ar}-\text{Ar} + \text{B}(\text{OH})_3 + \text{NaHCO}_{3(\text{s})} + \text{NaBr}_{(\text{s})}$. Under very basic conditions, the product boric acid may be converted to a borate, but this has not been included in the calculations here. Our calculations yield an overall Gibbs energy change for the reaction of -55.6 kcal mol⁻¹, confirming that the transformation as a whole is highly favoured thermodynamically.

Next we consider the Gibbs energy of the different bottlenecks along the reaction path. In previous work,¹ we found that for many ligands including PCy₃ and PPh₃, the Gibbs energy barrier for oxidative addition to Pd(0) species is of the order of 20 – 25 kcal mol⁻¹. The immediate product of oxidative addition is a tris-coordinate species ArPdLBr, which is usually slightly lower in Gibbs energy than the starting Pd(0) species, but can be stabilized by forming dimers with bridging bromide or by adding an extra ligand to form ArPdL₂Br. The relative Gibbs energy of the most stable product of oxidative addition was found¹ in all cases to be of the order of -15 or -20 kcal mol⁻¹ with respect to reactants, suggesting that oxidative addition will not in practical terms be reversible under catalytic conditions.

In the present sections 3.1, 3.2, 3.3 and 3.4 we consider the sequence of steps going from ArPdL₂Br to product. Along this route, there are a number of possible bottlenecks. The X to O substitution is the first of these. With typical ligands, both hydroxide and ArB(OH)₃⁻ nucleophiles lead to relatively low

barriers of the order of 15 kcal mol⁻¹, but when considering solid bases and/or bases that are present in a second, aqueous, liquid phase,⁴³ this step may nevertheless be demanding due to the low amount of nucleophile present in the organic phase. We calculate that forming the trihydroxyboronate ArB(OH)₃⁻ from solid Na₂CO₃ requires a standard Gibbs energy change of 18.3 kcal mol⁻¹, yielding an overall barrier of the order of 30 kcal mol⁻¹. After halide has been replaced by an oxygen nucleophile, one can form one of a variety of different species with a Pd-O-B linkage. With 'normal' phosphines present in a 2:1 or higher ratio to Pd, the most stable of these is ArPdL₂OB(OH)Ar **6**, while at lower phosphine loading the cyclic dipalladium species **9** may be significant. Interconversion of these different species occurs with relatively low barriers.

Transmetalation itself appears to occur through mono-palladium TSs such as **TS1**, which lie some 20 – 25 kcal mol⁻¹ above **6** or **9**, though our current calculations find **TS1** to lie rather too high compared to **6**. The diarylpalladium species **16** formed after the transmetalation step can undergo usually facile reductive elimination to generate product and regenerate the Pd(0) species that initiates the catalytic cycle. This TS can perhaps in some cases be relatively high in Gibbs energy relative to the coordinatively saturated species ArPdL₂Ar **17**, so it cannot be ruled out that it will also form an overall bottleneck to reaction in some cases.

These different bottle-necks are summarized in Figure 3. Given the uncertainties on the calculated Gibbs energies depending on the reaction conditions, on the ligand, but also on the remaining errors in the computations, this Figure should not be interpreted too quantitatively, but it does summarize which steps need to be taken into account. Overall, three steps have Gibbs energy barriers of 25 to 30 kcal mol⁻¹. With the higher of these values, assuming concentrations of most species of the order of 1 M, the predicted turnover rate per Pd atom would be of the order of 0.005 h⁻¹ at 80 °C, whereas barriers of 25 kcal mol⁻¹ predict about 8 turnovers per hour per Pd, roughly similar to observed reactivity in many Suzuki-Miyaura couplings. This suggests that the present calculations overestimate some of the barriers, probably due to underestimating the availability of oxygen nucleophiles.

Compared to one of the most systematically constructed previous overall Gibbs energy diagram for Suzuki-Miyaura cross-coupling,³⁵ this diagram differs in a number of respects. First, the oxidative addition TS lies higher in Gibbs energy relative to PdL_n reactant species, irrespective of *n*. Next, the X to O substitution TS is shown to play a role in the overall process of transmetalation, together with the actual transmetalation TS, with both lying some 30 kcal mol⁻¹ above the oxidative addition product, once the low concentration of oxygen nucleophiles in the reaction medium is considered. Finally, we show that oxidative addition, X to O substitution, transmetalation and perhaps even reductive elimination have similar Gibbs energy demands, which hints to the difficulties with finding optimal reaction conditions with different substrates.

Figure 3. Schematic overall Gibbs energy profile for Suzuki-Miyaura coupling reaction. Indicated relative Gibbs energies are 'best estimates' based on the present calculations with input from experiment, and are provided for guidance only.

Conclusions

In this paper, we present new quantum chemical calculations relating to the mechanism of Suzuki-Miyaura cross-coupling catalysis by palladium phosphine complexes. Compared to the existing voluminous computational literature on this reaction, there are several new aspects. First, we have extensively characterized the relative Gibbs energies of the range of pre-transmetalation species containing a Pd—O—B linkage, reaching broadly good agreement with the experimental results that have recently become available for these species. Next, we have accounted for the Gibbs energy requirements associated with introducing oxygen nucleophiles into the organic phase where the palladium-containing species are usually present. This has the effect of raising the predicted barrier of the X to O substitution step and of the transmetalation step relative to the product of oxidative addition, compared to many previous studies. The remaining significant uncertainties on the calculated Gibbs energies for the oxygen nucleophiles suggest that additional computational and experimental investigation of this aspect is warranted. Finally, we have suggested an overall Gibbs energy profile in which the role of the different steps is summarized, and which shows that a number of steps have similar Gibbs energy requirements. Quantitative agreement with observed turnover behaviour falls far short of what can be achieved for simpler processes, showing that further progress in modelling catalytic kinetics in such complex reactions is still needed.

Conflicts of interest

There are no conflicts to declare.

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