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Adenine as an organocatalyst for the ring-opening polymerization of lactide: scope, mechanism and access to adenine-functionalized polylactide†

Guilherme Nogueira,[ab] Audrey Favrelle,[a] Marc Bria,[c] João P. Prates Ramalho,[d] Paulo J. Mendes,[d] Andreia Valente[b] and Philippe Zinck*[a]

Nucleobase-functionalized polymers are widely used in the fields of supramolecular chemistry and self-assembly, and their development for biomedical applications is also an area of interest. They are usually synthesized by tedious multistep procedures. In this study, we assess adenine as an organoinitiator/organocatalyst for the ring-opening polymerization of lactide. L-Lactide can be quantitatively polymerized in the presence of adenine. Reaction conditions involving short reaction times and relatively low temperatures enable the access to adenine end-capped polylactide in a simple one-step procedure, in bulk, without additional catalyst. DFT calculations show that the polymerization occurs *via* hydrogen bond catalysis. The mechanism involves (i) a hydrogen bond between the NH9 of adenine and the carbonyl moiety of lactide, leading to an electron deficient carbon atom, and (ii) a second hydrogen bond between the N3 of adenine and the NH_2 of a second adenine molecule, followed by a nucleophilic attack of the latter activated amine on the former electron deficient carbon on the monomer. For longer reaction times and higher temperatures, macrocyclic species are formed, and a mechanism involving the imidazole ring of adenine is proposed based on literature studies. Depending on the reaction conditions, adenine can thus be considered as an organoinitiator or an organocatalyst for the ring-opening polymerization of lactide.

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Introduction

The use of organic molecules as catalysts for the ring-opening polymerization of cyclic esters and carbonates has gained much interest these past years.[1–5] Of particular interest is the functionalization of biocompatible aliphatic polyesters *via* organocatalysis, as this leads to macromolecular objects of interest for biomedical applications that do not contain any metallic traces. Monosaccharide[6–10] and cyclodextrin[8–13] end-capped polylactides and polylactones, together with other kinds of star-shaped polyesters,[14] were synthesized *via* organocatalysis. The use of a molecule of biological interest as an organoinitiator, *i.e.* a molecule able to initiate the ring-opening polymerization of cyclic esters without any cocatalyst, is even more interesting, as the resulting material will not contain any catalytic residue. Cyclodextrins, for example, were reported to initiate the ring-opening oligomerization of lactones[15–17] and lactides[18] without additional catalysts. Amino acids were also reported as organoinitiators for the polymerization of cyclic esters. L-Arginine and L-citrulline were reported to initiate the ring-opening polymerization of ε-caprolactone and L-lactide at 160 °C, yielding the resulting end-capped polyester.[19]

Nucleobase-functionalized polymers have been widely used in the field of supramolecular chemistry for accessing complementary hydrogen-bonding self-assembly polymers, having various applications, notably in the biomedical field.[20] These biological molecules are usually derivatized and then introduced in the polymer backbone through direct polymerization, acting as the monomer[21–23] or the initiator,[24,25] or by post-functionalization[26–30] of the polymer backbone. The synthesis of (adenine and uracil)-functionalized poly(ε-caprolactone) was for example reported by combining ring-opening polymerization and Michael addition.[24] The adenine molecule (Scheme 1) was derivatized by the heterocyclic secondary amine group (NH9) and used as the initiator of the polymerization along with

[a] Unité de Catalyse et Chimie du Solide (UCCS), UMR CNRS 8181, ENSCL, Université de Lille, F-59000 Lille, France. E-mail: philippe.zinck@univ-lille1.fr
[b] Centro de Química Estrutural, Faculdade de Ciências da Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal
[c] Centre Commun de Mesure RMN, Université de Lille, F-59000 Lille, France
[d] Departamento de Química and Centro de Química de Évora, Escola de Ciências e Tecnologia, Universidade de Évora, Rua Romão Ramalho, 59, 7000-671 Évora, Portugal

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