



# Experimental, computational and kinetic modelling of Hofmann–Löffler–Freytag Reaction

Gabrijel Zubčić,<sup>[a]</sup> Tomislav Friganović,<sup>[a]</sup> Luka Adrijanić,<sup>[a]</sup> Jiangyang You,<sup>[b]</sup> Iva Džeba,<sup>[b]</sup> Kristina Pavić,<sup>[a]</sup> Erim Bešić,<sup>[a]</sup>

Valerije Vrček,<sup>[a]</sup> and Davor Šakić<sup>[a]</sup>

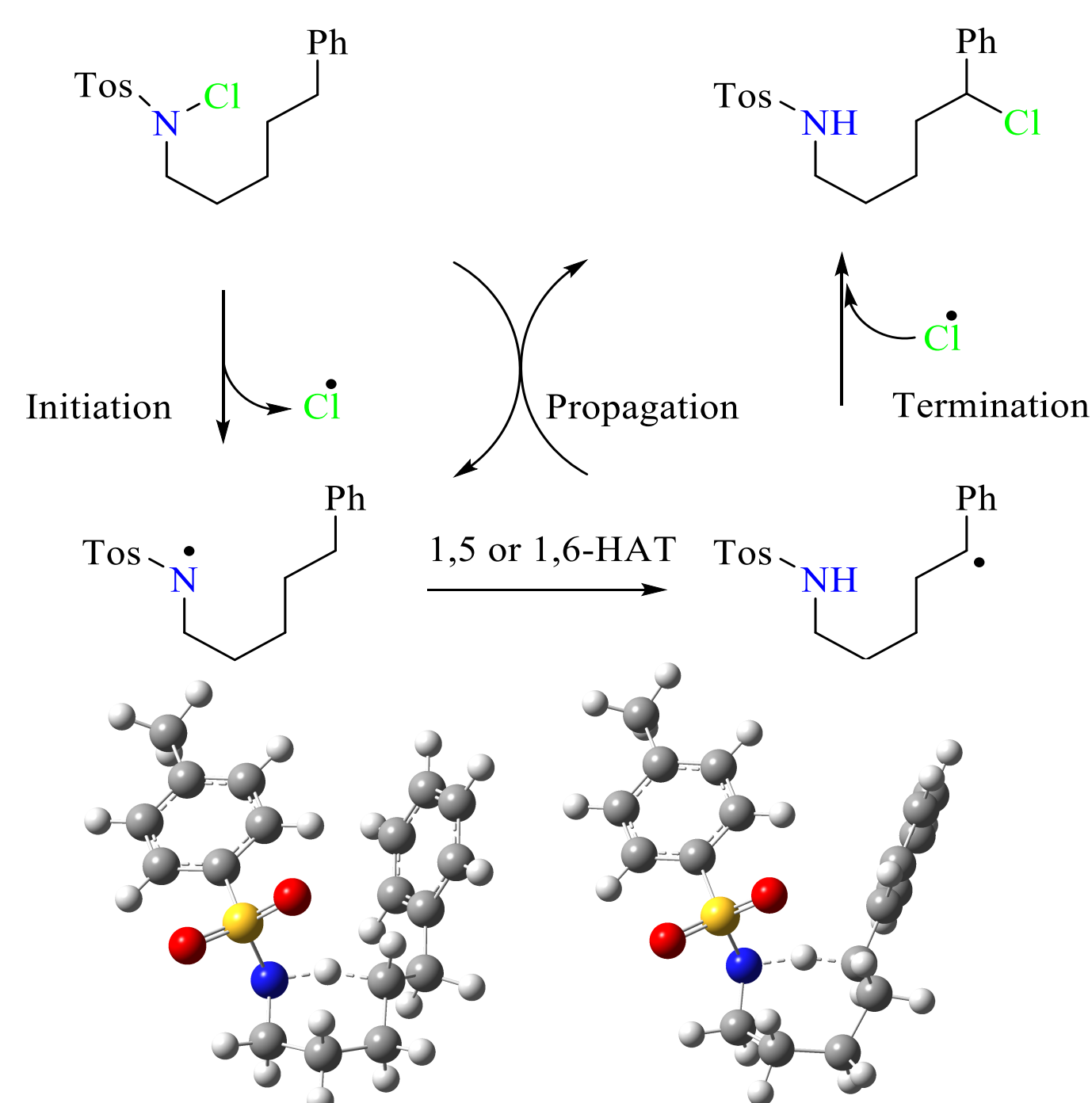
<sup>[a]</sup> University of Zagreb, Zagreb, Croatia

<sup>[b]</sup> Institute Ruđer Bošković, Zagreb, Croatia



## Introduction

- The Hofmann–Löffler–Freytag (HLF) reaction is used to functionalize distant C-H bonds<sup>[1]</sup>, producing pyrrolidine rings or C5-substituted compounds.
- The reaction mechanism involves a rearrangement from an N-centered radical via 1,5-hydrogen atom transfer (HAT).<sup>[2]</sup>
- Studies by Corey<sup>[3]</sup> and Short<sup>[4]</sup> groups have reported the formation of C<sub>5</sub>- and C<sub>6</sub>-halogenated products via 1,5-HAT or 1,6-HAT, while Muniz<sup>[5]</sup> has selectively made piperidine rings.



	TS(kj/mol)	product(kj/mol)
1,5-HAT	42.88	-18.35
1,6-HAT	31.33	-57.44

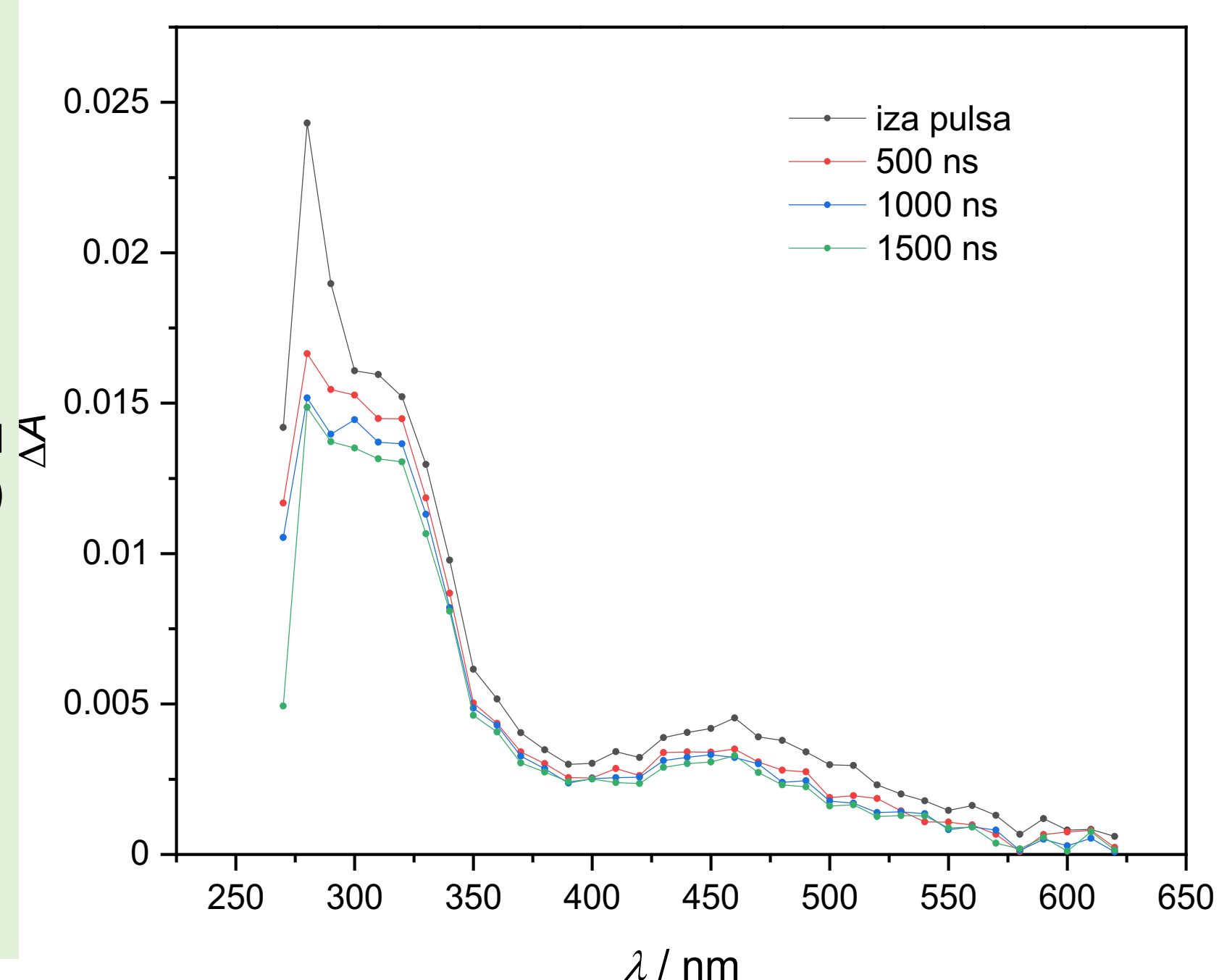
## Kinetic modelling

- We applied a steady-state approximation for the concentration of the N radical, this approximation also indirectly implies steady-states for the C<sub>5</sub> and C<sub>6</sub> radical intermediates.
- Additionally, the reverse reactions in the second step of the propagation cycle were neglected.
- This is supported by our DFT calculations.
- Using these approximations, we derived a simplified equation that describes the formation of all (final) chlorinated products, as presented in eq

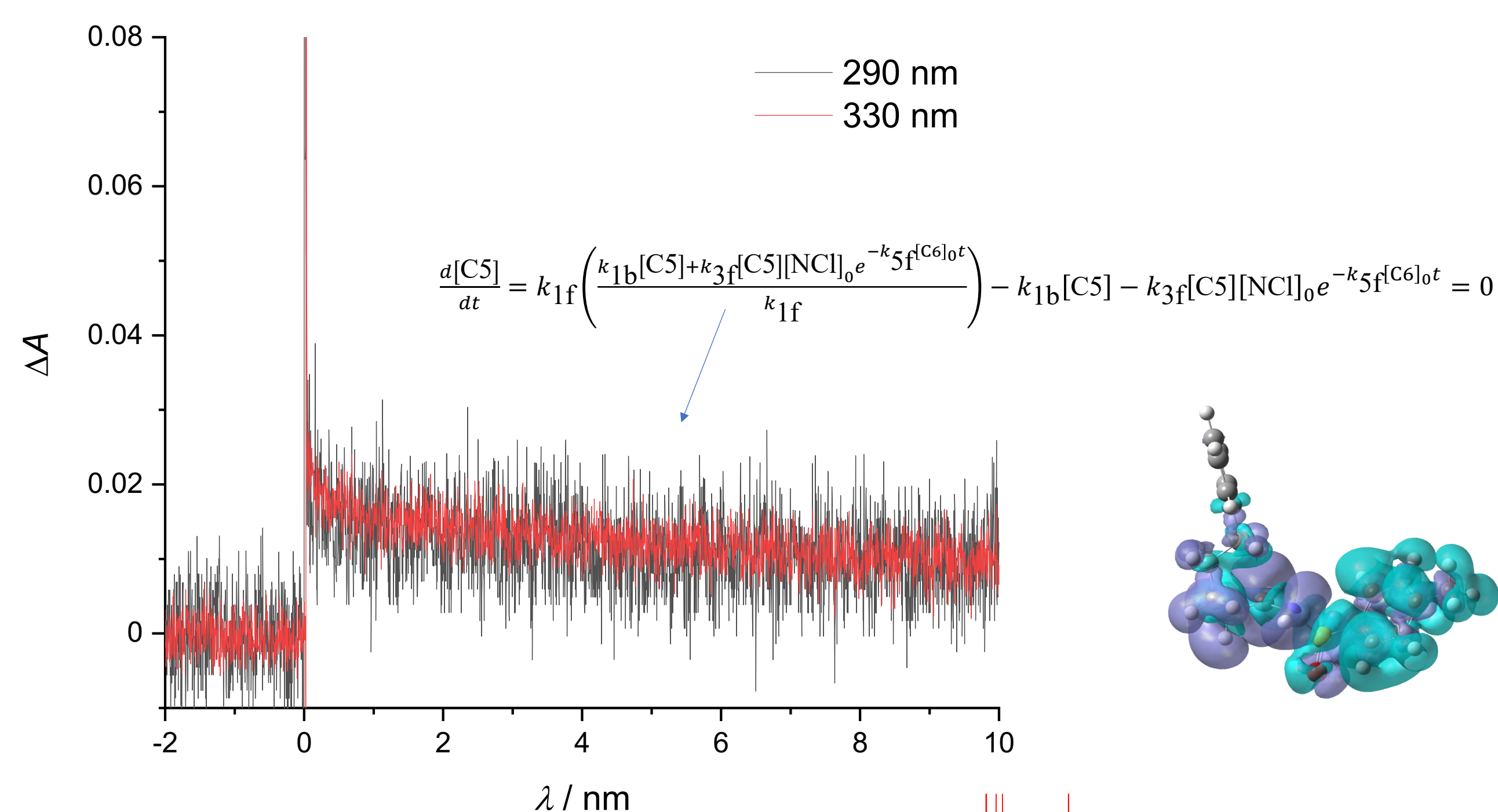
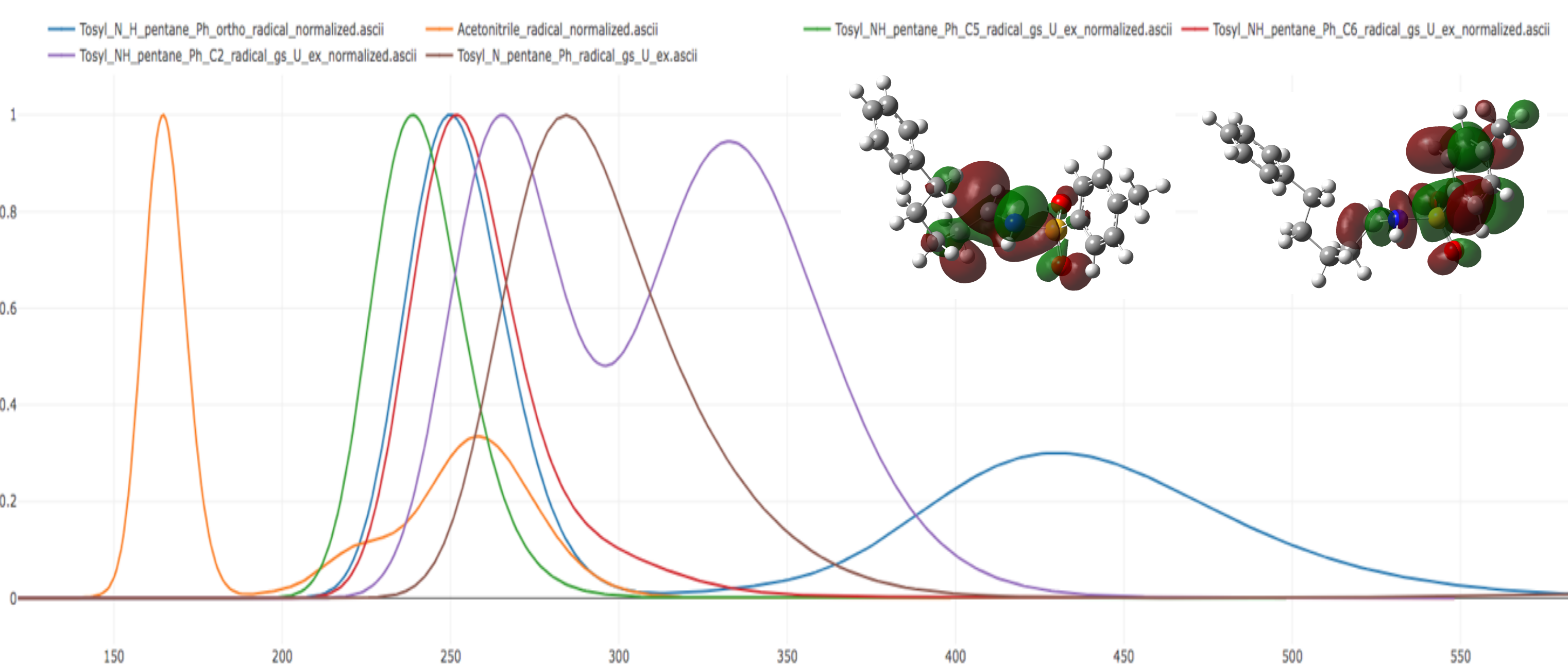
$$[\text{product}](t) = c_{\text{max}}(\text{product}) \left(1 - e^{-k_5 f[\text{C}_6]_0 t}\right)$$

- This pseudo-first-order approximation is in a good accordance with the experimental data from pulse photolysis, where C<sub>6</sub>Cl product accounts for over 99% of the total yield, highlighting the kinetic control of the reaction.

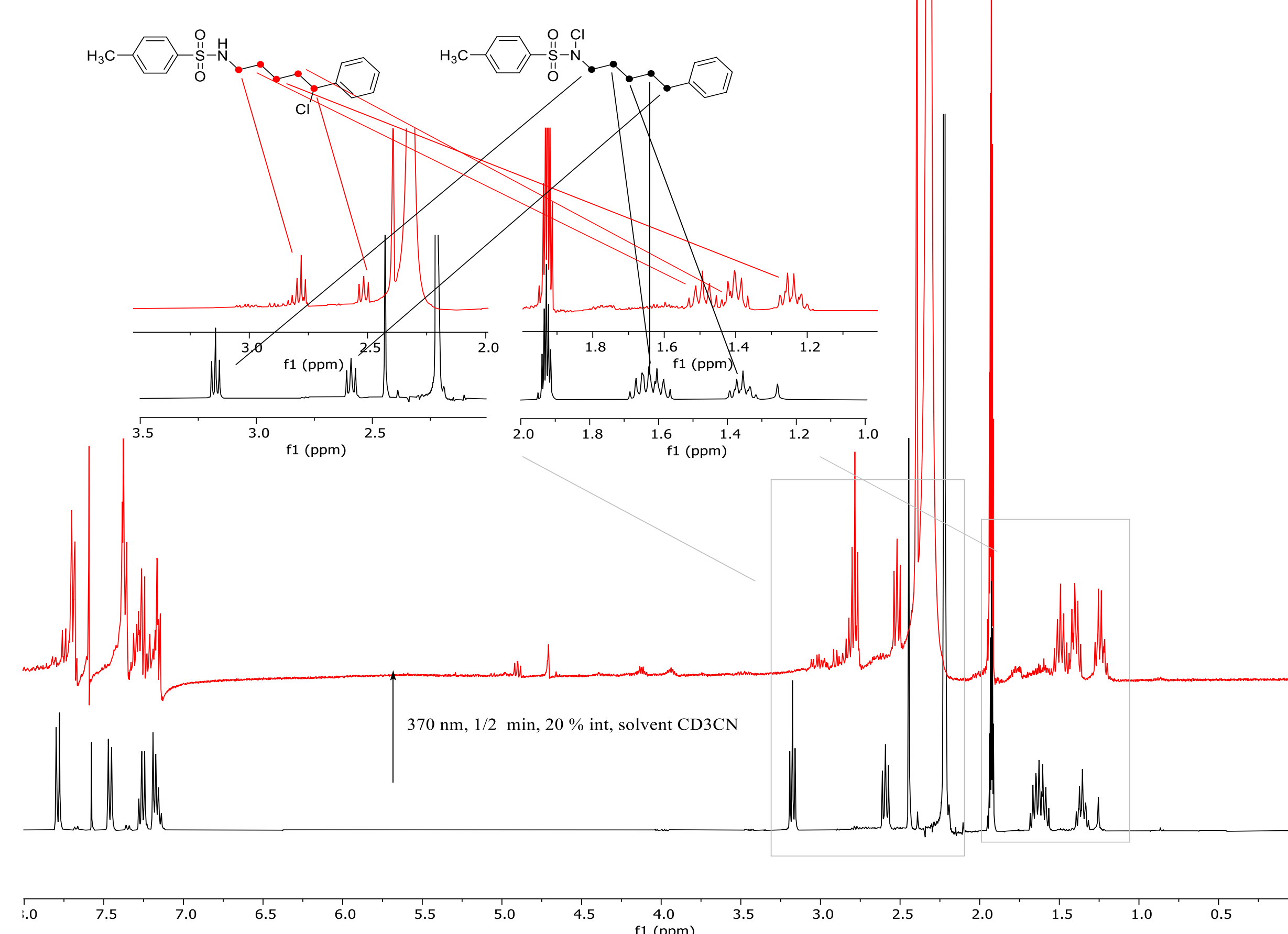
## LFP experiments



## UV calculations



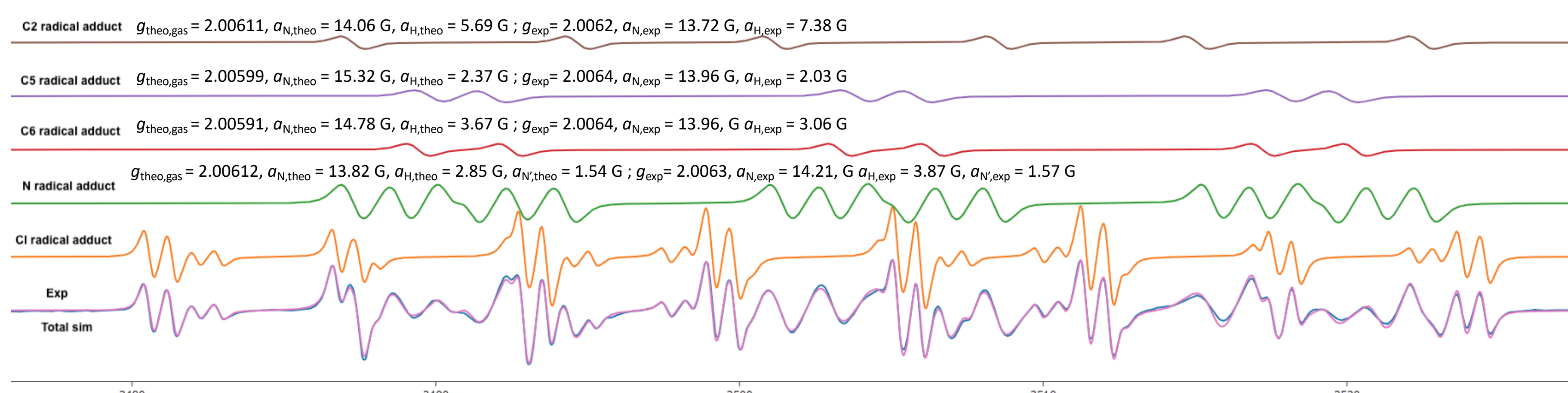
## NMR experiments



## Materials and methods

- Laser flash photolysis**
- Varian UV/VIS spectrophotometer Cary 4000
- Nanosecond pulsed Nd:YAG laser (Quantel, Q-smart 450, pulse duration 6 ns, pulsing 10 Hz, maximum energy up to 450 mJ at 1064 nm) with other excitation wavelengths of 532 nm, 355 nm and 266 nm.
- Detection via spectrometer (LP980, Edinburgh Instruments) with xenon lamp and a halogen lamp as radiation sources, a monochromator and a photomultiplier detector.
- Nuclear magnetic resonance**
- Varian Inova 400 NMR spectrometer.
- Probe: Varian OneNMR Probe, 1H-19F/15N-31P Z PFG for direct and indirect detection (-80 to 130°C)
- Electronic paramagnetic resonance**
- ELEXSYS E 500 EPR X-band spectrometer (Electron paramagnetic spectrometer)
- Spin trap, PBN, N-tert-butyl-α-phenylnitron
- Calculations**
- GaussView, IQmol
- Gaussian 16 opt+freq @B3LYP/6-31G(d)//RO-B2PLYPD3/ G3MP2-large
- EPR calculations: B3LYP/EPR-III(CHO)/def2-QZVP(S)/6-31G(d)(N)
- UV calculations: TD DFT @CAM-B3LYP/TZVP
- Klaster Supek @SRCE
- Klaster Padobran @SRCE
- Klaster sw.pharma.hr, FarmInova @FBF

## EPR experiments



## Conclusion

- LFP allowed observation of N and C<sub>6</sub> radical intermediates in acetonitrile.
- EPR allowed detection of all radical intermediates involved in toluene and n-heptane.
- NMR experiments confirmed one major product in deuterated acetonitrile and deuterated chloroform.
- DFT calculations explain and confirm these experimental results.
- A kinetic model of this reaction is derived based on these calculations and experiments.

## References

- T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, and S. W. Kraska, *Chem. Soc. Rev.*, **2016**, *45*, 546.
- G. Zubčić, J. You, F. L. Zott, S. S. Ashirbaev, M. Kolympani Marković, E. Bešić, V. Vrček, H. Zipse, and D. Šakić, *J. Phys. Chem. A*, **2024**, *128*, 2574.
- L. R. Reddy, B. V. S. Reddy, and E. J. Corey, *Org. Lett.*, **2006**, *8*, 2819.
- M. A. Short, J. M. Blackburn, and J. L. Roizen, *Synlett*, **2020**, *31*, 102.
- H. Zhang and K. Muñiz, *ACS Catal.*, **2017**, *7*, 4122.

