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Synthesis of Ferrocene-Functionalized Monomers for Biodegradable Polymer Formation

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Cyclic carbonate and δ-valerolactone substrates functionalized with ferrocene were synthesized via alkyne-azide "click" cycloaddition. The cyclic carbonates were polymerized using 1,8-diazabicycloundec-7-ene, 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea, and benzyl alcohol. The resulting polymers were characterized by GPC, NMR spectroscopy, and cyclic voltammetry studies. It was found that polycarbonate molecular weights fall in the range of 4.1 – 5.2 x 10^3 g/mol with polydispersities as low as 1.26. Electrochemistry studies allowed us to identify the monomer/polymer pair with the most desirable redox potentials for biological studies.

Introduction

Biodegradable and biocompatible polymers are finding more and more sophisticated applications in improving human health, ranging from the controlled release of active ingredients in drug delivery systems to tissue engineering and bone repair in surgery.[1-7] Although such polymers can be prepared from a variety of (natural) compounds according to specific synthetic routes, their formation by ring-opening polymerization of suitable cyclic monomers such as lactide, lactones, and cyclic carbonates is the preferred method since it offers good control of the resulting polymer structure. The choice of the repetitive unit(s) is important since it allows the modulation of the physico-chemical properties of the polymer, such as crystallinity, glass transition temperature, toughness, stiffness, adhesion, permeability, and degradability.[8-10]

Polymers containing ferrocene have been extensively researched due to potential materials properties,[11-14] but far less focus has been placed on the synthesis of biodegradable analogues.[15, 16] Ferrocene has already been utilized to increase the bioactivity of many pharmaceuticals, such as in the anticancer and antimalarial pharmaceutical drugs ferrocifen[17-19] and ferroquine.[20] With the abundance of biological activity attributed to the tunable redox couple of ferrocene,[21-23] functionalized biodegradable polymers have potential for application in medicinal chemistry by delivering ferrocene units to specific sites in the human body. However, only a few classes of biodegradable ferrocene-containing polymers are known[24-27] with only one class of polyesters being reported.[26, 27]

Biodegradable polymers with pendant functionalities have been well researched and used in numerous biological studies.[28-30] Previous approaches to ferrocene-functionalized biodegradable polymers utilized the synthesis of polyaspartamide bearing reactive amine functional groups, followed by the coupling of the side chain with a ferrocene carboxylic acid moiety (Chart 1)[31] or polycondensation between diol-terminated Schiff bases and 1,1'-ferrocenediyl diacid chlorides. To avoid difficulty with functionalization, we propose the use of the highly developed azide-alkyne "click" reaction to synthesize functionalized monomers for use in ring opening polymerization.[32-35] An improved route to functionalized polycarbonates utilized monomers derived from the commercially available 2,2-bis(methoxy)propionic acid (bis-MPA).[36, 37] In this paper, we employed the Huisgen alkyne-azide click reaction to functionalize δ-valerolactone and cyclic carbonates with ferrocene. We then used the novel monomers in ring opening polymerization and obtained ferrocene-functionalized biodegradable polymers.

Results and Discussion

Chart 1. Alkyne-functionalized carbonates 1-2 and lactone 3 and azidoferrocene precursors 4-6.

Synthesis and Characterization of Monomers. Nine novel ferrocene-functionalized monomers were prepared via click chemistry using 5-(propynyl)-1,3-dioxan-2-one (**1**), propargyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (**2**), and α-propargyl-δ-valerolactone (**3**) as alkynes (Chart 1). Cyclic carbonate **1** was prepared in only three steps from dimethyl malonate, while carbonate **2** was prepared by a protecting group strategy in five steps from 2,2-bis(methoxy)propionic acid (bis-MPA). δ-Valerolactone derivative **3** was synthesized in one step from its lactone precursor.[33] Compounds 1-methylazidoferrocene (**4**) and 1-azidoethylferrocene (**5**) were obtained in four and three steps, respectively, using known precursors,[38, 39] while 1-azidoferrocene (**6**) was prepared in two steps from ferrocene.[40]

Chart 2. Monomers M_1 to M_9 post azide-alkyne click reaction.

