

The CROP reaction of 2-oxazolines in silico

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Poly(2-oxazolines) are biocompatible pseudopeptides whose properties can easily be tuned. These polyamides are synthesized by cationic ring-opening polymerization (CROP) of various monomers, yielding polymers with distinct properties. Moreover, different properties can be obtained by chemical functionalization of the side chain of these polymers post-polymerization. Because of their versatility and biocompatibility, poly(2-oxazolines) are candidates for drug-delivery systems.

The experimental kinetics of the CROP reaction are determined by the choice of the monomer, although this influence is often hard to predict. Therefore, we have performed theoretical calculations in order to elucidate the factors governing this polymerization. Understanding these factors is a crucial step in the development of poly(2-oxazoline)s as drug-delivery systems.

A simple electrostatic model was developed in which the nucleophilicity of the oxazoline monomer and the electrophilicity of the oxazolinium chain correlate with homo- and copolymerization rates. For homopolymerizations, both the reactivity of the monomer and the chain, *i.e.* the electro- and nucleophilicity, contribute to the reaction rate. For copolymerizations, however, multiple monomers compete for the same chain end and the reactivity of different monomers determines the incorporation rate. This conceptual model was used to rationalize the polymerization rate differences of several propyloxazolines [1] as well as oxazolines bearing methyl ester groups. [2, 3] Currently, several alkenyl and alkynyl side chains are being investigated. In the next step, larger systems will be built to take into account the effect of the solvent and supramolecular interactions.

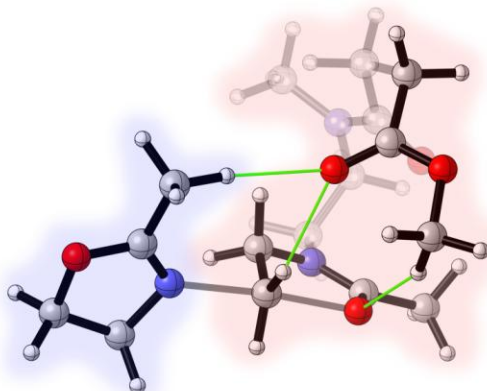


Figure: Stabilizing interactions during the CROP synthesis of 2-methylcarboxyethyl-2-oxazoline (MestOx)

- [1] Goossens, H.; Catak, S.; Glassner, M.; de la Rosa, V. R.; Monnery, B. D.; De Proft, F.; Van Speybroeck, V.; Hoogenboom, R. *ACS Macro Lett* **2013**, 2(8), 651-654.
- [2] Bouten, P.J.; Hertsen, D.; Vergaelen, M.; Monnery, B.D.; Boerman, M.A.; Goossens, H.; Catak, S.; van Hest, J.C.; Van Speybroeck, V.; Hoogenboom, R. *Polym. Chem.* **2015**, 6(4), 554-518.
- [3] Bouten, P.J.; Hertsen, D.; Vergaelen, M.; Monnery, B.D.; Catak, S.; van Hest, J.; Van Speybroeck, V.; Hoogenboom, R. *J. Polym. Sci. A Polym. Chem.* **2015**, 53(22), 2649-2661.