Synthesis and Characterization of a New Family of Poly(ortho ester)s

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ABSTRACT: A previously reported synthesis of ointment-like poly(ortho ester)s prepared from a flexible triol and an alkyl orthoacetate has been extended to the preparation of solid materials by replacing the flexible triol with a rigid triol. The hydrolysis products of the polymer have been determined, and the hydrolysis has been shown to proceed exclusively by cleavage of the exocyclic alkoxy group of the ortho ester linkage. The lowest alkyl analog is crystalline, but the higher alkyl analogs are amorphous. The polymer is hydrolytically labile, and the rate of hydrolysis increases as the pH of the erosion medium decreases.

Introduction

In a previous paper[1] we have described the synthesis of a new family of poly(ortho ester)s prepared by the reaction between a triol and an alkyl ortho acetate as shown in Scheme I.

When the triol is 1,2,6-hexanetriol, the polymers have a highly flexible backbone and an ointment-like consistency at room temperature even though molecular weights can be as high as 20 000. Such materials are of considerable interest in the controlled delivery of sensitive therapeutic agents because they can be incorporated into the polymer by a simple mixing procedure at room temperature without the use of solvents. Application of this material in topical delivery[1] and in the controlled delivery of proteins is currently under investigation.[2]

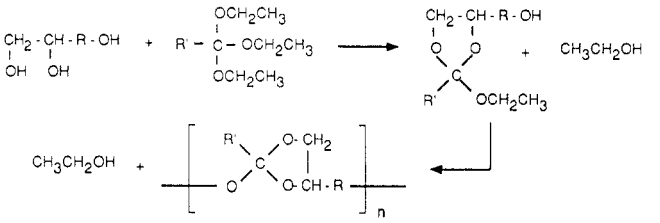
When the flexibile triol is replaced with a rigid triol, the resulting polymer is a solid, and in this paper we describe the synthesis and characterization of this polymer.

Experimental Section

Materials. (a) 1,4-Cyclohexanedimethanol Monoacetate. A mixture of *cis*- and *trans*-1,4-cyclohexanedimethanol (930 g, 6.448 mol) was dissolved in 3 L of tetrahydrofuran, and 550 mL of pyridine (7.69 mol) was added. The solution was cooled in an ice bath and stirred under argon. An acetyl chloride solution (506.4 g, 6.45 mol) in 500 mL of tetrahydrofuran was then added dropwise over a 2-h period. The ice bath was removed and the reaction mixture stirred for 2 h at room temperature, filtered to remove the pyridine hydrochloride salt, and then evaporated to remove the tetrahydrofuran. The residue was dissolved in 2 L of ethyl acetate and the solution extracted with diluted aqueous HCl (2 × 300 mL), warm water (2 × 300 mL), and aqueous $NaHCO_3$ solution (2 × 300 mL). The ethyl acetate solution was dried over anhydrous $MgSO_4$ and the ethyl acetate removed on a rotoevaporator. Vacuum distillation of the residue yielded 335 g of product. GC analysis showed that the product contained 59% cyclohexanedimethanol monoacetate and 41% cyclohexanedimethanol diacetate. The overall yield of the monoacetate was 16.5%.

(b) 4-(Acetoxymethyl)-1-cyclohexanecarboxaldehyde. Under anhydrous conditions, oxalyl chloride (358 g, 2.82 mol) was dissolved in 2.5 L of methylene chloride, and the solution was cooled to −40 °C. Dimethyl sulfoxide (407 g, 5.2 mol) dissolved in 200 mL of methylene chloride was then added via a dropping funnel while the reaction mixture was vigorously stirred and the temperature maintained between −40 and −20 °C. Next, a solution of cyclohexanedimethanol monoacetate (600 g, 59% pure, 1.9 mol) in 200 mL of methylene chloride was added dropwise while the reaction temperature was kept below −20 °C. After the addition of cyclohexanedimethanol monoacetate solution was completed, the reaction mixture was stirred for an additional 15 min and triethylamine (658 g, 6.5 mol) added. The cooling bath was removed and the reaction mixture stirred for 2 h. It was then extracted successively with diluted aqueous HCl, aqueous $NaHCO_3$, and aqueous NaCl. After drying over anhydrous $MgSO_4$, the methylene chloride solution was distilled under argon to remove the solvent. The residue was distilled at 80 °C at 0.4 mmHg to give the aldehyde (248 g, 70.8% yield).

Scheme I



(c) 4-(Acetoxymethyl)-1,1-cyclohexanedimethanol. A mixture of 4-(acetoxymethyl)-1-cyclohexanecarboxaldehyde (248 g, 1.46 mol), a 37 wt % formaldehyde solution (700 mL, 8.6 mol), and tetrahydrofuran (200 mL) was cooled in an ice water bath. Calcium oxide was then added in small portions while the mixture was vigourously stirred with an overhead mechanical stirrer. After the addition of CaO was completed, the ice bath was removed and the mixture stirred for 2 h. It was then evaporated to dryness and the product extracted into acetone. Evaporation of the acetone solution produced a viscous oil.

(d) 1,1,4-Cyclohexanetrimethanol. The crude 4-(acetoxymethyl)-1,1-cyclohexanedimethanol was added to 1 L of an aqueous 2 N NaOH solution and the mixture heated at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was neutralized with aqueous HCl and extracted with methylene chloride. The aqueous solution was evaporated to dryness and the residue extracted with acetone. After drying over anhydrous $MgSO_4$, the acetone solution was evaporated to dryness. Distillation of the crude product from the acetone solution at 175 °C and 0.1 mmHg yielded a viscous liquid. Repeated trituration with methylene chloride produced a solid product (150 g, 59% yield, 98.8% purity by GC).

Polymerization. Under anhydrous conditions, 1,1,4-cyclohexanetrimethanol (3.524 g, 20 mmol), trimethyl orthoacetate (2.403 g, 20 mmol), *p*-toluenesulfonic acid (~3 mg), and distilled cyclohexane (80 mL) were added to a predried flask. The flask was fitted with a spinning band column and heated at 100 °C under argon. Methanol was removed azeotropically at 56 °C at a fast rate, and as the boiling point began to rise, the distillation rate was reduced to 4 drops/min and heating continued for 15 h. The polymer thus prepared precipitated out of cyclohexane. The powdery polymer was crystalline with a melting point (DSC) of 212 °C. It was insoluble in the usual organic solvents such as methylene chloride, chloroform, ether, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, and dimethyl sulfoxide.

In a similar manner, 1,1,4-cyclohexanetrimethanol (3.524 g, 20 mmol) was allowed to react with triethyl orthopropionate (3.634

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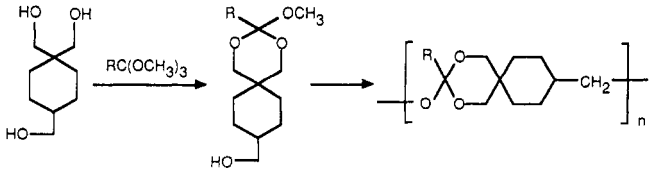
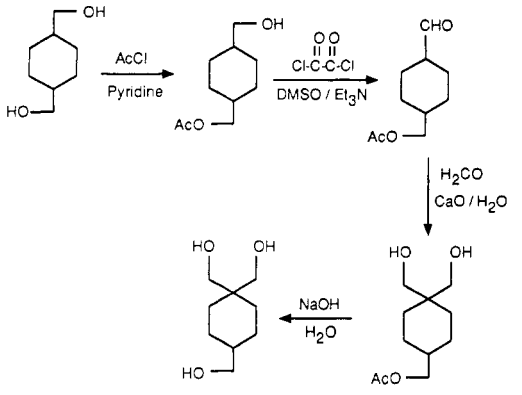
Scheme II



Scheme III



g, 20 mmol). This reaction produced a polymer which remained in the cyclohexane solution. Precipitation into methanol yielded a polymer having a MW of 51 000 and a T_g of 67.8 °C. The polymer was soluble in organic solvents with low or medium polarities such as methylene chloride, chloroform, ether, tetrahydrofuran, and ethyl acetate.

(a) Polymer Hydrolysis. The acetate polymer (100 mg) was stirred with 5 mL of a pH 7.4 phosphate buffer at room temperature overnight and the reaction mixture then evaporated to dryness. The residue was stirred with 2 mL of acetone and the acetone solution dried over anhydrous $MgSO_4$.

(b) Polymer Characterization. GPC determinations were carried out using a Waters 150C instrument with 10^3- and 10^4-Å Waters μStyrogel columns. Molecular weight calculations were done using Waters Expert software on a Waters 840 chromatography data station using polystyrene standards.

X-ray powder diffractions were carried out using a Phillips 3KVA full-wave generator, a Phillips "copper" 1800-W long-fine-focus tube, a Phillips goniometer, and a Bicron scintillator.

Gas chromatography was carried out using a Hewlett-Packard Model 5890 Series II instrument with a 50-m DB5 column maintained at 120 °C for 1 min, then programmed at 15 °C/min to 220 °C, and finally maintained at 220 °C for 15 min.

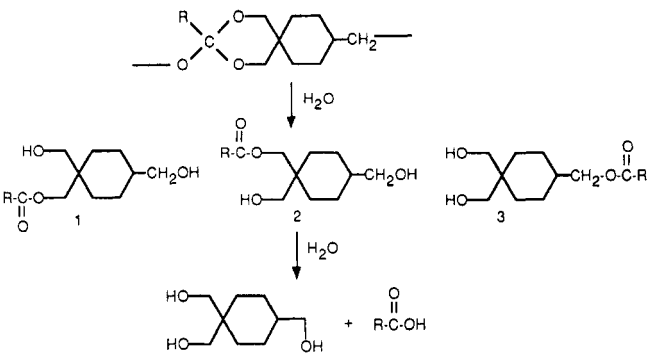
Results and Discussion

The synthesis of solid polymers was carried out as shown in Scheme II using the cyclic triol 1,1,4-cyclohexanetrimethanol. The triol, 1,1,4-cyclohexanetrimethanol, was prepared as shown in Scheme III.

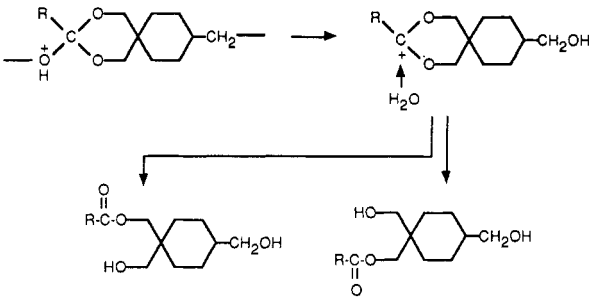
Poly(ortho ester)s contain acid-sensitive linkages in the polymer backbone so that their rate of hydrolysis can be regulated by means of excipients physically incorporated into the polymer matrix.[3] This is a significant advantage, and drug delivery devices with widely varying rates of erosion and drug release can be constructed by using acidic excipients to accelerate hydrolysis rate and basic excipients to retard hydrolysis rate.

When these poly(ortho ester)s are place in an aqueous environment, they hydrolyze as shown in Scheme IV. Because ortho ester linkages are much more reactive than aliphatic ester linkages, the initial cleavage occurs exclusively at the ortho ester bonds and the subsequent final hydrolysis takes place later. For this reason, hydrolysis of the polymer is not autocatalytic because the neutral hydrolysis products can diffuse away from the polymer before the carboxylic acid is formed. As with the other poly(ortho ester)s studied previously,[4,5] the exact hydrolysis path depends on whether initial protonation and bond cleavage occur at the exocyclic or endocyclic alkoxy group of the ortho ester linkage. If cleavage occurs at the exocyclic alkoxy group, then the 1- and 2-isomers are produced as shown in Scheme V. If cleavage occurs at the endocyclic alkoxy group, then the 1- and 3-isomers are produced as shown in Scheme VI.

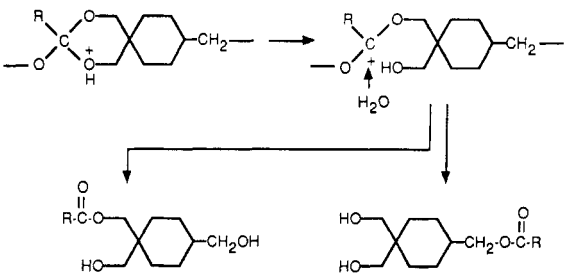
Scheme IV



Scheme V

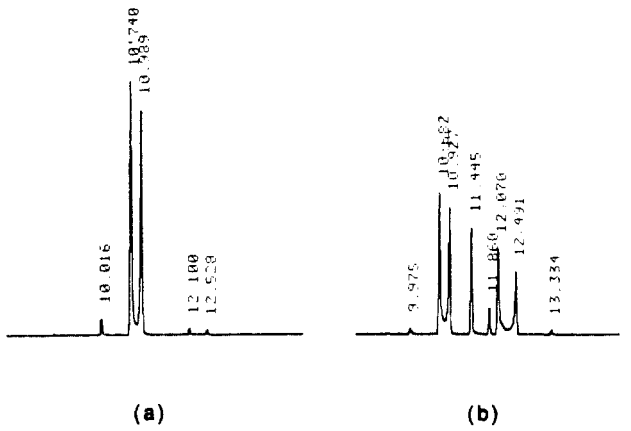


Scheme VI



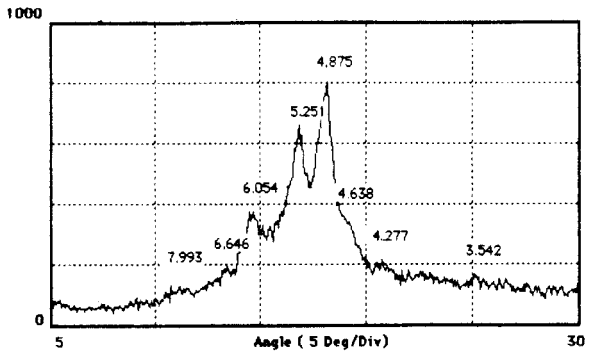
The relative importance of these two paths was ascertained by a careful hydrolysis of the acetate polymer and analysis of the hydrolysis products by gas chromatography. Results are shown in Figure 1. Figure 1b represents a chromatogram of products obtained by acetylating 1,1,4-cyclohexanetrimethanol and shows two sets of three peaks. These correspond to the three monoacetates and to the three diacetates. Figure 1a shows the products obtained when the acetate polymer is carefully hydrolyzed in acid. Two major peaks are noted. Because the 3-isomer was available from the synthesis shown in Scheme III, the two peaks in the chromatogram shown in Figure 1a have been identified as the 1-isomer and the 2-isomer. The three very minor peaks are the triol (10.016) and two diacetates (12.100 and 12.528). These diacetates correspond to polymer end-groups which are detectable because the crystalline acetate polymer precipitates out of solution as a relatively low molecular weight material.

The complete absence of the 3-isomer indicates that this polymer hydrolyzes exclusively by an exocyclic cleavage of the alkoxy groups. This result is entirely consistent with the hydrolysis of the polymer prepared from 1,2,6-hexanetriol, which also hydrolyzes exclusively by an exocyclic cleavage of the alkoxy group.[3]

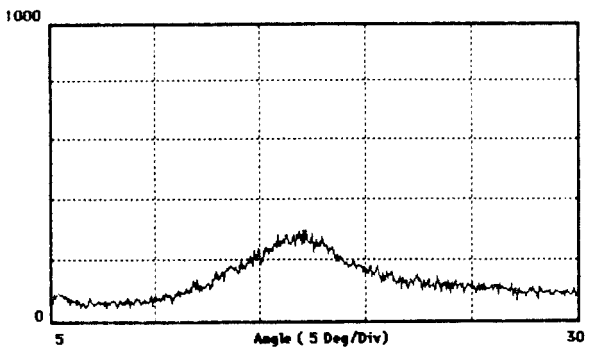


(a) (b)

Figure 1. Gas chromatogram of (b) products from acetylation of 1,1,4-cyclohexanetrimethanol and (a) acetate polymer (R = CH_3) hydrolysis products.



(a)

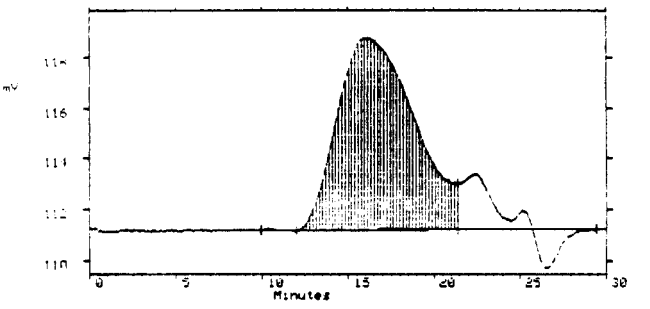


(b)

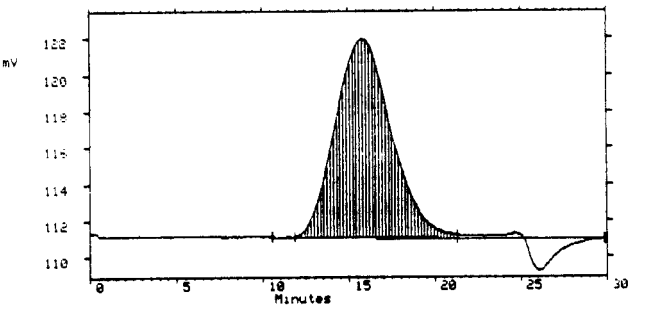
Figure 2. X-ray diffractometer traces of (a) acetate polymer (R = CH_3) and (b) propionate polymer (R = CH_3CH_2).

When R = CH_3, the polymer is crystalline and precipitates out of the reaction mixture. It is completely insoluble in the usual organic solvents such as methylene chloride, chloroform, ether, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, and dimethyl sulfoxide. When R = CH_3CH_2, the polymer remains in solution and, as isolated, is amorphous and readily soluble in the usual organic solvents. The same observation holds for polymers with higher alkyl groups. Figure 2 shows powder X-ray diffraction patterns of the methyl and ethyl polymers. Attempts to anneal the ethyl polymer were not successful, and the polymer remained amorphous.

By careful attention to stoichiometry, high molecular weight polymers can be readily produced for the higher homologs which remain in solution. Figure 3a shows molecular weight and polydispersity determined by gel permeation chromatography of a propionate polymer isolated by precipitation of the cyclohexane polymerization product into an excess of methanol. When the reaction product is precipitated into a 60/40 methanol/tetrahydrofuran mixture, the low molecular weight component is eliminated and the molecular weight distribution is significantly narrowed, as shown in Figure 3b.



(a)



(b)

Figure 3. Gel permeation chromatogram of (a) polymer precipitated into methanol and (b) polymer precipitated into a 40/60 mixture of tetrahydrofuran and methanol.

Table I
Erosion Times of Polymer Disks, 0.25 × 7 mm, in Various Buffers at 37 °C (R = CH_3CH_2)

pH	time to total erosion	pH	time to total erosion
1	4 h	6	30 days
3	48 h	7.4	unchanged after 30 days

Preliminary data on the behavior of the polymer in various buffers are shown in Table I. The data show that the polymer is quite sensitive to acid so that use of various excipients should make possible the construction of bioerodible devices with a wide range of lifetimes.

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References and Notes

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