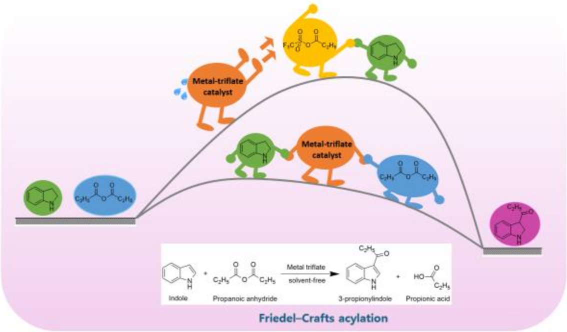
DFT - Proposed Mechanism of Friedel–Crafts Acylation of Indole Using Metal Triflate Catalysts

Kieu Van T Nguyen,[1,2] Khung M Trang,[1,2] Tam T V Mai,[1,2] Quan Phung,[1,2]
Phuong Hoang Tran,[1,2] Yoshiyuki Kawazoe,[3] and Nguyen Nguyen T Pham[1,2]

[1]*Faculty of Chemistry, University of Science, Ho Chi Minh City, 700000, Vietnam;*
[2]*Vietnam National University, Ho Chi Minh City, 700000, Vietnam;*
[3]*New Industry Creation Hatchery Center, Tohoku University, Sendai, 980–8579, Japan;*
ptnnguyen@hcmus.edu.vn

Friedel-Crafts acylation of indole with propionic anhydride (named as $(PrO)_2O$) using metal-triflate catalyst is a fast and eco-friendly method to synthesize 3-acylindole - a valuable intermediate in pharmaceutical synthesis - with high selectivity up to 97% over the N-H and C-2 positions without the protection of the NH position.[1,2] However, the role of the triflate catalyst in directing the regioselective acyl substitution on the indole remains unclear. This study used density functional theory (DFT) calculations to investigate the mechanism of substitution at three different positions on the indole ring in the presence and absence of the catalyst to demonstrate the crucial role of metal-triflate catalysts in synthesizing 3-acylindole. Specifically for the reaction mechanism of 3-acyl product formation using triflate catalyst, we proposed two pathways. In the first, the catalyst indirectly generated the electrophilic intermediate, trifluoromethanesulfonic propionic anhydride (PrOTf), by catalyzing the reaction between $(PrO)_2O$ and the triflate ligand (OTf^-). This intermediate then participated in an acyl substitution reaction on indole. In the second pathway, indole and $(PrO)_2O$ directly reacted at the metal core of the catalyst, proceeding through acylation and hydrogen transfer processes. Transition states and energy profiles for each pathway were calculated using varying central metal elements, including In, Y, Bi, and La, with the B3LYP/6-31+G(d,p) level of theory. Results showed that the second pathway, particularly with the $Y(OTf)_3$ catalyst, had the most favorable Gibbs activation energy. This finding aligned with experimental results from previous studies, supporting the second pathway as the most efficient for 3-acylindole synthesis.[3]



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