Theoretical Rationalization of the Propagation Rate Order of 2-Methyl-2-oxazoline and a Methyl Ester Functionalized 2-Oxazoline in Cationic Ring-opening Polymerizations

Dietmar Hertsen,[a)] Saron Catak,[a,b)] Hannelore Goossens,[a)] Petra JM Bouten,[c)]
Bryn D Monnery,[c)] Veronique Van Speybroeck,[a)] Richard Hoogenboom [c)]
a) Center for Molecular Modeling (CMM), Ghent University, Technologiepark 903, Zwijnaarde 9052, 9000 G hent, Belgium; b) Bogazici University, Department of Chemistry, Bebek 34342 Istanbul, Turkey Address; c) Supramolecular Chemistry Group, Department of Organic and Macromolecular Chemistry, Ghent University, Krijgslaan 281 S4, 9000 Ghent, Belgium

Poly(2-oxazoline)s (POxs) are an interesting class of biocompatible polyamides whose physical and chemical properties can easily be tuned. These polymers are readily synthesized via cationic ring-opening polymerization (CROP) of various monomers, yielding polymers with distinct properties. The characteristics of the resulting pseudo-polypeptides can be altered even further by chemical functionalization of the residue side chains. Because of their versatility and biocompatibility, poly(2-oxazoline)s are candidate drug-delivery systems.

The CROP propagation step of 2-methoxycarbonylethyl-2-oxazoline (MestOx) was shown to be faster than the incorporation of 2-methyl-2-oxazoline (MeOx) during homopolymerizations. However, the copolymerization of both monomers revealed an increase of the MeOx propagation rate and decrease in MestOx polymerization rate, leading to a rate order inversion. This remarkable behavior was investigated by means of Density Functional Theory (DFT) calculations.

The presence of nearby MestOx residues in the growing polymer chain close to the cationic reactive center was shown to stabilize the propagation transition state (Figure 1). This explains the faster MestOx homopolymerization and the MeOx rate increase in the copolymerization. The specific interactions between the MestOx residue and the monomer were characterized by Natural Bond Orbital (NBO) interaction energies and Hirshfeld-I (HI) charges. The nucleophilicity of the monomer was increased in the pre-reactive complex due to these reactions. Furthermore, it is indicated that isolated MeOx monomers are more nucleophilic than MestOx monomers, supporting the inversed rate order in the copolymerization.

In conclusion, stabilization of the propagation transition state by interactions between nearby MestOx residues and the monomer, and the higher nucleophilicity of MeOx explain the experimentally observed homo- and copolymerization rate order.

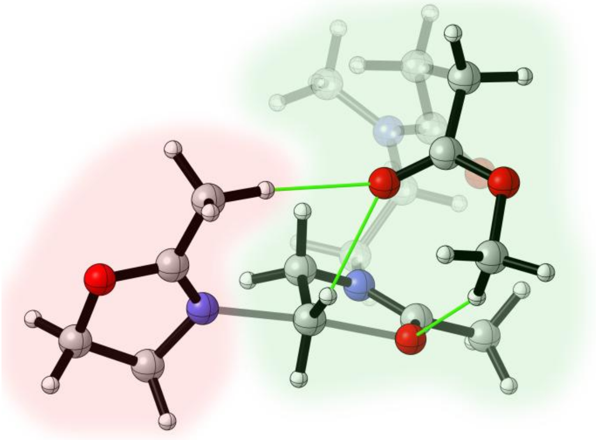

Figure 1. Transition state structure of the incorporation of a MeOx monomer (red) in a MestOx-MeOx$^+$ chain (green)