Synthesis of Functionalized Polyphosphazenes for Vascular Tissue Engineering

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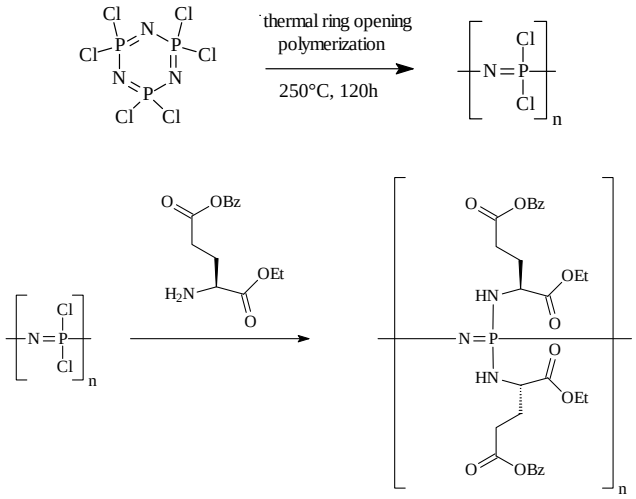
Introduction:

Three-dimensional (3D) scaffolds play an important role in the fabrication of vascular grafts for the treatment of diseases, such as atherosclerosis. Research to date has focused mainly on the development of biomaterials, such as natural and synthetic polymers[1, 2], as scaffolds for engineering blood vessels, although an ideal material has yet to be identified. Poly(amino acid ester)phosphazenes have been shown to biodegrade into neutral products[3], unlike the toxic acidic products formed by other materials.[2] Also, their degradation rates and mechanical properties can be tailored based on the choice of organic side chains bound to the phosphorus atoms of the polymer backbone.[3] This is useful in coordinating the rates of degradation of the polymer scaffolds to extracellular matrix growth in the neo tissue and matching the material properties of the polymers to the natural tissues, both of which are problematic with current materials. Therefore, the objective of this research is to develop functionalized poly(amino acid ester)phosphazenes that have the potential to overcome the biodegradability, mechanical properties, and cell interaction issues experienced with traditional materials.

Materials and Methods:

The synthesis of the poly[(amino acid ester)phosphazene]s used a previously developed method from Singh *et al.*[3] for the thermal ring opening polymerization of hexachlorocyclotriphosphazene to poly(dichlorophosphazene) and subsequent macromolecular substitution of amino acid esters for chloride on the polyphosphazene backbone (Scheme 1). The amino acid esters were reacted with the poly(dichlorophosphazene) with their side chains appropriately protected using standard peptide chemistry protecting groups, as is shown in Scheme 1 with the macromolecular substitution of a benzyl protected aspartic acid ethyl ester nucleophile for example.

Scheme 1. Reaction scheme of the polymerization and macromolecular substitution reactions



Results:

The polymerization method described by Singh *et al.*[3] involved heating flame-sealed Pyrex tubes of approximately 200g of starting material to 250°C for 120 hours, although pilot experimentation showed that these conditions were not suitable for small-scale (1 - 5g) polymerizations. Therefore, multiple polymerization experiments were performed and have allowed the optimization of reaction conditions for the small-scale polymerization of poly(dichlorophosphazene) and its purification. The starting materials and resulting polymers were analyzed by nuclear magnetic resonance (NMR) techniques. The thermal ring opening polymerization of the cyclic trimer (hexachlorocyclotriphosphazene) to the linear polymer (poly[dichlorophosphazene]) was characterized by a shift from +19.1 ppm to -19.2 ppm in the ^{31}P-NMR spectrum (see Figure 1). The substitution reactions of the amino acid esters (with protected side chains) were performed and analyzed using ^{1}H- and ^{31}P-NMR techniques.

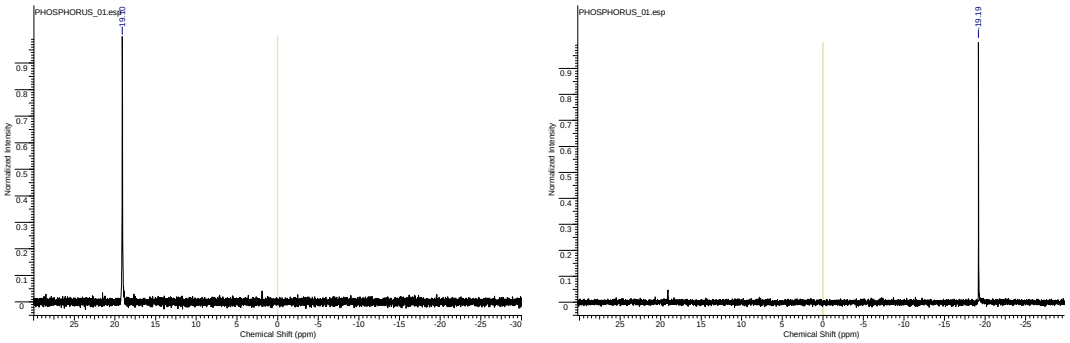


Figure 1. 31P-NMR of cyclic trimer (left) and linear polymer (right) after a thermal ring opening polymerization for 27 hours at 220°C (1g scale).

Discussion:

Since current biomaterials used in scaffold fabrication have their limitations, the development of alternative materials, such as polyphosphazenes, has become an important area of research. Functionalization of the polyphosphazene polymers will be investigated through deprotection and coupling of the amino acid side chains to biomolecules, such as growth factors and other proteins that are known to enhance cell adhesion and proliferation properties. Using the tunability of material properties of polyphosphazenes according to their side chains and functionalization with biomolecules, properly designed polyphosphazenes have the potential to solve the problems experienced with current scaffold materials.

References:

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