Green Alternative Solvents for the Suzuki Coupling – a DFT Study of Reaction Mechanisms and Method Validation

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The Suzuki-Miyaura coupling reaction is commonly used to create carbon-carbon bonds in the synthesis of organic molecules. It has widespread applications in drug synthesis. One appealing feature is that the reaction can be potentially carried out in a broad range of solvents, including those that are sustainably sourced and environmentally benign. This work is part of a study to understand the impact of the solvent on the reaction. Particularly, it aims to investigate how the physicochemical properties of the solvent impacts activation barriers of the reaction and, if possible, to formulate general selection rules for benign and effective solvents. This poster discusses the results from studying esters, ethers and hydrocarbons as solvents, including candidates that are considered "green" alternatives, i.e. safe and benign.

To study solvent effects on the reaction, the free energy of activation for the rate-determining step was predicted using density functional theory in combination with geometry optimization respectively transition state searches. For a representative test reaction, the aryl-aryl coupling reaction between p-chlorotoluene and phenylboronic acid catalyzed by the N-heterocyclic carbene/palladium catalyst $[\mathrm{Pd(IPr)(allyl)Cl}]$, where $\mathrm{IPr} = \mathrm{N,N'-bis[2,6-(diisopropyl)phenyl]imidazol-2-ylidene}$ was studied. Geometries and free energy corrections were predicted at the PBE-D3(BJ)/def2-SVP level of theory. Single point energies were calculated at the ωB97X-D3/def2-TZVPP level of theory. Solvation effects were investigated using different solvation models, including C-PCM and SMD. This study investigated different approaches for obtaining initial geometries for the transition state searches and critically assesses their accuracy.

It was found that the solvent choice has substantial impact on the activation barrier of the reaction. Correlations with physicochemical properties of the solvents were studied and the strongest correlation was found with solvent polarity, as described by the solvent dielectric constant. Correlations with other physicochemical properties such as the refractivity are also present, but were found to be less important. These trends were investigated by studying the contributions of the electronic energies and free energy corrections and molecular origins were proposed. In addition, the impacts of different initial geometry choices on the free energies were compared and substantial differences were found for the latter solvents.

In summary, trends in solvent impacts on the activation barrier of the Suzuki-Miyaura coupling were studied and molecular origins analyzed. This study leads to better molecular understanding of solvent impacts and aids in the formulation of simple criteria for the selection of solvents for this important reaction.