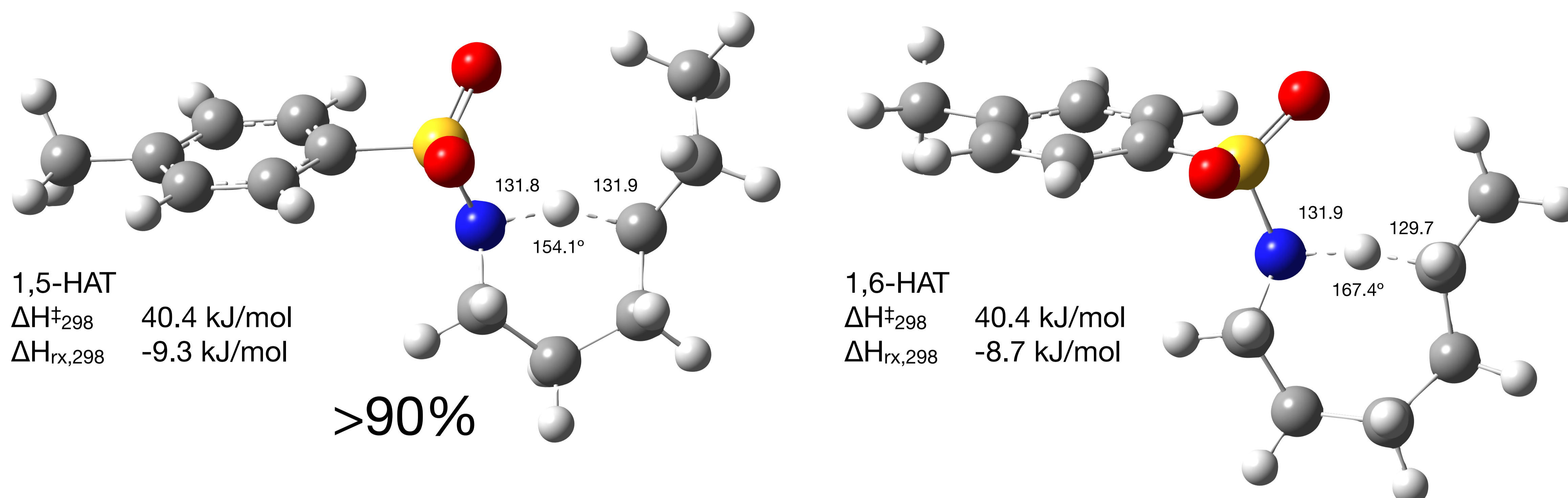
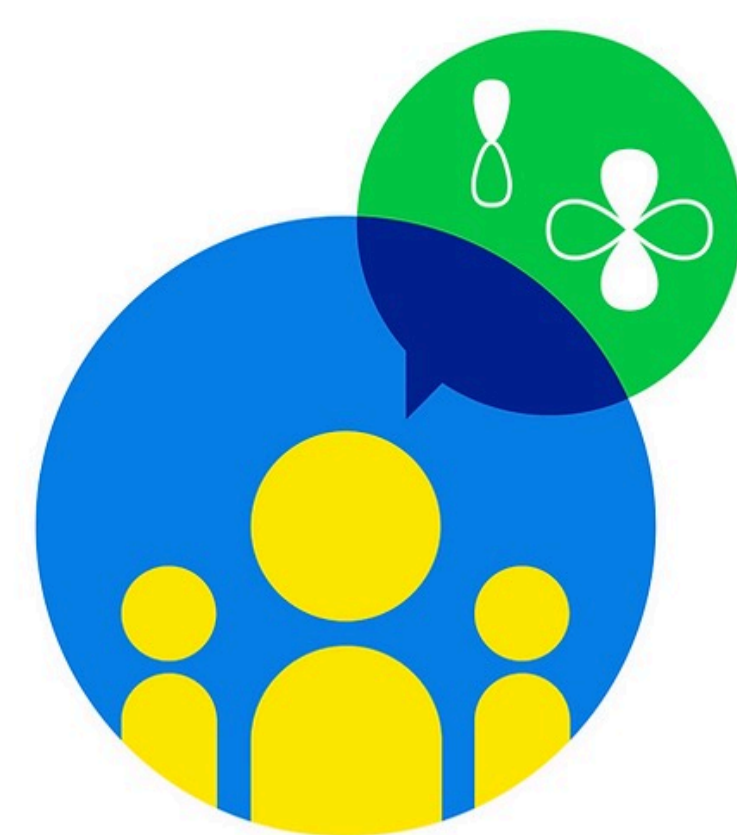




Pyrrolidine vs. piperidine in Hofmann-Löffler-Freytag reaction. A thermodynamic perspective on rearrangement reactions

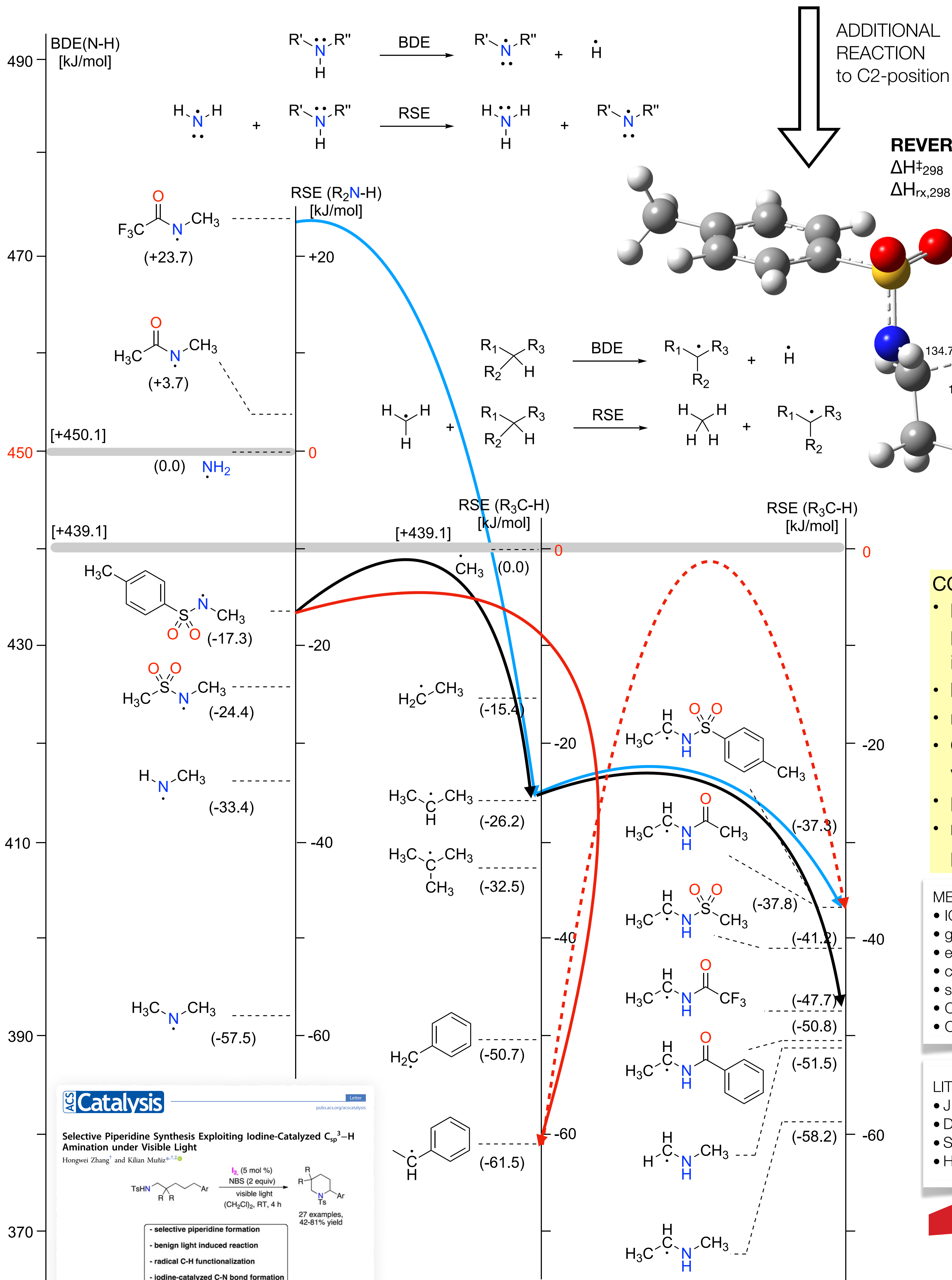
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INTRODUCTION:
 Hofmann-Löffler-Freytag (HLF) reaction has seen a resurgence in interest due to shift from metal-based catalysis to organo-catalysis. Recent one-pot approach requires hypervalent iodine compound with source of iodine (I_2 or NaI) for generating radical precursor, that can under UV irradiation form N -centered radical. Rearrangement to a more stable C -centered radical via 6-membered ring transition state is well described and produces predominately pyrrolidine, while trace amounts of piperidine is formed via 7-membered ring transition state. Regioselective synthesis of piperidine is usually done when C5 position is blocked, or when C6 position provides greater thermodynamic driving force.

RADICAL STABILISATION ENERGIES



N-trifluoroacetyl-hexylamine

	ΔH_{298}^\ddagger [kJ/mol]	$\Delta H_{rx,298}$ [kJ/mol]
1,5-HAT	36.6	-37.9
1,6-HAT	38.0	-30.3
REVERSE 1,5-HAT	57.6	-15.5

N-tosyl-(5-phenyl)hexylamine

	ΔH_{298}^\ddagger [kJ/mol]	$\Delta H_{rx,298}$ [kJ/mol]
1,5-HAT	58.9	-13.3
1,6-HAT	40.0	-44.2
REVERSE 1,5-HAT	88.1	25.0

CONCLUSIONS

- pyrrolidine (1,5-HAT) and piperidine (1,6-HAT) pathways are kinetically and thermodynamically indistinguishable
- location of the most stable radical in the molecule
- molecular fragments can be used in prediction
- C6 radical may rearrange to more stable C2 radical via 1,5-HAT
- probable reason for pyrrolidine regioselectivity
- radical stabilities play crucial role in determination of products

METHODS

- IQmol, GaussView & Gaussian 16
- geometry optimisation, frequency and IRC @B3LYP/6-31G(d)
- every reaction is modelled as separate
- conformation analysis: XTB-GFN2
- single point energies @B2-PLYP-D3/G3MP2Large
- Cluster Isabella @SRCE
- Cluster SW @SW.PHARMA.HR

LITERATURE

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