ing order: EDTA = NPA > IDA > NTA. According to eqs. (17) and (18), the values of $k_b/k_a$ and $k_a/k_b$ were evaluated (Table VI). The EDTA system showed the largest value of $k_b/k_a$. It confirmed that there involved significant oxidative termination in the EDTA system mentioned above.

In conclusion, the free radicals generated from the Co(IV) chelated complexes still possessed the chelating abilities with the cation. Therefore, the termination reactions induced by Co(IV) were more significant than the other Ce(IV) redox systems. Consequently, the molecular weight of polymer obtained was relatively small. The performances of the chelating agent redox initiators in the aqueous polymerizations of acrylamide varied with the nature of the chelating agent. The larger $K$ and $k_a$ values (such as EDTA) would not necessarily result in better performance of polymerization. The NTA system showed a promising polymerization rate and limiting conversion.

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REFERENCES AND NOTES


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COMMUNICATIONS

Synthesis and Characterization of Bio-compatible and Biodegradable Poly-ε-caprolactone-b-γ-Benzyglutamate) Diblock Copolymers

Keywords: biodegradability • biocompatibility • biomaterial poly(ε-caprolactone) • poly-γ-benzyl glutamate • block copolymer

INTRODUCTION

The successful block polymerization of a lactone or lactide and an amino acid might be major progress towards the preparation of biocompatible and biodegradable hydrogels and solvents. Since the 50's, some aliphatic polyesters, e.g., poly(e-caprolactone) (PCL), are well-known for their low toxicity and their hydrolytic and enzymatic biodegradability. Accordingly, the association of these polyesters to a polypeptide block would provide versatile original materials. Indeed, the rate of biodegradation and the amphiphilicity of such di- and tri-block copolymers might be controlled by the nature and composition of the two components.

The ring-opening polymerization of unsubstituted lactones as well as of amino acid-N-carboxy anhydrides (NCA) has proved very efficient to control the molecular characteristics and the end-functionalization of the related polysteres and polypeptides. Furthermore, NCA's are known to be polymerized by aliphatic primary amines in such a way that the initiator is attached to the growing chain and the propagation is living. α-Amino prepolymers (PA-NH₂) are thus potential macrorinitiators for the NCA's polymerization, which opens the way to P(α-amino) copolymers, where PA can be poly(methylmethacrylate), poly(lactide), polyethylene oxide, polystyrene, or polypropylene oxide. This communication reports the original preparation of completely biodegradable polypeptide-based block copolymers initiated by α-amino PCL.

RESULTS AND DISCUSSION

Functional aluminum alkoxides such as Bu₃Al—O—R—X (where X is a functional group) are effective initiators for the living polymerization of ε-caprolactones (ε-CL) and lactides leading to α,ω-hydroxy, ω-X chains. Although halogen atoms, tertiary amines, and double bonds (e.g., of the methacrylic type) have been successfully

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Figure 1. IR Spectrum of the copolymerization product (film).
used as the X functional group, a primary amino failed to provide the expected amino-terminated polyester. Indeed, dichloraluminum 3-amine, 1-propanol led to the formation of a,ω-hydroxy PCL. Recently, an alternative pathway using an alkylborane as the functional group led to the expected ω-NH₂ PCL. It was based on the conversion of the bromo end group into an amino group which was subsequently reduced into the primary amine [eq. (1)]:

\[
\begin{align*}
B-(CH₂O)n-Cl &+ \text{(metal)H₂} \rightarrow B-(CH₂O)n-\text{(metal)H} + \text{(metal)Cl} \\
\rightarrow &-\text{[C-(CH₂O)n-CH₂]-} + B-(CH₂O)n-\text{(metal)H} + \text{(metal)Cl} \\
&-\text{[C-(CH₂O)n-CH₂]-} + B-(CH₂O)n-\text{(metal)H} + \text{(metal)Cl} \\
&\text{H₂N-(CH₂O)n-CH₂-O-[C-(CH₂O)n-CH₂]-} + H \\
\end{align*}
\]

Before it can initiate the NCA polymerization, the hydroxyl end group of α-hydroxy, ω-amino PCL has to be protected in order to avoid any side nucleophilic attack of the monomer. The protective reaction has been achieved onto the α-bromo, ω-hydroxy PCL by a quantitative reaction with acetic anhydride under basic conditions [eq. (2)]:

\[
\text{HO-PCL} + \text{Br}-\text{CH₃COO} + \text{H₂O + CH₃COO⁻} \rightarrow \text{CH₃COO-PCL} + \text{H₂O} + \text{Br⁻}
\]

Obviously this protective acetate end group does not perturb the course of the forthcoming reactions leading to ω-NH₂ PCL.

In a first series of experiments, γ-benzylglutamate NCA (BG-NCA) has been selected as the amino acid component. BG-NCA has the advantage of being synthesized at a very high yield (> 98%) by direct precipitation of the benzyl ester of the parent amino acid[16] [eq. (3)]:

\[
\text{NH₂} \quad \text{NHCO} \quad \text{CH₂CO} \quad \text{CH₂CO} \quad \text{CH₂CO} \quad \text{CH₂CO}
\]

Furthermore, the polybenzylglutamate can be easily hydrolyzed into polyglutamic acid (PGA), i.e., a hydrophilic polypeptide, Pε(ε-L-L-GA) is thus a potential surfactant, whereas Pε(ε-L-L-GA-b-ε-L) triblock copolymers might be swollen by water and thus give rise to hydrogels.

The copolymerization of BG-NCA has been initiated by a low molecular weight a-acetyl, ω-primary amino PCL (M₀ = 5700, M₉/M₀ = 1.15) in dry chloroform at room temperature for 1 h. The copolymerization product has been precipitated in diethyl ether and recovered with a conversion of ca. 90%.

The ring-opening polymerization of BG-NCA (ε-L-GA = 1710 and 1805 cm⁻¹) has been assessed by the IR spectroscopy, which clearly shows the formation of the polypeptide block (ε-L-GA = 1650 cm⁻¹, ε-L-GA = 1549 cm⁻¹) (Fig. 1). The absorption at 1729 cm⁻¹ is characteristic of both PCL (ε-L-GA = 1729 cm⁻¹) and polybenzylglutamate (ε-L-GA = 1730 cm⁻¹).

Figure 2 shows the 1H-NMR spectrum of the recovered block copolymer. The relative intensities of the aromatic protons (i) and protons (d + m) at 4.05 ppm allow the molecular weight of the polypeptide block to be estimated at 920 ± 10% which is in close agreement with the theoretical M₉ (10%) taking into account the degree of conversion.

In order to make sure that no homopolymers contaminate the Pε(ε-L-L-GA-b-ε-L) block copolymer, SEC and selective fractionation experiments have been conducted. Unfortunately, polybenzylglutamate is strongly adsorbed on the SEC columns which excludes this method. Furthermore, the solubility of PCL and PBG in common solvents are so close that selective fractionation fails at this stage. Nevertheless, a decisive observation in favor of the block copolymerization is certainly the 1H-NMR signal at 3.46 ppm (protons g, see Fig. 2) which is characteristic of an amide linkage between PCL and polypeptide component. Moreover, the comparison of the intensity of those N-amide methylene protons (δH = 3.46 ppm) with the intensities of the benzyl protons (δH = 5.04 ppm) and the PCL protons (δH = 4.05 ppm), respectively, attests for the blocky structure of the copolymer in absence of any homopolymers.

The DSC curve of Pε(ε-L-L-GA-b-ε-L) copolymer is shown on Figure 3. Two melting endotherms are clearly observed attesting the crystallization of both PCL (Tₓ = 60°C) and PEG (Tₓ = 110°C).

The preliminary results reported in this communication convincingly show that ω-sulfhydryl primary amino PCL is an efficient macroinitiator for the ring-opening polymerization of amino acid N-carboxy anhydrides. 1H-NMR analysis supports the selective formation of Pε(ε-L-L-GA-b-ε-L) block copolymer. Since diblock bears a primary amine at the end of the polypeptide component, a coupling reaction could lead to Pε(ε-L-L-GA-b-ε-L) triblock macromolecules. Characterization and potentialities of these biocompatible and biodegradable multicomponent materials will be reported in the near future, as well as the extension of the method to polylactides.

**EXPERIMENTAL PART**

**Materials**

e-C-L (Japanes Chimon) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. Phosgene solution in toluene (1.93 M) was purchased from Fluka, γ-Benzylglutamate (Alrich) and 4-dimethylamino pyridine (Janssen) were dried by three acetonitrile distillations of toluene before use. Tetrahydrofuran (THF) were dried by refluxing over benzenophene Na complex. Chloroform was successively dried over

![Figure 2](image-url)  
**Figure 2.** 1H-NMR spectrum of the copolymer resulting from the copolymerization of BG-NCA initiated with an acetyl, ω-amino PCL.

![Figure 3](image-url)  
**Figure 3.** Typical DSC curve (first scan) of P(ε-L-L-GA) (20°C/min).
REFERENCES AND NOTES


EXPERIMENTAL

Monomers

Triaminocarbonyl, 4-aminoanisic acid, and phenylhydroxipiperone were gifts of Bayer AG (D-4100 Krefeld, FRG) and used without further purification. Isophthalic acid was purchased from Aldrich Co. (Milwaukee, Wis., USA) and purified by distillation (mp 45–44°C).

N-(4'-chloroformylphenyl)-4'-chloroformylphthalaldehyde was prepared from the corresponding dicarboxylic acid in refluxing thiocyanic acid and recrystallized from CHCl$_3$-lignin (mp 173–175°C lit. 174–175°C).

Phenylhydroxipiperone was silylated with a slight excess of hexamethyldisilazane in refluxing toluene and isolated by distillation in cesco; yield 91%, n = 1.5008.

Phenylhydroxipiperone was prepared according to the literature. In agreement with the literature it was not feasible to prepare the corresponding dichloride by means of boiling chloroform; therefore the di

carboxylic acid was silylated with hexamethyldisilazane in toluene and the resulting crude bistrihydroxilated was treated with refluxing thiocyanic acid. However, even this reaction failed. Finally, treatment with PCl$_3$ in diethyl ether gave the desired dichloride; yield 95%, mp 25–28°C (lit. 28–29°C).

Polycondensations

Phenylhydroxipiperone bistrihydroxilated (10 mmol) a mixture of two dicarboxylic acid chlorides (together 10 mmol) and benzotriethylammonium chloride (0 mg) were weighed into a cylindrical glass reactor equipped with stirrer gas inlet and outlet tubes. The reaction vessel was placed into a metal bath preheated to 180°C, and the temperature was then gradually raised to 200°C over a period of 3.5 h. This temperature was then maintained for 0.5 h whereby vacuum was applied. After cooling the reaction product was powdered extracted with hot acetone and dried in vacuo. In the case of 2b and 2e the maximum reaction temperature was limited to 250°C to avoid cross-linking. In consequence lower viscosity values were obtained.

Measurements

The DSC measurements were conducted with a Perkin-Elmer DSC-4 in aluminum pans under nitrogen at a heating rate of 20°C/min.