SYNTHESIS OF BACTERIOSTATIC POLYLACTIDE BY USING ZIRCONIUM (IV) AND ZINC (II) CHELATE COMPLEXES WITH AMINO-ACIDS BASED LIGANDS

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Introduction

One of the big risks that may be overlooked in the current viral pandemic is the increase in disease caused by drug-resistant bacteria. Metal complexes (metallodrugs) look like an excellent alternative to classical antibiotics for treating diseases caused by bacteria [1]. Such a compound should demonstrate a strong antibacterial and antifungal activity on a large spectrum of microorganisms, and at the same time, low toxicity.
Compounds of this type are zinc and zirconium complexes containing ligands based on Schiff's bases. By appropriate selection of such a compound, it is possible to obtain metal complexes with bactericidal properties and being a good initiator of ROP. By using this kind of complex can allow to obtain biologically active biodegradable polymers with uniform morphology and containing an antibacterial complex in the ideal dispersed molecular form, which is practically impossible to obtain by blending bioactive substance in a high-molecular polymer.

Materials and Methods

Zinc (II) acetylacetonate monohydrate (Alfa Aesar, USA), Zirconium acetylacetonate L-tryptophan, L-phenylalanine, 4-pyridinecarboxaldehyde, methanol anhydrous 99.8%, benzene anhydrous 99.8%, chloroform anhydrous 99%, tetrahydrofuran anhydrous 99.9% was purchased from Sigma - Aldrich, Poland, and potassium hydroxide reagent grade was received from Merck. All these chemicals were used as received.
L-lactide (Forusorb, medical-grade) was received from Foryou Medical Device Co., Ltd. China and before use was purified by recrystallization from dry ethyl acetate.
Schiff base ligands HPhe and HTrp were synthesized using a previously reported method [2]. Zinc complexes; $Zn[(acac)(LPhe)H_2O]$, $Zn[(acac)(LTrp)H_2O]$ and Zircon complexes $Zr[(acac)_3(LPhe)]$, $Zr[(acac)_3(LPhe)]$ obtained by the method, was a modification of the previously published [3]. The lactide polymerization process was investigated under bulk conditions at 120°C with different contents of the zinc and zirconium initiators (M/I molar ratio as; 150:1, 400:1, and 600:1).
Estimation of the antibacterial and antifungal activities of the tested samples was done using a microtiter broth dilution method, as recommended by the Clinical and Laboratory Standards Institute [4]. In vitro cytocompatibility of polymeric materials and initiators was studied using the human normal CCD-11Lu fibroblast cell line (ATCC; CCL-202).
The conversion of the reaction and structure of obtained products was determined with NMR spectroscopy (Bruker Avance IITM 500 MHz at 25°C in DMSOd6).
The number-average and weight-average molar masses of the oligomers were determined by gel permeation chromatography with a Viscotek RImax chromatograph (Malvern Panalytical Ltd). FTIR spectra were recorded on JASCO FTIR-6700. The percentage of carbon, hydrogen, and nitrogen in the complex samples was determined by the VARIO EL III Element analyzer. All geometric structures of the zinc and zirconium complexes were fully optimized at the B3LYP/6-311G* density functional (DFT) level by using the Gaussian 03 Rev. E.01-SMP program [5].

Results and Discussion

Polylactide was obtained by ring-opening polymerization of lactide initiated with selected low-toxic zinc and zircon complexes $Zn[(acac)(L)H_2O]$ or $Zr[(acac)_3L]$ where L represents N-(pyridin-4-ylmethylene) tryptophan or N-(2-pyridin-4-ylethylidene) phenylalanine. These initiators were obtained by reaction of $Zn[(acac)_2H_2O]$ or $Zr(acac)_4$ with previously synthesized Schiff bases, the product of the condensation of amino acids and 4-pyridine carboxaldehyde. Both zinc complexes showed the geometry of a distorted trigonal bipyramid. Zirconium complexes presented a square antiprismatic form. Virtually all of these complexes as initiators of L-lactide polymerization showed high efficiency and made it possible to obtain high molecular weight polylactide. All these complexes were much more active in polymerization compared to the starting acetylacetonates. The synthesized high molecular polylactide (M/I molar ratio as 1:400) showed antibacterial properties, especially the product obtained by polymerization initiated by a zinc(II) complex with ligand-based on L-phenylalanine. The obtained polylactide quite unexpectedly showed a particularly strong antimicrobial effect against *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Aspergillus brasiliensis*. At the same time, this polymer shows biocompatibility, does not exhibit fibroblast cytotoxicity.

Conclusions

By using selected non-toxic zinc or zirconium complexes showing a strong antibacterial effect and being effective ROP initiators, it is possible to obtain bioresorbable polymers showing significant antibacterial and antifungal activity.

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