Computational Method Effects on the Reaction-Energy Profile of Acetylation of Phenol with Acetic Anhydride

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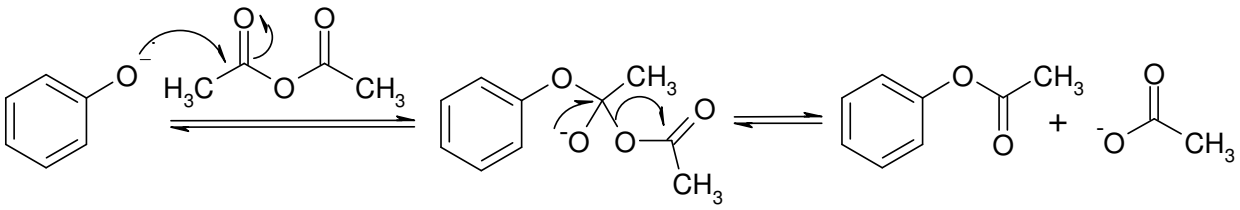
Acetylation reactions are prevalent within genetics and pharmaceutical industry through such processes as gene regulation and the production of aspirin. These reactions frequently occur in aqueous solution and, as such, to gain a more complete understanding of these reactions we must better understand how solvent affects the geometry and energy of these reaction types. This project examined the ability of several computational methods to model the reaction profile of a reaction that occurs in aqueous solvent, the acetylation of phenol in acetic anhydride.

The rate-limiting step is either the formation or decomposition of the tetrahedral intermediate. The Density Functional Theory B3LYP/6-31+G(d) method and *ab initio* Hartree-Fock/6-31+G(d) method were utilized to determine the gas-phase energies resulting from the manipulation of the phenolic and acetate geometrical bond distance along the reaction coordinate. Frequency and Synchronous Transit-Guided Quasi-Newton (STQN) Method calculations were also performed to confirm structures as minima and transition states along the reaction path. The resulting reaction-energy profiles were then plotted for the formation and decomposition of two separate conformers of the tetrahedral intermediate. These results have demonstrated a method dependency for the resulting bottom-of-the-well and Gibbs free energy profiles. Current analysis indicates that formation of the intermediate is limiting at the Hartree-Fock/6-31+G(d) level and decomposition is rate limiting at the B3LYP/6-31+G(d) level. The effects of implicit solvation on the acetylation reaction were examined using PCM solvation methods. Further research will analyze the changes between the gas-phase and solution-phase structural geometries and energies.



Tetrahedral Intermediate