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Implementation of metal-free ring-opening polymerization in the preparation of aliphatic polycarbonate materials

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ABSTRACT

Environmental concerns along with the need to develop aliphatic polycarbonate materials free of any toxic compounds have driven scientists to implement macromolecular engineering processes by replacing potentially toxic and carcinogenic metal-based catalysts traditionally used for the ring-opening polymerization of cyclic carbonates by organic compounds. This issue is of particular importance as aliphatic polycarbonates are gaining increasing credibility for biomedical applications owing to their biocompatibility and bioresorbability. This review provides a complete account of the various metal-free catalysts that has been developed so far as well as comprehensive investigations on the related polymerization mechanisms.

Contents

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1. Introduction

The development of polymeric materials that possess desirable physicochemical properties but also answer environmental concerns are required to realize a new generation of materials that can be valorized in added-value applications such as micro-electronics, medicine, coatings and adhesives amongst others. In this context, aliphatic polycarbonates (APCs) are gaining increasing attention over the last decade owing to their biodegradability, non-toxicity and *in vivo* bioresorbability [1], making them very suitable materials for green technologies and biomedical applications (scaffolds for tissue engineering or drug carriers) [2]. While polyesters hold a leading status as synthetic polymers in the biomedical field, APCs offer many advantages on account of their relatively low degradation rate in water, their more amorphous nature and the ease to introduce lateral (reactive) functionality. Moreover, *in vivo* application of APCs is also strongly motivated by the absence of an acidic microenvironment being generated in the surrounding tissue upon degradation, unlike that generated by polyester degradation [3–7]. In turn, erasing this side effect prevents a local aseptic inflammation response and deactivation/denaturation of loaded drugs such as proteins or plasmid DNA, and justifies the recent commercialization and clinical use of APCs.

APCs can be synthesized by three distinct methods: (1) polycondensation, (2) copolymerization of carbon dioxide with epoxides and (3) ring-opening polymerization of cyclic carbonate monomers. Polycondensation between alkanediols with phosgene, triphosgene or dialkylcarbonates is the process currently applied industrially for the production of aliphatic polycarbonates [8]. However, since phosgene derivatives have disadvantageous toxicological effects, many attempts to produce aliphatic polycarbonates in a safer and greener way are still under investigation. While benefits of a CO_2-consuming process are obvious from an ecological viewpoint, the up-scaled synthetic applicability of the copolymerization of CO_2 with epoxide is hampered by the release of 5-membered cyclic side-products, ether linkage formation and the need of air-sensitive catalysts [9–11]. While significant advances have been made in this field, including the report of a metal-free copolymerization of CO_2 with epoxide had been referred in the literature [12], ring-opening polymerization (ROP) is by far the preferred mechanism for APC synthesis on account of its versatility and the mild reaction conditions required. From the preliminary works by Carothers on the thermally induced ROP of trimethylene carbonate (TMC) [13,14], many ring-opening processes have been developed and classified by mechanism of action such as anionic [15–17], cationic [18–21] and coordination–insertion [22–28] processes. Beyond the fact that ionic routes require anhydrous conditions and highly pure monomers, several side reactions arising from the mechanisms themself have limited the extent of cyclic carbonate ROP. These side reactions include: ether link formation that arises from decarboxylation and cyclic polymer/oligomer impurities or large discrepancies between theoretical and experimental molecular weights which arise from back-biting reactions. While research has been conducted with the goal to limit the extent of these side-reactions [21,22,29,30], the use of metal-based catalysts remains a safety concern as their complete removal is still challenging.

In the recent years, development of green catalysts for the ROP of lactones and cyclic carbonates has been spawned by the will to revolutionize polymer chemistry together with the need to answer to biomedical and environmental concerns. In this context, both enzymes [31–33] and metal-free catalysts [34–38] have been successfully applied to the ROP of lactones and cyclic carbonates. Some of these catalytic species were found to be particularly advantageous for the ROP of six-membered carbonates such as TMC and were readily extended to the ROP of other functional cyclic carbonates, allowing the synthesis of various polymer topologies for diverse targeted applications. Recent advances in the design of functional cyclic carbonates [2,39–42] have provided an additional impetus to promote the development of metal-free processes to further broaden the application of APCs in biomedicine. Indeed, functional groups introduced to the polymer side chains are usually responsible for material biocompatibility and enable the ready manipulation of the macroscopic properties such as hydrophilicity/hydrophobicity, membrane permeability, bioadhesive ability, and biodegradability of the resultant polymers. Current applications of this metal-free ROP approach to functional cyclic carbonates have paved to way to the use of functional APCs as drug carriers for gene [43,44] or cancer drug delivery [45,46], heavy metal ion capture [47] and antifouling surfaces [48–50].

In line with the growing interest in APCs for biological and environmental applications, this review surveys the up-to-date advances performed in the field of metal-free ring-opening (co) polymerization of cyclic carbonates using enzymes, Lewis and Brønsted acids and bases as well as their mechanistic investigations.

2. Metal-free ring-opening polymerization

2.1. Enzymatic ROP of cyclic carbonates

Enzymes were the first family of "environmentally friendly" catalysts that were exploited for the preparation of biodegradable polymers and quickly became a rapidly emerging synthetic tool in polymerization. In contrast to traditional chemical polymerization processes, enzyme-catalyzed polymerization offers several advantages as enzymes (1) operate under relatively mild reaction conditions, (2) are biocompatible meaning that the catalyst does not need to be removed from the resultant polymer, (3) can be recyclable, (4) can mediate ROP in bulk conditions hence eliminating the need for organic solvent and (5) are insensitive to many impurities in the monomer and hence eliminating the requirement for tedious monomer purification. Interest for using lipophilic enzymes was further motivated by their higher thermal stability, the solubility of a wide range of substrate types, and no requirement for pH adjustments throughout the reaction [51,52]. An *in vitro* enzyme-catalyzed reaction in organic solvent was first demonstrated through a transesterification reaction