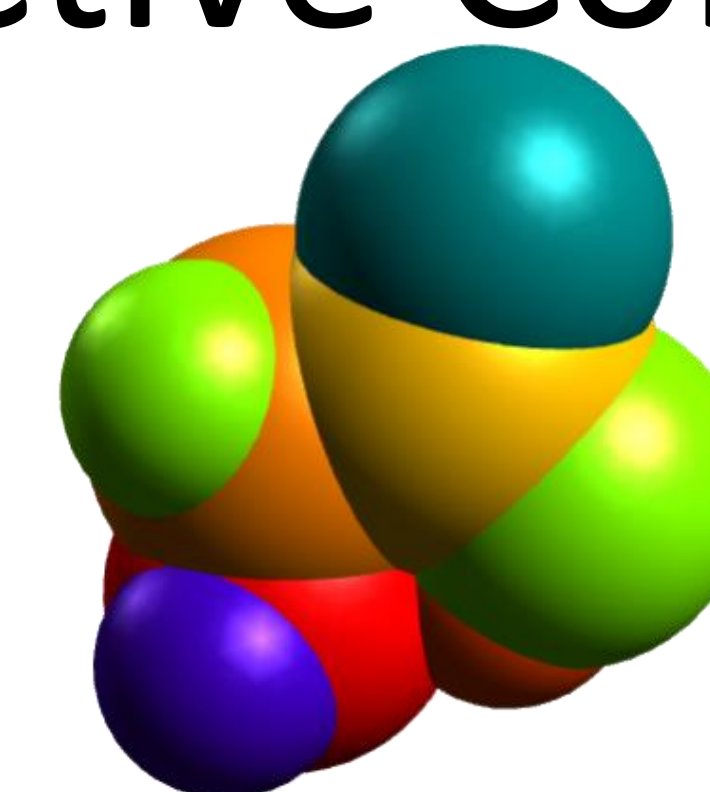




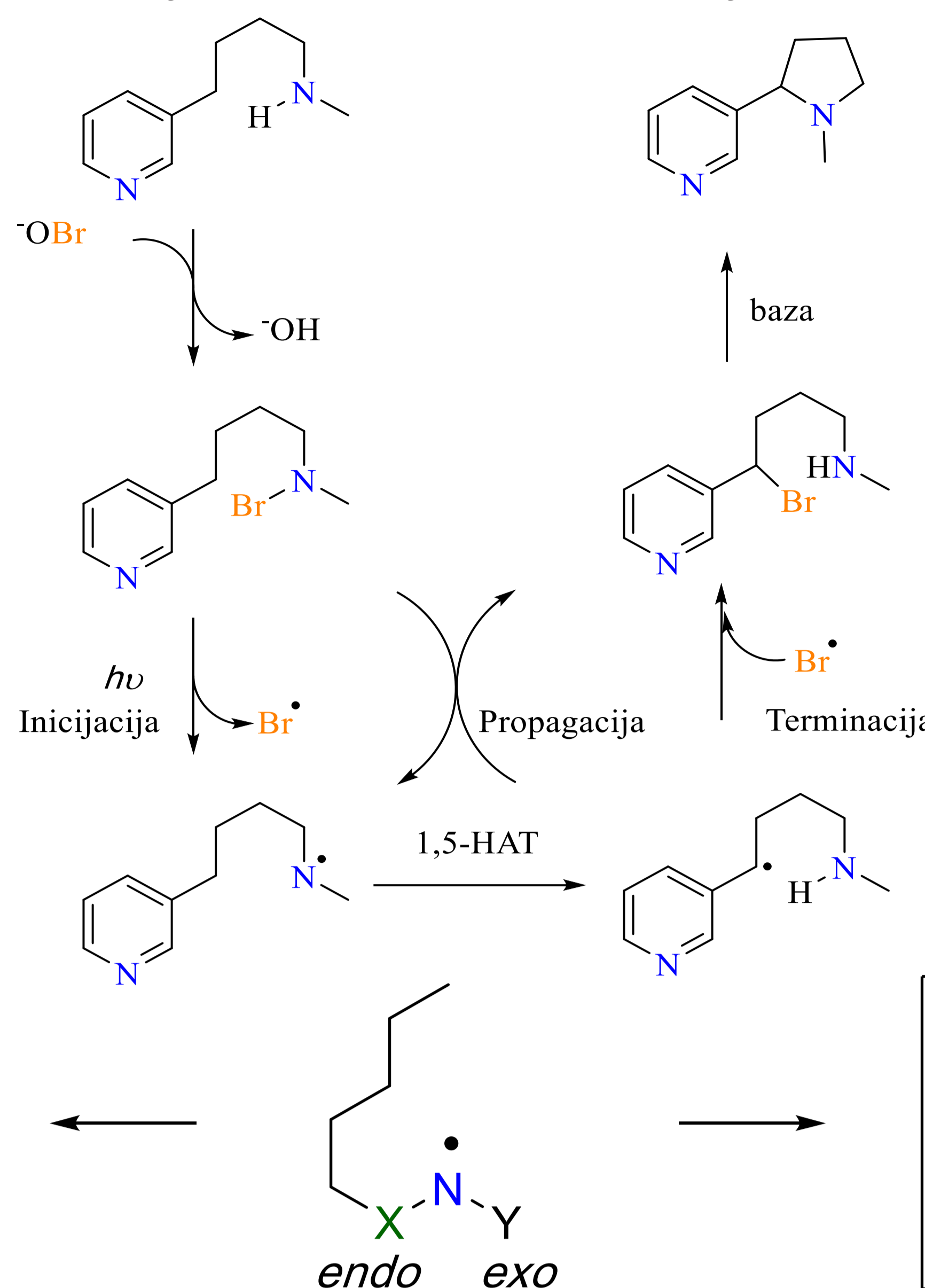
Theoretical Research Aimed at Achieving Regioselective Control Within the Hofmann-Löffler-Freytag Reaction

Gabrijel Zubčić, Davor Šakić

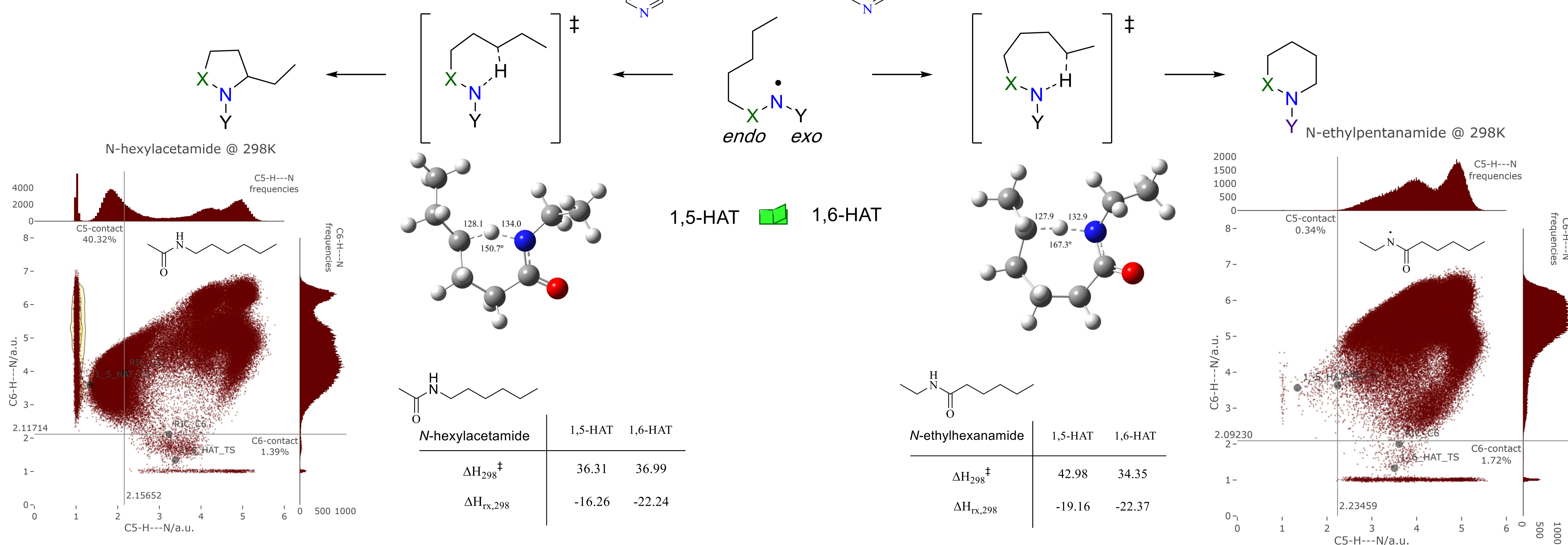
University of Zagreb, Faculty of Pharmacy and Biochemistry, Ante Kovačića 1, 10000 Zagreb



- Hofmann-Löffler-Freytag reaction represents a distinctive radical-based procedure for the synthesis of nitrogen-containing heterocycles.
- Although the formation of piperidine and pyrrolidine rings is equally likely, pyrrolidine rings are dominant product.
- Finding a mechanistic switch that governs whether 1,5-HAT or 1,6-HAT reaction occurs is, therefore, challenging.



- When C5-radical \approx C6-radical stability
- Activating group endo guides the product distribution in such a manner that a predominant piperidine product is formed.
- Activating group exo guides formation of pyrrolidine ring due to increased population of the 1-5-RIC.
- Effect of bulky groups exo and endo; Thorpe-Ingold effect
- Group on C2-position may block unwanted rearrangement; Thorpe-Ingold effect



N-(2,3,4-trimethylpentan-3-yl)hexanamide

	1,5-HAT	1,6-HAT
$\Delta H_{298}^{\ddagger}$	61.30	67.85
$\Delta H_{rx,298}$	-6.21	7.53

N-(3-isopropyl-2-methyloctan-3-yl)acetamide

	1,5-HAT	1,6-HAT
$\Delta H_{298}^{\ddagger}$	35.58	50.06
$\Delta H_{rx,298}$	-21.53	-16.11

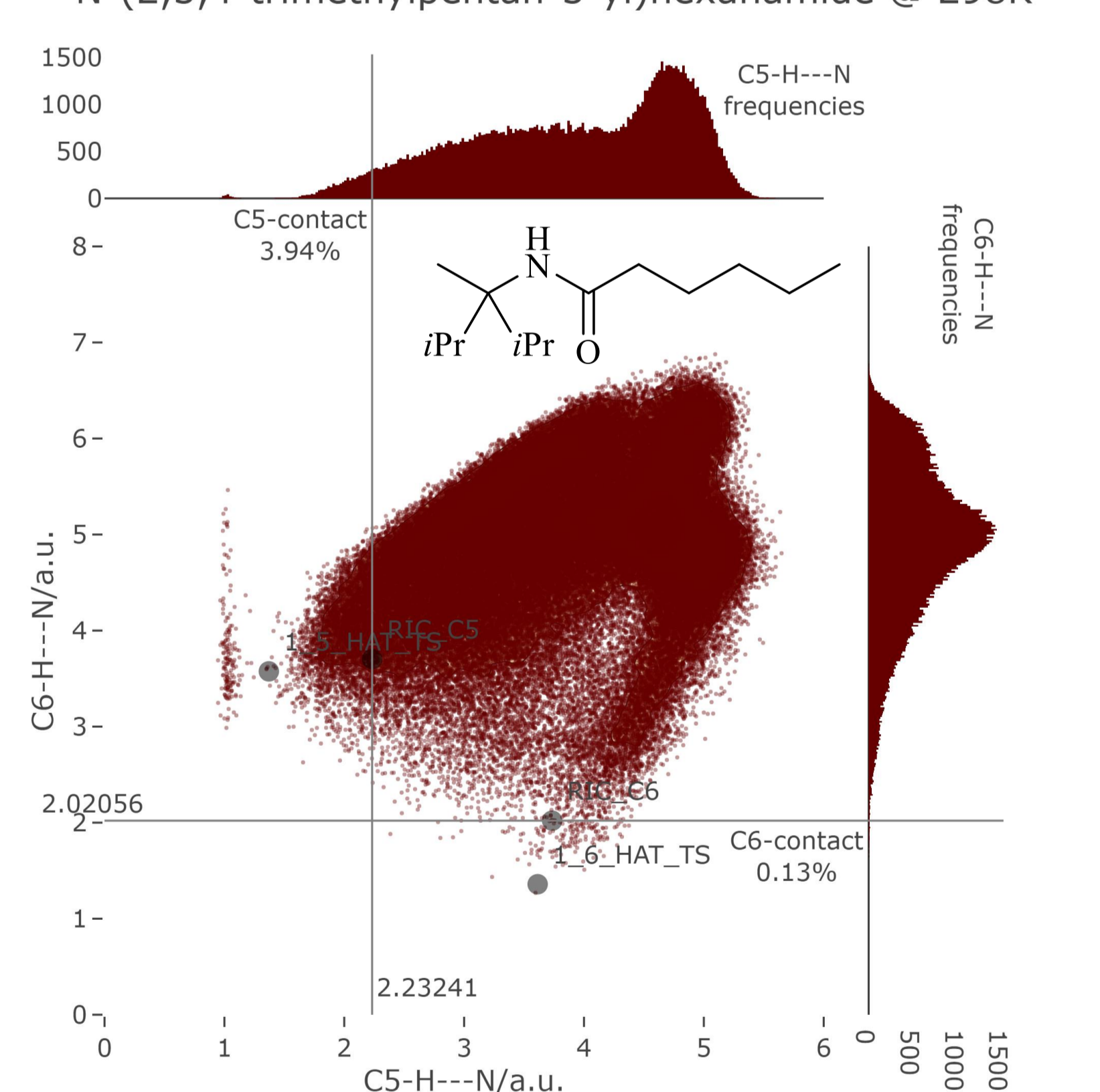
N-ethyl-3-isopropyl-2-methyloctan-3-amine

	1,5-HAT	1,6-HAT
$\Delta H_{298}^{\ddagger}$	70.07	78.13
$\Delta H_{rx,298}$	30.89	45.50

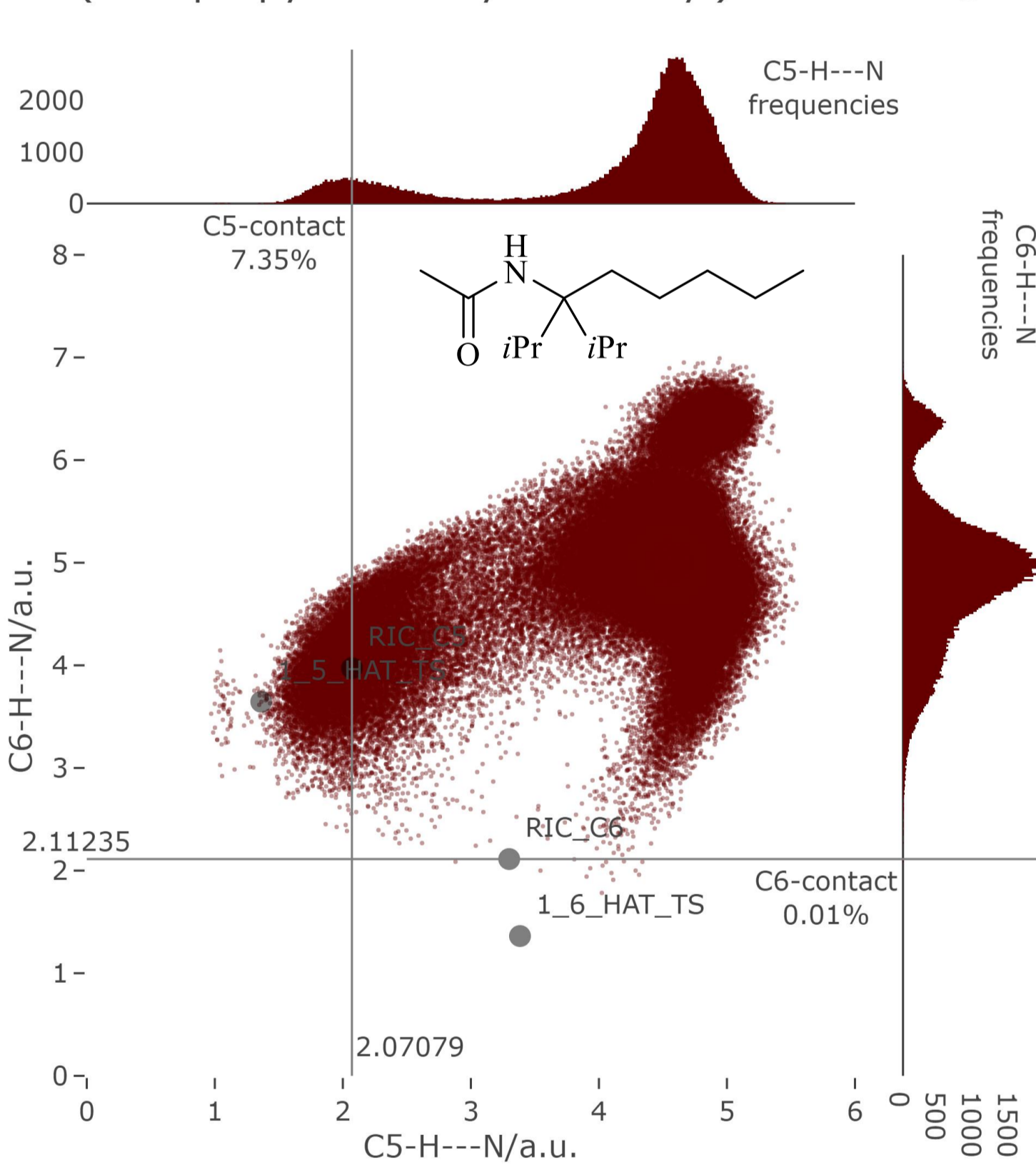
N-(2,3,4-trimethylpentan-3-yl)hexan-1-amine

	1,5-HAT	1,6-HAT
$\Delta H_{298}^{\ddagger}$	81.47	70.53
$\Delta H_{rx,298}$	38.46	35.35

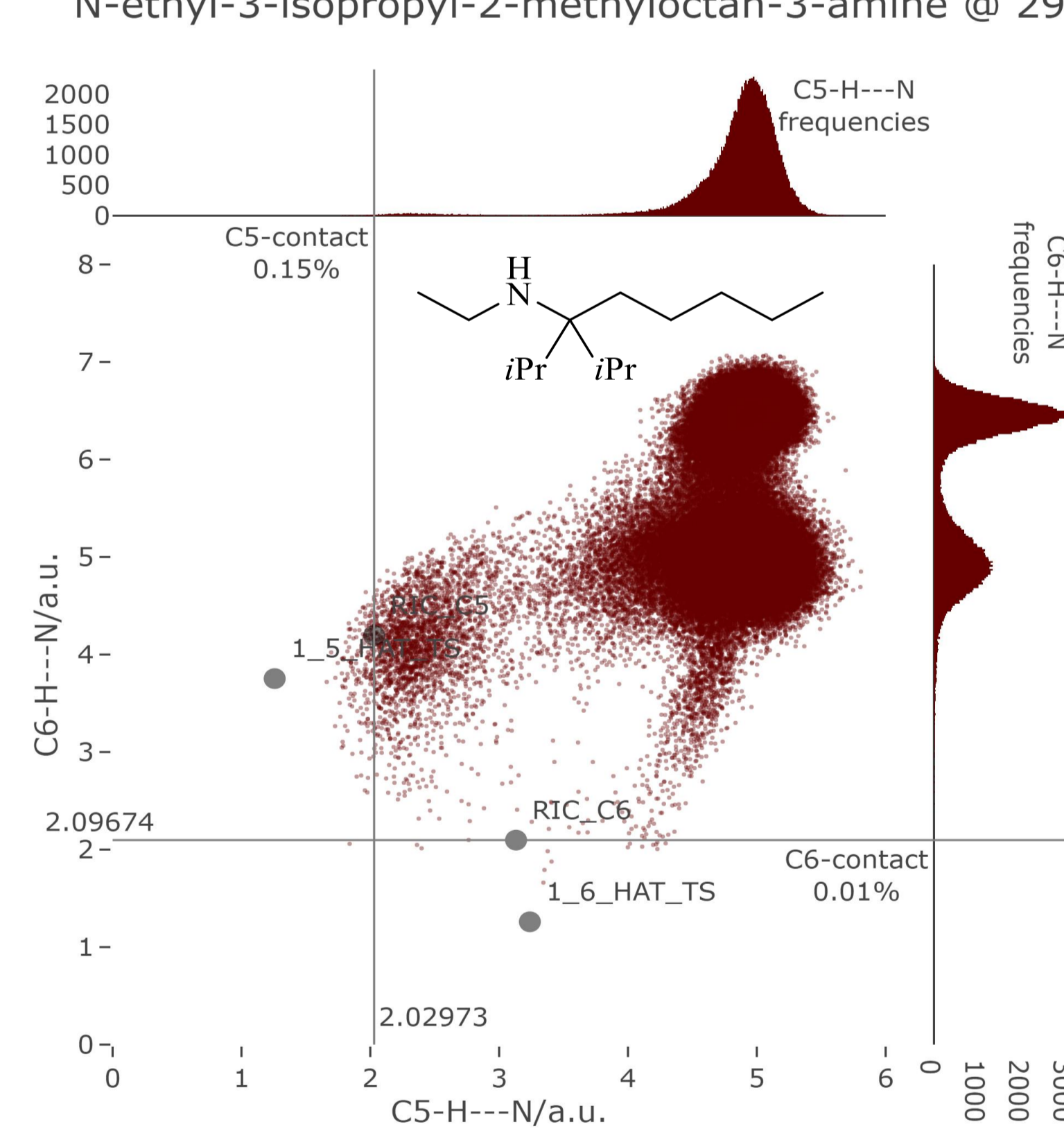
N-(2,3,4-trimethylpentan-3-yl)hexanamide @ 298K



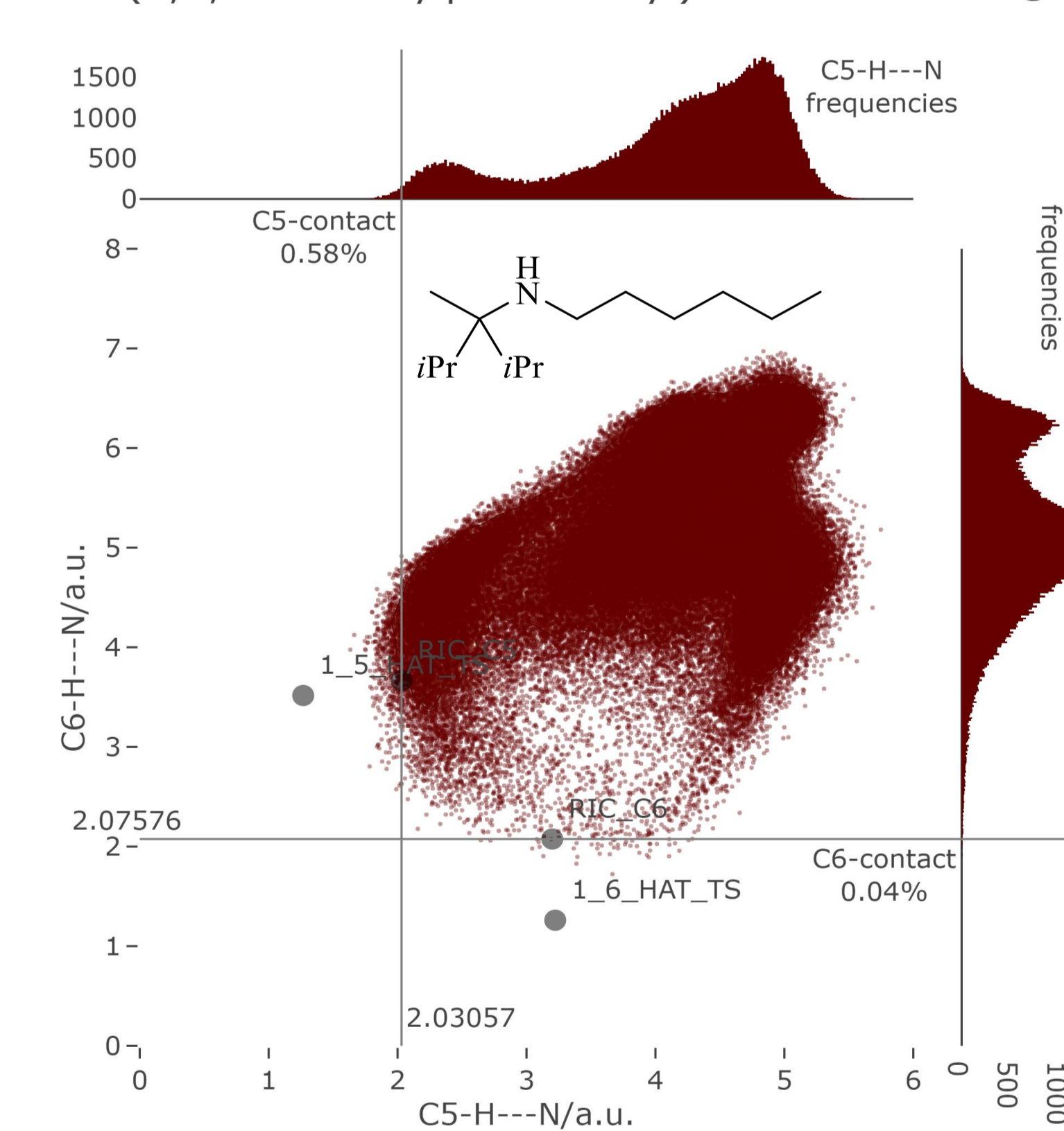
N-(3-isopropyl-2-methyloctan-3-yl)acetamide @ 298K



N-ethyl-3-isopropyl-2-methyloctan-3-amine @ 298K



N-(2,3,4-trimethylpentan-3-yl)hexan-1-amine @ 298K



N-(3-isopropyl-2-methyloctan-3-yl)methanesulfonamide

	1,5-HAT	1,6-HAT
$\Delta H_{298}^{\ddagger}$	50.82	61.83
$\Delta H_{rx,298}$	17.55	27.69

butyl (3-ethyl-2,4-dimethylpentan-3-yl)sulfamate

	1,5-HAT	1,6-HAT
$\Delta H_{298}^{\ddagger}$	89.89	72.88
$\Delta H_{rx,298}$	28.52	22.95

N-(2,3,4-trimethylpentan-3-yl)pentane-1-sulfonamide

	1,5-HAT	1,6-HAT
$\Delta H_{298}^{\ddagger}$	87.72	70.64
$\Delta H_{rx,298}$	33.12	24.91

methyl (3-isopropyl-2-methyloctan-3-yl)sulfamate

	1,5-HAT	1,6-HAT
$\Delta H_{298}^{\ddagger}$	41.93	51.11
$\Delta H_{rx,298}$	7.17	13.47

Methods

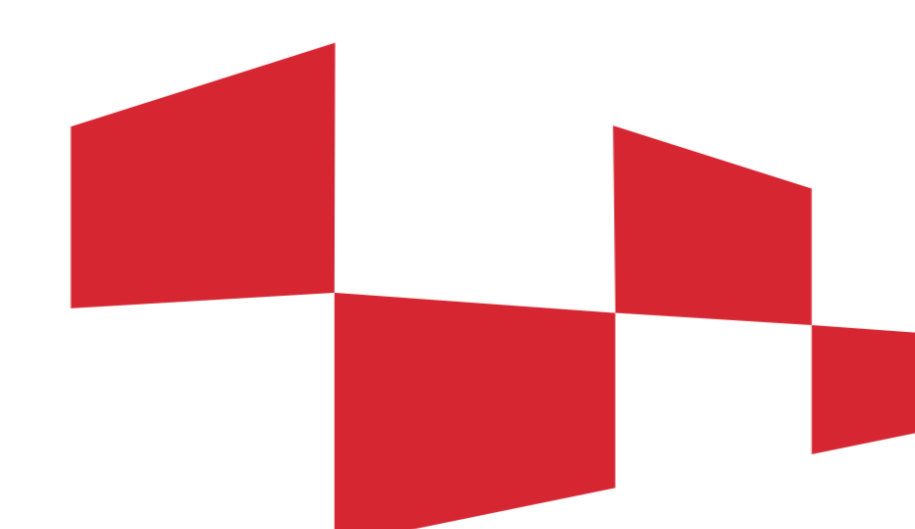
- GaussView, IQmol
- Gaussian 16 opt+freq+IRC @B3LYP/6-31G(d)
- XTB 6.41. CREST, MD @GFN-2-xtb
- Klaster Isabella @SRCE
- Klaster sw.pharma.hr, FarmInova @FBF

Conclusion

- Activating group endo \Rightarrow 1,6-HAT process.
- Activating group exo \Rightarrow 1,5-HAT process.
- Bulky group endo \Rightarrow 1,5-HAT process.
- Bulky group exo \Rightarrow 1,6-HAT process.
- Bulky group exo & activating group endo \Rightarrow 1,6-HAT
- Bulky group endo & activating group exo \Rightarrow 1,5-HAT process.

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Light-driven functionalization of Unreactive sites Using Oxidative Amination

LIGHT-RING