

Poly(2-alkyloxazoline)s (PAOx)

High synthetic versatility
Biocompatible

→ highly functional (biocompatible) materials can be created

Why π -bonds ?

→ Facile post-functionalization:

to introduce 'new' functional groups via click chemistry:

- Radical thiol-ene and -yne additions
- Copper catalyzed azide-alkyne cycloaddition

Cross linking to produce cross-linked micelles and hydrogels via e.g. bifunctional thiols

Cationic ring-opening polymerization (CROP): propagation reaction

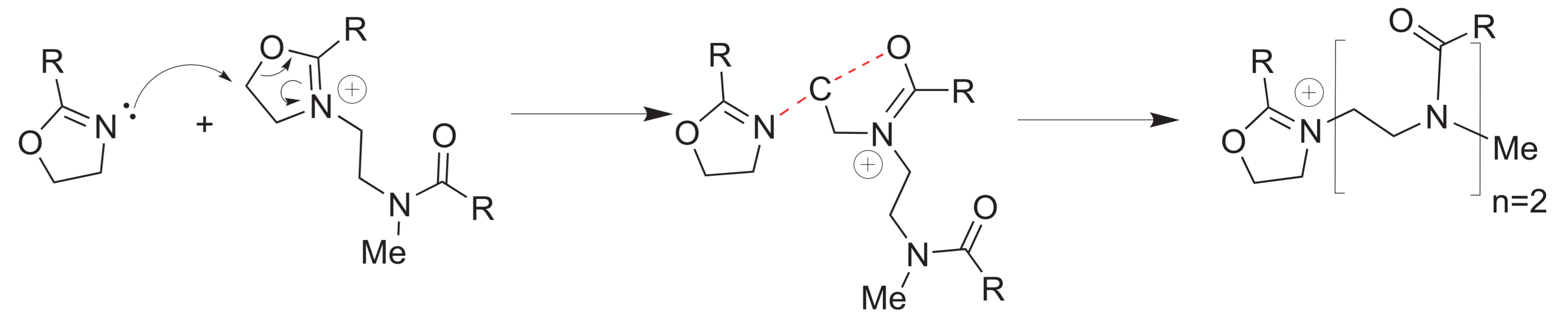


Figure 1: the propagation reaction for the cationic ring-opening polymerization of alkyl-2-oxazolines with an S_N2 -like transition state.

Controlling factors:

- Steric effects
- Electronic effects: Inductive/mesomeric effects of R chain

↔ Previous work:

dipole-cation interactions increase the polymerization rate¹

what about π -cation interactions?

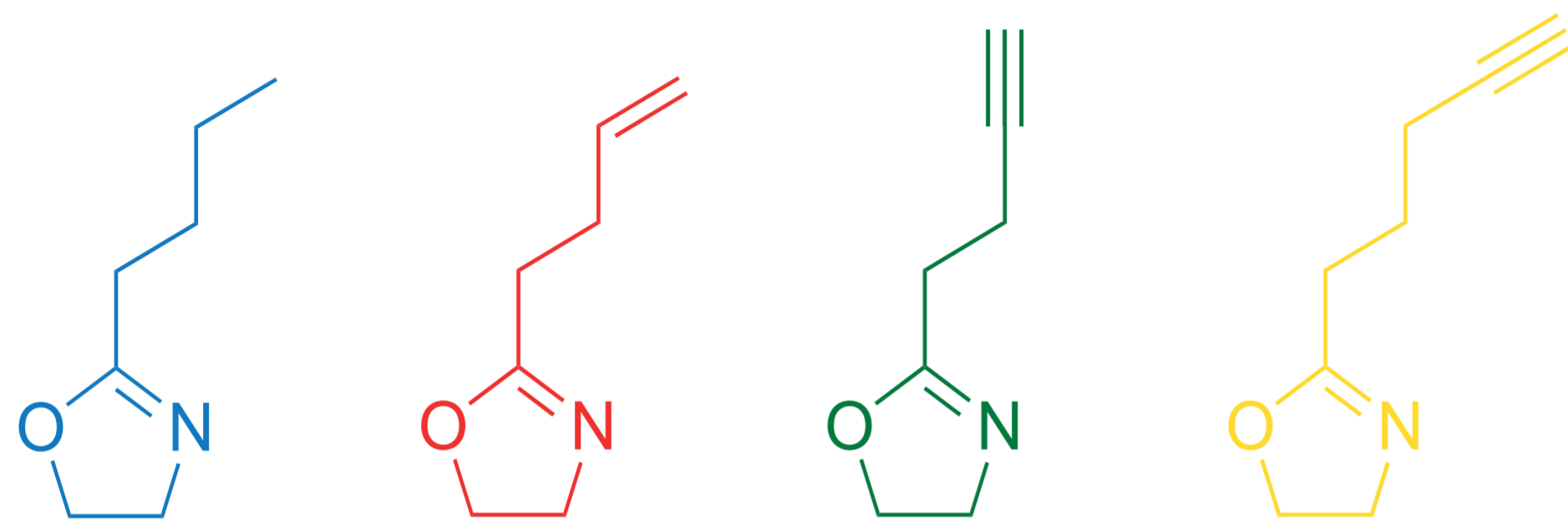


Figure 2: Investigated alkyl-2-oxazolines: *n*-Butyl-2-Oxazoline (*n*-ButyOx, blue), Butenyl-2-Oxazoline (ButenOx, red), Butynyl-2-Oxazoline (ButynOx, green), Pentynyl-2-Oxazoline (PentynOx, yellow).

Proposals

- π -cation interaction have a rate-enhancing effect
- increase in the degree of unsaturation has a rate-enhancing effect
- a proximity effect of the unsaturation should occur with a shorter sidechain length enhancing the polymerization rate

Computational results

Question 1: Are cation- π interactions present?

Question 2: What is the influence on the activation barriers?

→ Advanced MD to circumvent large number of degrees of freedom

Question 3: What interactions are controlling the TS-region?

Question 4: Do experiments confirm our observations?

Answer 2: Umbrella sampling results

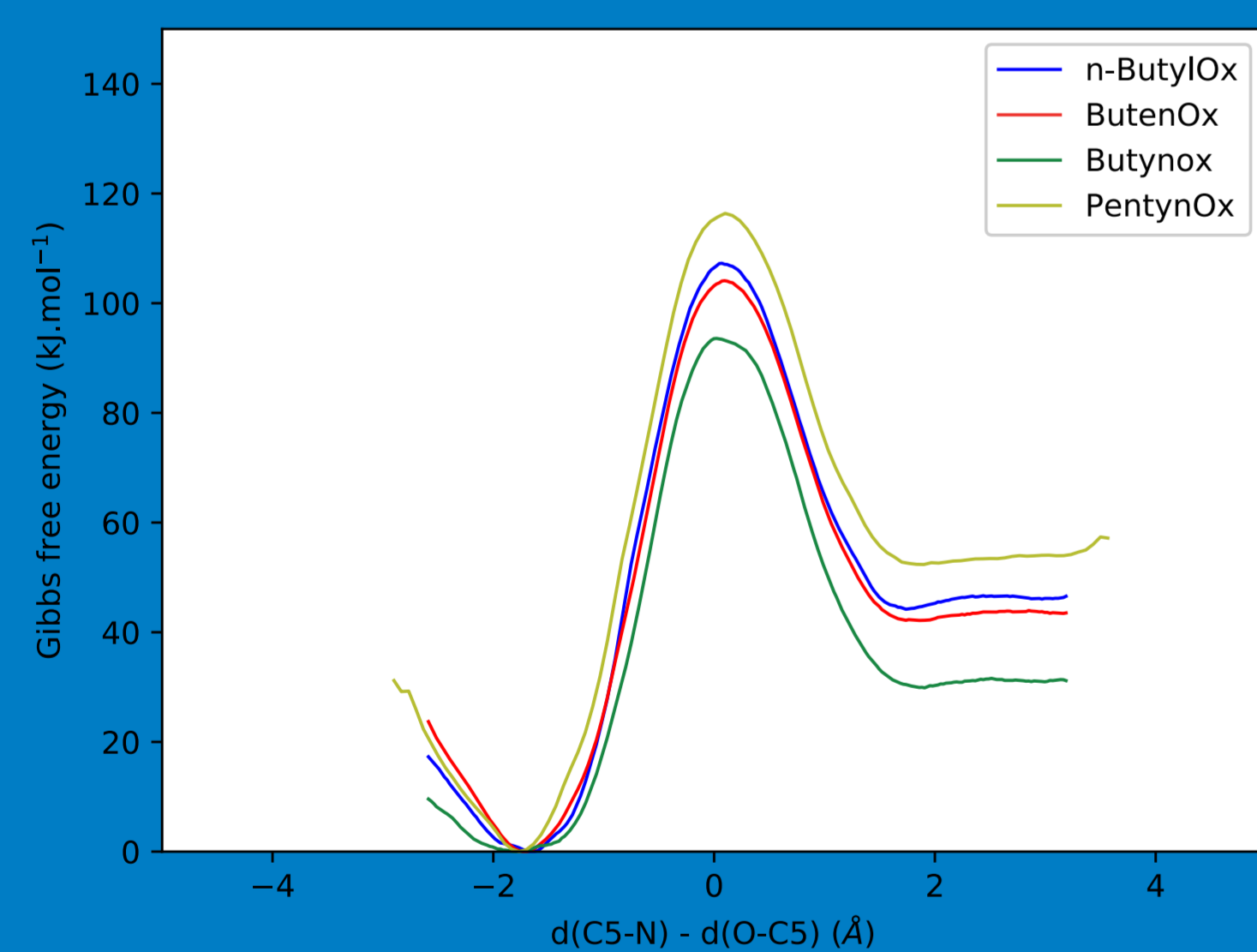


Figure 3: Free energy profiles for the second propagation reaction of the systems under investigation. Forward activation barriers for *n*-ButyOx, ButenOx, ButynOx and PentynOx are 66, 65, 67 and 68 kJ.mol⁻¹ respectively. (BLYP-D3 with TZVP-GTH basis sets, NVT, 413K)

Answer 1: Molecular dynamics results

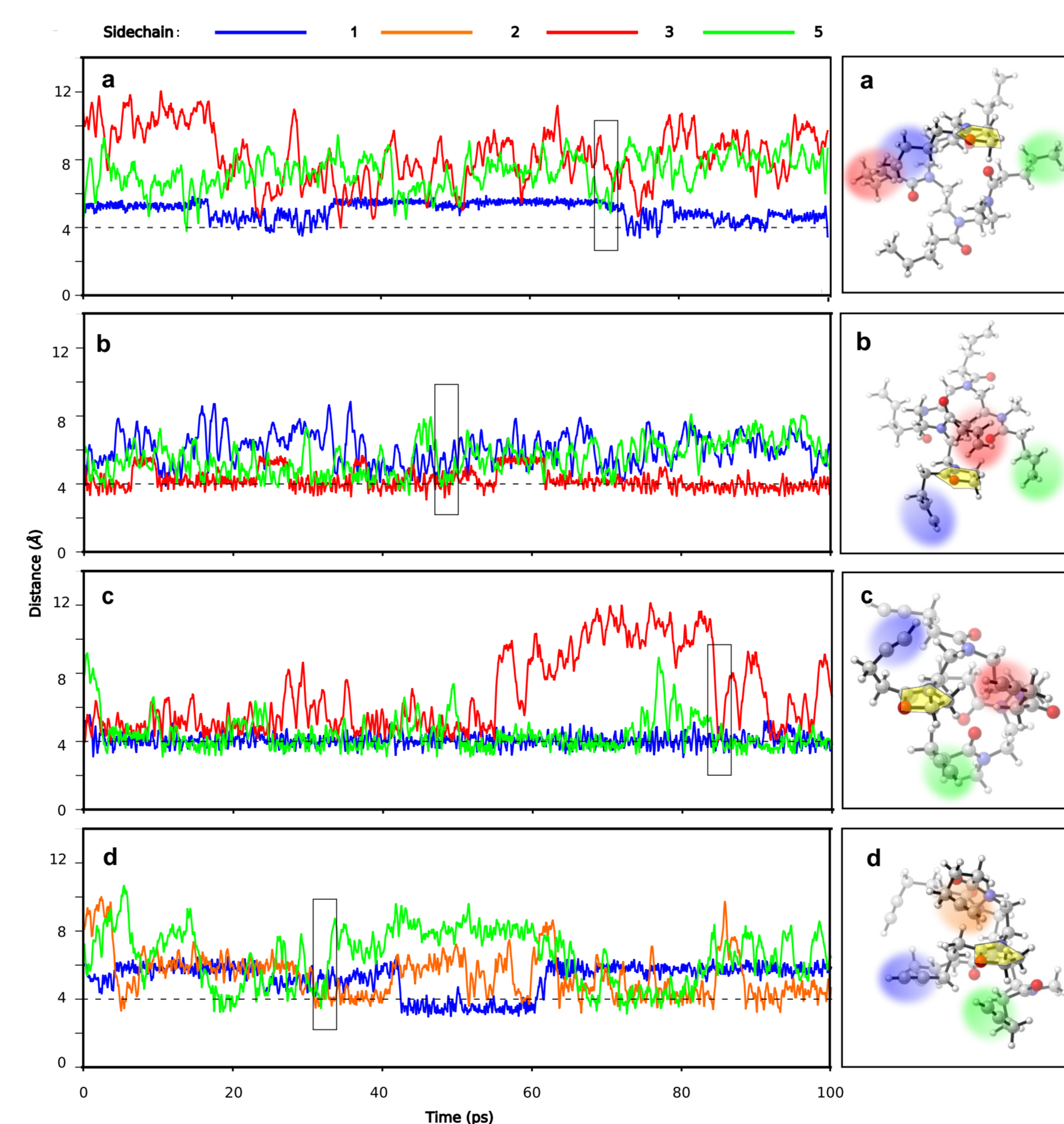


Figure 4: *ab initio* Molecular dynamics simulations for a pentameric polymer of *n*-ButyOx (a), ButenOx (b), ButynOx (c) and PentynOx (d), snapshots are shown with representative cation- π interactions between the sidechains and the oxazolinium. Y-axis: Distance between oxazolinium center (yellow) and the center of the penultimate sidechain bonds. Time (% of total simulation time (3 x 100ps)) at least one sidechain is interacting: **0% a**, 85.1 % **b**, 99.5 % **c**, 75.1 % **d**. (BLYP-D3 with TZVP-GTH basis sets, NVT, 413K)

Answer 3: Governing interaction in TS region using NCIPLOT

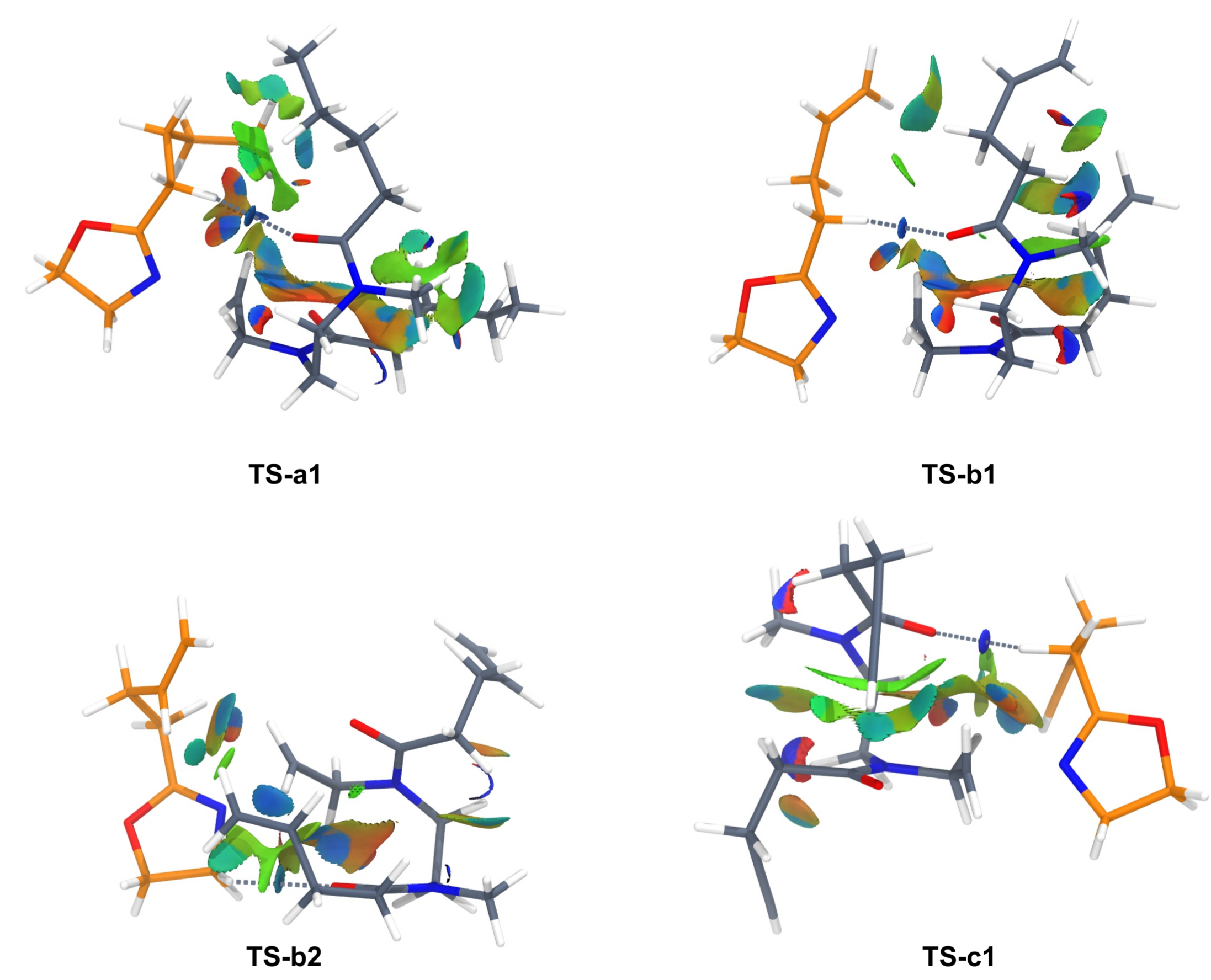


Figure 5: Static post-analysis to understand the controlling non-covalent interactions governing the transition states (TSs) using the NCIPLOT. Most stable TSs are shown for *n*-ButyOx (TS-a1), ButenOx (TS-b1 and TS-b2) and ButynOx (TS-c1). Blue surfaces are stabilizing, red surfaces are steric hindrance and green are weak dispersion interactions, attacking monomers are displayed in orange. (B3LYP-D3/6-311+G(d,p)) One can distinguish, CH- π (between sidechains), cation- π (with both amide and penultimate bonds), hydrogen bonding (between attacking monomer and growing dimer) and Van der Waals interactions

Answer 4: Experimental results

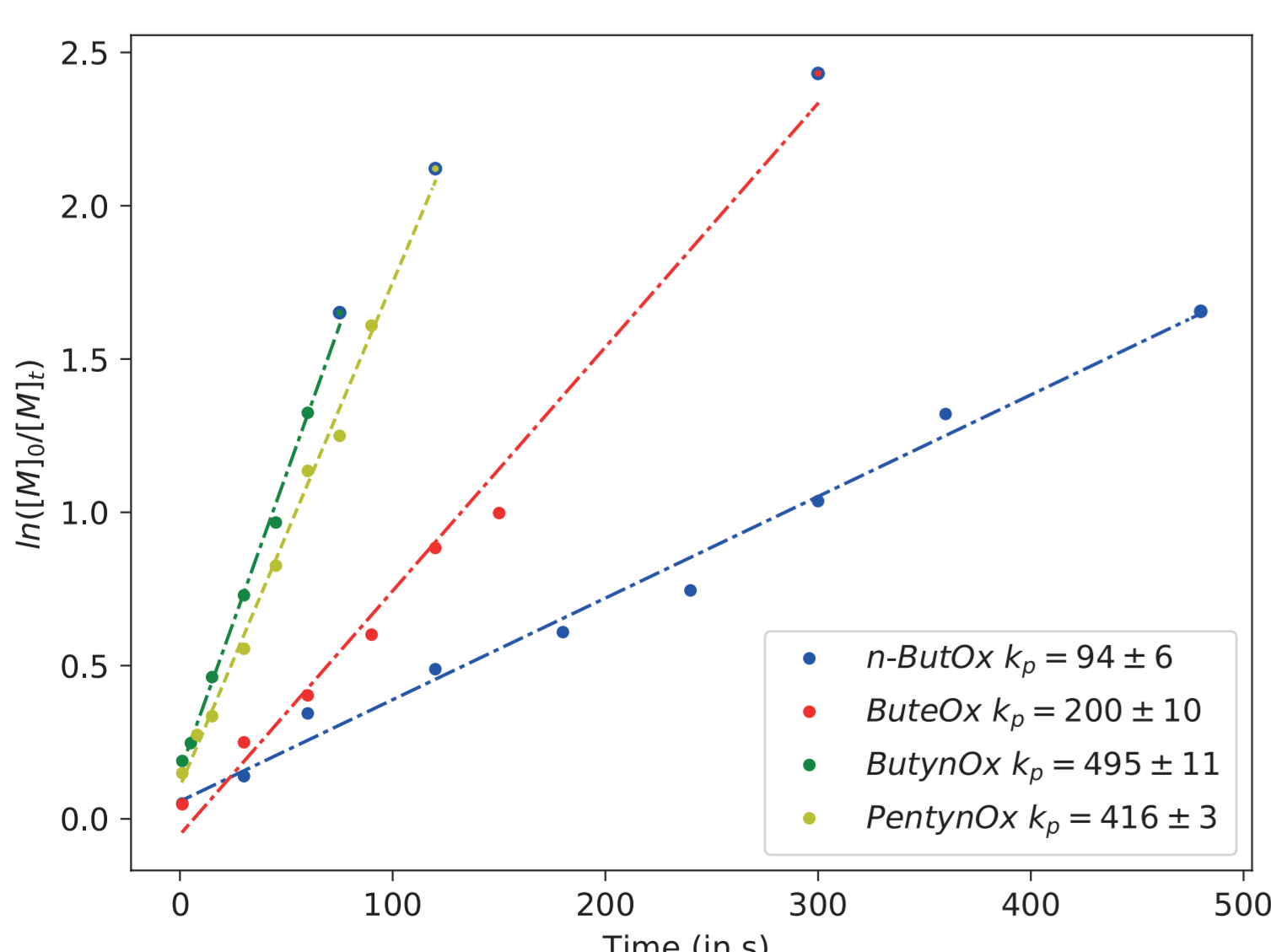


Figure 6: Polymerization kinetics of *n*-ButOx, ButenOx, ButynOx and PentynOx. The k_p 's are given in 10³ L.mol⁻¹.s⁻¹

Conclusion

- Cation- π interactions are present in pentamers of the relevant systems
- Activation barriers show very limited influence of the π -bonds.
- Thorough analysis of the interactions governing the transition states, show far more complex interaction patterns as first expected.
 - Next to cation- π interactions, π - π , C-H... π , cation-dipole are also stabilizing the transition states.
- Degree of unsaturation has influence on type, strength and time of the interactions.
- A proximity effect is indeed observed, as an increase in chainlength lowers the time one of π -bonds interacts with the oxazolinium.
- Experiments confirm the relatively limited effect of π -bonds on the rate constant.
 - Additionally, in accordance with computations, a proximity - and degree of unsaturation effect is observed.

References:

- 1) Bouten, P. J. M.; Hertsen, D.; Vergaelen, M.; Monnery, B. D.; Boerman, M. A.; Goossens, H.; Catak, S.; Van Hest, J. C. M.; Speybroeck, V. Van; Hoogenboom, R. *Polym. Chem.* 2014, 6, 514–518.; Bouten, P. J. M.; Hertsen, D.; Vergaelen, M.; Monnery, B. D.; Catak, S.; van Hest, J. C. M.; Van Speybroeck, V.; Hoogenboom, R. *J. Polym. Sci. Part A Polym. Chem.* 2015, 53 (22), 2649–2661.
- 2) Contreras-Garcia, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J.-P.; Beratan, D. N.; Yang, W. J. *Chem. Theory Comput.* 2011, 7 (3), 625–632.