הטכניון - מכון טכנולוגי לישראל

TECHNION - ISRAEL INSTITUTE OF TECHNOLOGY

הפקולטה להנדסה כימית
ע״ש וולפסון
The Wolfson Department of Chemical Engineering

Wolfson Department of Chemical Engineering Seminar

Monday, December 15th, 2025 at 13:30

Room 6

Automated Transition State Search for Neutral Hydrolysis Reactions, and Applications for Retrosynthesis

Leen Fahoum

MSc Seminar

Advisor: Asst. Prof. Alon Grinberg Dana
Department of Chemical Engineering, Technion-Israel Institute for Technology

Hydrolysis reactions are central to organic synthesis, biomolecular chemistry, and retrosynthetic analysis. Despite their importance, locating transition states (TSs) for these reactions remains a major challenge. Hydrolysis involves a bimolecular, solvent-mediated mechanism in which the attacking water molecule must approach the reactive center in a highly specific three-dimensional orientation while simultaneously mediating proton transfer. Because TS optimization is highly sensitive to the initial guess geometry, even small deviations in water placement commonly lead to optimization failure. As a result, no existing automated quantum-chemical workflow can reliably generate transition-state guesses (TSGs) for hydrolysis across diverse chemical families.

This study addresses this fundamental gap by developing a fully automated, heuristics-based TSG generator for solution-phase neutral hydrolysis reactions, used here as a mechanistically rich benchmark for bimolecular, solvent-mediated processes. The approach is integrated within the Automated Rate Calculator (ARC) software and relies on reaction-family recognition and geometry based heuristics that enable consistent and chemically sensible positioning of the water molecule across diverse neutral hydrolysis mechanisms.

The algorithm development, its integration into ARC software, and a comprehensive validation across more than 90 reactions spanning several neutral hydrolysis sub-families will be presented, demonstrating high success rates in converging to chemically meaningful TSs. By enabling automated TSG generation for one of the most structurally demanding classes of solution-phase reactions, this work establishes a first mechanistic bridge between classical retrosynthetic planning and quantum-chemical reaction evaluation.

(Refreshments will be served at 13:15.)