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ARTICLE

Explicit account of solvation is essential for modeling Suzuki-Miyaura coupling in protic solvents.

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We compared explicit and implicit solvation approaches in modeling free energy profile of the final step of Suzuki-Miyaura coupling. Both approaches produced similar ΔG^\ddagger in all studied solvents (benzene, toluene, DMF, ethanol, water). Solvation free energies of individual reaction components reasonably correlated for explicit and implicit models in aprotic solvents (RMSE=30-50 kJ/mol, $R^2>0.71$). However for ethanol and water the correlation was poor. We attributed this difference to the formation of Pd---H-O hydrogen bond with Pd(PPh₃)₂ which was surprisingly observed in explicit modeling. Further QM calculations of Pd(PPh₃)₂ – H₂O system confirmed direction (Pd---H) and stability of this bonding. Therefore we stress the need for considering explicit solvation for modeling Pd-catalyzed reactions in protic solvents.

Introduction

Being discovered almost 40 years ago¹⁻³, metal-catalyzed cross-coupling reactions have revolutionized the way of C-C bond construction, providing elegant and simple routes to otherwise hardly accessible compounds. Despite the simplicity of the overall transformation (which formally represents a substitution reaction), the underlying molecular mechanisms can be extremely complex and involve a plenty of intermediates distributed over a variety of alternative reaction pathways^{4, 5}. Suzuki-Miyaura cross-coupling reaction proceeds via three major steps: 1) oxidative addition of R-X to PdL₂, 2) transmetalation reaction between RXPdL₂ and R'B(OH)₂ yielding RR'PdL₂ and 3) reductive elimination producing R-R' and PdL₂⁶. Two of these steps, reductive elimination and oxidative addition are also presented in a number of other organometallic reactions. Experimental studies of the reductive elimination step are hampered by short living time of intermediates, but computational chemistry methods can provide an invaluable information about electronic structure⁷ and size⁸ of the reacting species and allows one to select correct reaction mechanism from several alternatives⁹, explain the influence of ligands on catalytic activity¹⁰⁻¹² and address the effect of solvent on the reaction outcome¹³. Actually the free energy of solvation can be comparable to the activation free energy⁶ and the reaction selectivity can be controlled by using appropriate solvent¹³, however problem of choosing the

solvation model gained little attention. In ONIOM (Own N-layer Integrated molecular Orbital molecular Mechanics) calculations^{14, 15} of metal-catalyzed reactions continuum solvent model is routinely used (ONIOM-PCM)¹⁶. Despite high computational performance, implicit solvation models can produce serious errors as was demonstrated in several macromolecular simulations¹⁷⁻¹⁹. On the other hand, explicit QM treatment of solvent molecules has still unacceptably high computational costs while pure MM calculations are justified only for modelling non-covalent interactions. Thus a specific protocol preserving advantages of both approaches could employ QM for calculating energy profile of reaction in vacuum and MM FEP^{20, 21} for estimating the solvation impact. This protocol was originally proposed by Jorgensen for studying S_N2 reactions^{22, 23} and then further expanded to enzymatic reactions²⁴. However to our knowledge such approach has not been yet applied to metal-catalyzed processes. Thus we employed a QM/MM FEP method to study a model reductive elimination step of two Ph ligands from Pd(PPh₃)₂Ph₂ (final step of Suzuki-Miyaura cross-coupling)^{1, 6, 25} and compared the results with traditional continuum model of solvation. First, QM calculations were used to determine free energy and equilibrium parameters (atomic coordinates, atomic charges, force constants, etc) of reagents and products in vacuum. Then for each molecule the free energy of solvation was calculated using FEP method by averaging energy change over statistical ensemble generated during molecular dynamics simulation. Such approach slightly differs from the original Jorgensen's method (which implied alchemical FEP transition from reagent to TS and products in explicit solvent rather than complete desolvation of each reaction component) since the main interest of the article was to evaluate absolute solvation free energy. Free energy profile of reaction was

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obtained by summing its free energy profile in vacuum and corresponding solvation increments. One can use this method to compare the reaction free energy profile in different solvents and in different media by directly assessing solute-solvent interactions that can be of particular interest for optimization of reaction conditions.

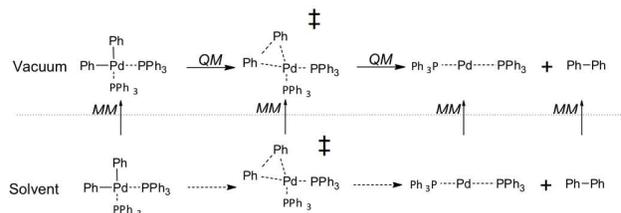
Methods

The reaction was modelled in a diverse set of solvents (benzene, toluene, DMF, ethanol, water) using both QM+MM FEP and PCM SMD²⁶ methods (SMD is a standard method for calculation of solvation free energy in Gaussian09). Equilibrium geometries of initial state, TS (transition state) and products as well as corresponding Gibbs free energies in vacuum were calculated using 2-layer ONIOM approach as previously described²⁷ with Gaussian09²⁸. Briefly, complexes were divided into two layers: the first layer included palladium, phosphorus atoms and palladium-bound phenyl rings (and water for Pd(PPh₃)₂ – H₂O complexes), the second layer included the substituents at the phosphine ligand. The first layer was treated at the high B3LYP/BSI level (B3LYP is commonly used for studying Suzuki coupling⁶; BSI basis set consists of SDD basis set for Pd^a and 6-311G(d) for the other atoms). The second layer was treated at relatively low HF/Lanl2mb level. SMD solvation energies were calculated for solvent-optimized geometries.

CHARMM27³⁰ MM parameterization was performed with Paratools plugin for VMD³¹ to reproduce QM molecular energies for 10 different MD-generated atomic coordinates. Charges were determined by RESP and Lennard-Jones parameters for Pd were taken from³². 4-site TIP4P water model was used³³. MM FEP solvation free energies were calculated in Gromacs³⁴. Briefly, a solute molecule was placed in 70 Å cubic box of solvent using Gromacs utility genbox. Then FEP was used to switch off the solute-solvent interaction. FEP calculations were performed in 10 λ steps (separately for VdW and coulomb interactions), each step included 100 ps NVT equilibration, 500 ps NPT equilibration and 10 ns NPT production dynamics. Phase space overlap — a control parameter that shows how likely the neighbouring λ-states are properly sampled — was estimated based on relative state entropies by calculating Π values described in³⁵. Computational details for phase space overlap parameters are provided in the Supporting Information (Tables 1-5). Independently, classical block averaging method was applied to estimate statistical errors of free energy calculations, which show whether the selected length of molecular dynamics trajectory is enough to yield a statistically robust mean value.

^a Dispersion correction for Pd was not used, since implementation of GD3BJ dispersion correction²⁹ produced wrong Pd(PPh₃)₂ geometry in vacuum (∠P-Pd-P = 134°). Nevertheless for hydrated systems optimized geometry was the same as with pure B3LYP. This result may indicate possible limitations of GD3BJ for 2-coordinated Pd complexes.

The resulting ΔG of reactants, TS and products were calculated as a sum of vacuum QM energy and MM solvation free energy (Scheme 1).



Scheme 1. QM calculations were performed to obtain ΔG in vacuum, and MM FEP provided the solvation free energy of reactants and products.

Results and Discussion

FEP transitions proceeded smoothly (see Chart 1 as an example) and demonstrated good stability over entire 10 ns simulation period as was confirmed by relatively small statistical error (<1 kJ/mol for all perturbations) estimated by block averaging. Π values calculated for each λ window of each transition were mostly positive (except small negative values not less than -0.5 for a few steps) indicating that bias in free energy calculations potentially caused by insufficient phase space overlap was negligible (see Supporting Information, Tables 1-5). Few particular transitions with the Π value < 0.5 (last stages of Pd(PPh₃)₄ and TS VdW decoupling) were re-simulated with reduced window size (Δλ=0.05). Resulting free energies were essentially the same as for Δλ=0.1 (see Supporting information, Table 8) while Π value was >0.5 indicating that adequate phase space overlap was finally achieved.

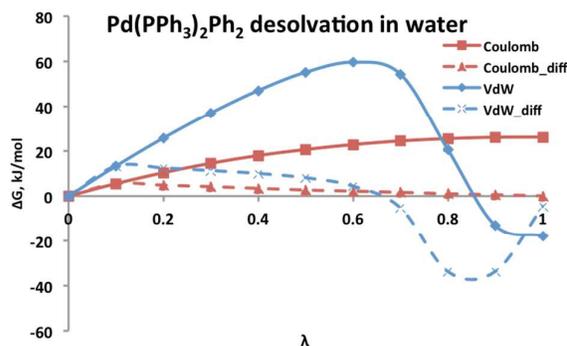


Chart 1. Cumulative and differential free energy change during FEP desolvation of Pd(PPh₃)₂Ph₂ in water.

Fair agreement between SMD and QM+FEP for activation energy was observed in non-polar benzene and toluene (Chart 2). For polar solvents difference was considerable, comprising 3-6 kJ/mol. Activation energy in all solvents was greater than in vacuum mainly due to electrostatic solvation which significantly differed between initial complex and less polar transition state (μ=10.9 vs 7.2 respectively), while non-electrostatic component remained almost unchanged due to

similar molecular surface area (see Supporting information, Table 6).

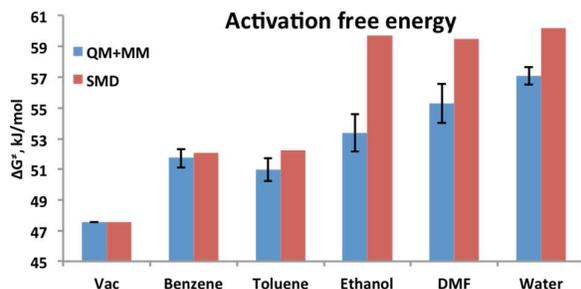


Chart 2. Activation free energy of reductive elimination of PhPh from Pd(PPh₃)₂Ph₂ in different solvents. Error bars for $\Delta G_{\text{QM+FEP}}^{\ddagger}$ were derived from block averaging.

However a considerable quantitative and qualitative difference between SMD and QM+FEP models was observed for the total reaction free energy change (ΔG_r) (Chart 3). QM+FEP predicted a ΔG_r of about -200 kJ/mol for all solvents studied, while SMD ΔG_r varied from -125 kJ/mol (water) to -156 kJ/mol (toluene), and there was no agreement between SMD and FEP results. Even larger difference was observed between classical PCM and FEP (Supporting Figure 1).

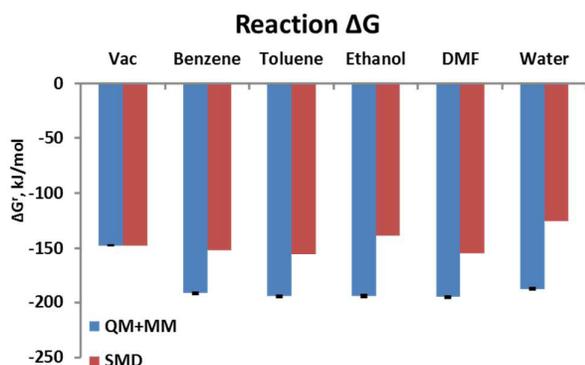


Chart 3. Free energy of reaction of reductive elimination of PhPh from Pd(PPh₃)₂Ph₂. Error bars for $\Delta G_{\text{QM+FEP}}$ represent FEP statistical errors.

To explore the intrinsic reason of this difference we have compared solvation free energies of reagents, TS and products in each of studied solvents (Chart 4, Supporting Information, Tables 6-7). A large difference between FEP and SMD solvation ΔG were observed for all solvents, with average RMSE of about 30-50 kJ/mol (Table 1). Good correlation ($R^2=0.71-0.85$) was observed for aprotic solvents (benzene, toluene and DMF). Fairly worse agreement however was observed for ethanol ($R^2=0.41$) and water (negative correlation with $R^2=0.69$).

Table 1. Correlation between SMD and FEP solvation energy for different solvents.

	RMSE, kJ/mol	Error, kJ/Mol	R ²
Benzene	32.6	-25.0	0.75
Toluene	31.7	-25.3	0.81
Ethanol	40.4	-29.4	0.43
DMF	48.0	39.6	0.71
Water	28.7	-8.5	0.69 (a<0)

Chart 4 clearly indicates that there was a major outlier in water (marked with *), which turned to be Pd(PPh₃)₂. Analysis of MD trajectories revealed that central Pd atom of Pd(PPh₃)₂ formed a Pd---H-O bond (Fig. 1) which was not accounted for in SMD calculations. Since one could expect reverse (i.e. Pd---O-H) polarity for Pd - water interaction, we have performed additional QM calculations to find out which polarity is correct. Starting from different initial geometries, and using either 6-311G(d) or 6-311G(p,d) basis sets, optimization of Pd(PPh₃)₂ - H₂O system inevitably resulted in formation of Pd---H-O bond (Figure 1). Feasibility of this interaction is additionally supported by studies of crystal structures of metal-ligand complexes³⁶⁻³⁸.

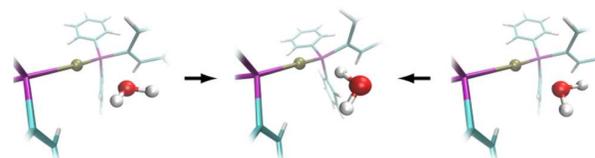


Figure 1. QM optimization of Pd(PPh₃)₂-H₂O leads to formation of Pd---H-O bond.

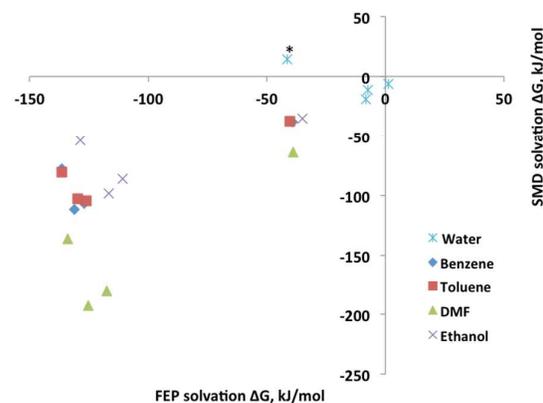


Chart 4. Free energies of solvation for reactant, products and transition state calculated with either SMD or MM FEP in a set of solvents. Individual data can be found in Supporting Information, Tables 6-7.

To demonstrate the contribution of Pd---H hydrogen bonding to the whole solvation energy we have repeated SMD calculation of Pd(PPh₃)₂ solvation with 3 first-layer water molecules treated explicitly (Figure 2). This approach, known as cluster-continuum model³⁹ can be used for systems with specific short-range solvent-solute interactions⁴⁰. The free energy of solvation of optimized complex approached the FEP value much closer (-66 kJ/mol vs -41 kJ/mol by FEP) than purely implicit approach (14 kJ/mol vs -41 kJ/mol by FEP).

Therefore this interaction might contribute to the observed difference between explicit and implicit solvation energies.

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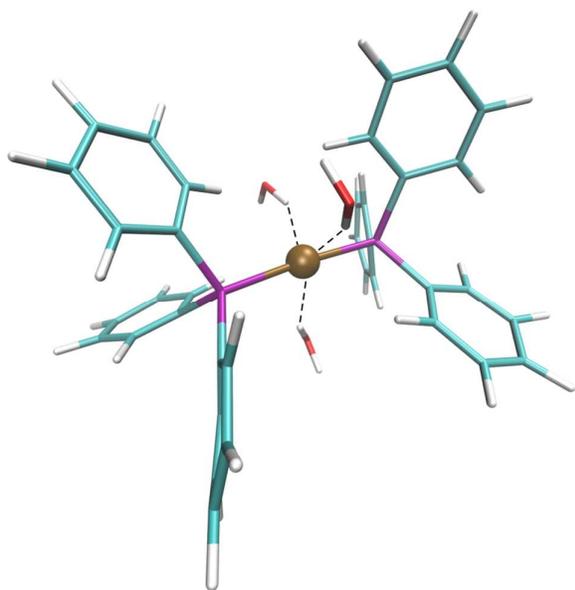


Figure 2. Unshielded Pd atom in Pd(PPh₃)₂ forms Pd–H–O bonds with water molecules according to MM FEP modeling.

Poor numerical agreement observed for DMF seems to be caused by inadequate parameterization of this solvent for SMD. Literature data on R_{solv} for DMF are controversial and vary from 2.44 Å⁴¹ to 2.64 Å⁴² and 3.48 Å⁴³ thus indicating the need for further validation.

Conclusions

In conclusion, we have compared explicit and implicit protocols for simulating solvent effects in a model metal-catalyzed organic reaction. Good correlation was observed for activation free energy, however a large difference (of dozens kJ/mol) emerged for solvation free energy of individual reaction components that was partially cancelled in activation energy but not in total reaction energy.

The most alarming result we have obtained was the lack of proper implicit description of specific interactions of Pd(PPh₃)₂ with the protic solvents which was observed with a more elaborate model of MM-FEP and confirmed by QM calculations. However, to be objective, we can not currently judge which computational approach is more accurate due to the lack of experimental solvation data for this particular reaction. Therefore explicit solvation should be at least seriously considered as an alternative for PCM when modelling Pd-catalyzed reactions in protic solvents.

Acknowledgements

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