Polymer Bulletin 39, 21-28 (1997)

Polymer Bulletin

# Nonlinear biodegradable polyanhydrides synthesized from natural fatty acids through a new way

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Received: 8 October 1996/Revised version: 14 April 1997/Accepted: 22 April 1997

## Summary

Ricinoleic acid was esterified by fatty diacid chlorides to yield intermediate diacids, which were next converted to corresponding polyanhydrides by vacuum-melt polycondensation. The intermediates and polymers were characterized by means of $^1$H NMR, IR spectroscopy, differential scanning calorimetry (DSC), X-Ray diffraction and light scattering. The optimized reaction conditions of melt polycondensation were investigated and copolyanhydride with molecular weight (weight average) up to $1.38\times10^5$ and intrinsic viscosity of 126 $cm^3/g$ was obtained. DSC and X-ray diffraction analysis showed that the synthesized copolyanhydrides exhibited much lower crystallinity and improved thermal properties in comparison with aliphatic linear homopolyanhydrides.

## Introduction

Nowadays there is a growing interest in research on novel biodegradable materials. Aliphatic polyesters and polyanhydrides have been regarded as excellent biodegradable polymers mainly due to the hydrolytic instability of their ester or anhydride linkages as well as the high biocompatibility of these polymers and their degradation products[1-2]. These two kinds of polymers showed desirable properties especially in medical and pharmaceutical applications[3-6]. However, poor mechanical properties of the aliphatic homopolyanhydrides due to their high crystallinity[7] have greatly limited their utility. Copolymerization of aliphatic polyanhydrides has proved to be an extremely effective way to lower the crystallinity and improve the thermal and mechanical properties[8-9]. Synthesis and characterization of nonlinear copolyanhydrides based on ricinoleic acid and aliphatic diacid have been reported recently, and these polymers turned out to be totally degradable and thus suitable for drug delivery application[10].

In this paper, we used novel synthetic procedure employing diacid chlorides for esterification of ricinoleic acid in order to obtain intermediate diacids, which by a high-vacuum melt polycondensation process yielded copolyanhydrides with high molecular weights and lower crystallinity.

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## Experimental

### *Materials*

Sebacic acid, adipic acid were purified by recrystallization from ethanol before use. Ricinoleic acid was dried under vacuum at 25°C overnight.

Cadmium acetate dihydrate and calcium acetate hydrate ground to less than 30µ particle size were used as catalysts in polymerization.

Fatty diacid chlorides, sebacoyl chloride and adipic chloride, were prepared by refluxing the corresponding diacids in thionyl chloride and then distilling under reduced pressure as described in the literature[11].

All solvents were analytical grade and were dried prior to use.

### *Preparation of intermediate diacid and mixed anhydride prepolymer*

Ricinoleic acid (298g, 1mol) and fatty diacid chloride (2mol) were added to a dried round-bottomed flask. The flask was immersed in a glycerin bath at 60°C and a vacuum of 267Pa was supplied. The reaction mixture was magnetically stirred until gas evolution ceased. Aliphatic diacid (2mol) was added and the reaction temperature was raised to 80°C. The mixture was then stirred to no gas bubble emerging.

The mixed anhydride prepolymers were prepared according to literature report[8] as follows: intermediate diacid reacted with excess acetic anhydride for 30min at 120°C, then the excess of acetic anhydride was removed by vacuum distillation, the residue was dissolved in dried chloroform and precipitated from petroleum.

### *Polymer synthesis*

Copolyanhydrides were synthesized by melt polycondensation[8-9]. Typically, mixed anhydride prepolymer and reaction catalyst (1wt%) were added to a carefully dried polymerization tube equipped with a side arm, then high vacuum (below 66.7Pa) was introduced. The tube was immersed in a 210°C oil bath. During the polymerization, an intensive nitrogen stream swept the melt with vigorous agitation for 1-2min every 15min, by-product (acetic anhydride) was distilled out. The crude polymer was dissolved in chloroform, catalyst was removed by filtration, polymer was obtained by precipitation in dried petroleum ether from the chloroform solution.

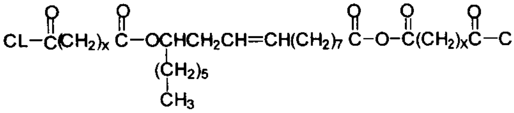
### *Measurements*

Intermediate diacids and prepolymers were characterized by IR spectrometry, $^1$H NMR. The FTIR used was a Perkin-Elmer 1600, solid samples were pressed into KBr pellets.The NMR spectra were recorded on a Varian-200 and a DMX-300 using tetramethylsilane (TMS) as an internal reference, intermediate diacids and prepolymers were dissolved in deuteroacetone and deuterochloroform respectively. Absolute molecular weight (weight average) of polymer was determined at 25°C by means of light scattering employing Zimm plotting, the apparatuses used were a DLS-700 and a differential refractometer RM-102, all samples were dissolved in chloroform and stored below 0°C before measurements. A Perkin-Elmer DSC-7 calibrated with In was used to analyze the thermal properties of polymers, the heating rate was 10°C/min. Crystallinity of polymers was measured by a D/MAX-RB X-ray diffractometer (Japan), scanning rate was 40 times/min, time constant Rc=0.2. Intrinsic viscosity of polymer in chloroform solution was measured at 25°C in a Ubbelodhe viscosimeter (2mL, 0.39 mm).

## Results and discussion

### *Preparation of intermediate diacids and prepolymers*

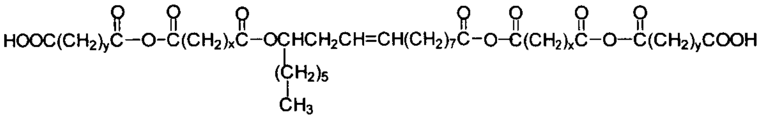
Both hydroxyl and carboxyl groups of ricinoleic acid can undergo nucleophilic substitution with acid chloride to yield corresponding ester and anhydride groups. Because of the strong electrophilic reactivity of acid chloride, above mentioned reactions are easy to perform at moderate temperature (below 100°C) and reduced pressure. Typically, the reaction of ricinoleic acid and fatty diacid chloride (molar ratio = 1/2) yielded an intermediate diacid with structure as follows:



$\mathrm{CL{-}\overset{O}{\overset{\|}{C}}(CH_2)_x\overset{O}{\overset{\|}{C}}{-}O\underset{\substack{|\\(CH_2)_5\\|\\CH_3}}{C}HCH_2CH{=}CH(CH_2)_7\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}(CH_2)_x\overset{O}{\overset{\|}{C}}{-}CL}$

A

Further reaction of intermediate A with aliphatic diacid in a molar ratio of 1/2 yielded the goal intermediate diacid B, this reaction was also found to be very fast under the given reaction conditions.



$\mathrm{HOOC(CH_2)_y\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}(CH_2)_x\overset{O}{\overset{\|}{C}}{-}O\underset{\substack{|\\(CH_2)_5\\|\\CH_3}}{C}HCH_2CH{=}CH(CH_2)_7\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}(CH_2)_x\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}(CH_2)_yCOOH}$

B

The IR spectra of intermediate A showed strong characteristic absorption bands at 1735cm$^{-1}$ (C=O stretching vibration of ester), 1800cm$^{-1}$ (C=O stretching vibration of anhydride) and 3100-3700cm$^{-1}$ attributed to the characteristic absorption of O-H stretching vibration of carbonyl of diacid. $^1$H NMR spectra of A showed, in addition to the typical peak of chloride at 3.0ppm, a peak at 2.53ppm indicating reaction of carboxyl end group with chloride to form anhydride.

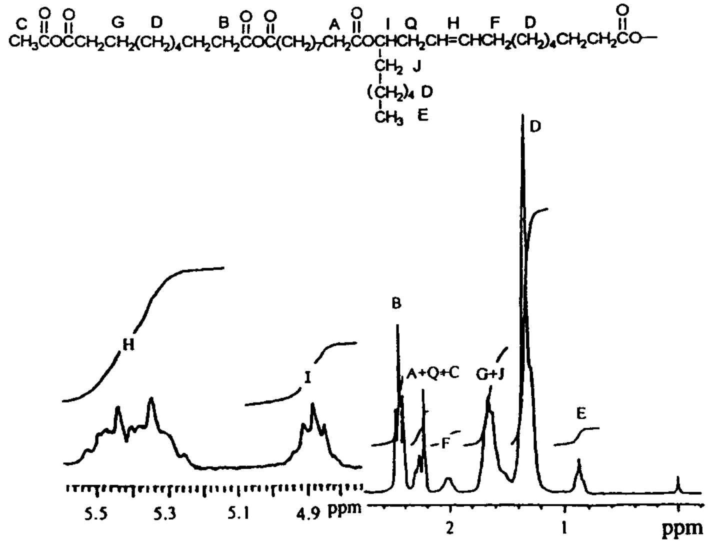


Figure 1. A typical 200 MHz $^1$H NMR spectrum of prepolymer ( x, y = 8 )

The IR spectra of B showed characteristic absorption bonds at 1820cm$^{-1}$, 1740cm$^{-1}$ and 1710cm$^{-1}$ respectively attributed to the C=O stretching vibrations of carboxylic anhydride, ester and acid. $^1$H NMR spectra of B showed an enhanced absorption peak at 2.53ppm from the methylenes connected with anhydride groups.

***Synthesis of polyanhydrides***

Similarly to the synthesis of other aliphatic polyanhydrides[8], melt polycondensation of mixed anhydride prepolymers synthesized in this work was also found to be affected by reaction time, temperature as well as selected acetate catalysts.

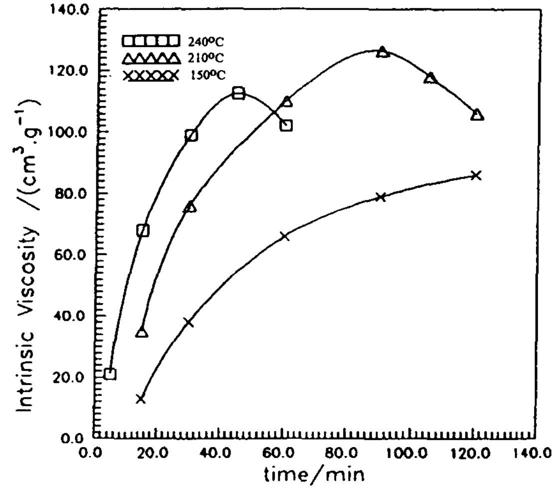


Figure 2. Relationship between polymer intrinsic viscosity and reaction time/temperature in polymerization of a prepolyanhydride (x,y = 8, see the structure of intermediate B)

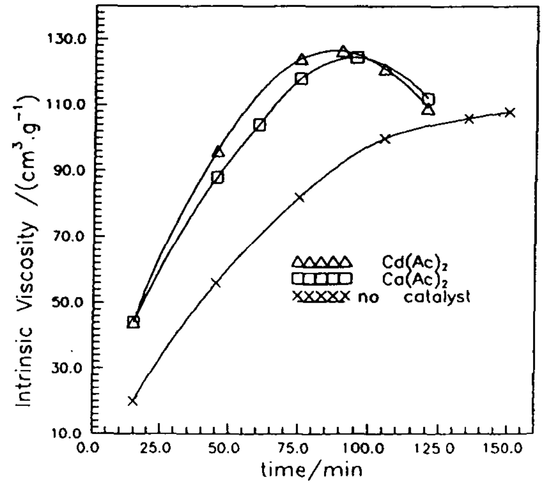


Figure 3. Relationship between polymer intrinsic viscosity and reaction time in 210°C polymerization of a prepolyanhydride (x,y = 8, see the structure of intermediate B)

The polymer intrinsic viscosity was observed to decrease again in higher reaction temperature (210°C and 240°C) and longer reaction time. The cause for this phenomenon was ascertained to be the interchange reactions of intramolecular anhydride groups leading to ring-shaped products with lower molecular weights. This tendency didn't exhibit in lower temperature (150°C) because of the very slower total reaction rate, which meant that it would take relatively longer time to observe this variation, as well as the unfavorable influence of lower reaction temperature to ring-forming reactions.

The optimized conditions of copolyanhydride polycondensation were: temperature 210°C, acetates of Ca or Cd as catalysts and reaction time 90min. In these conditions, copolyanhydride with intrinsic viscosity $[\eta]=126 cm^3/g$ and molecular weight $M_w=13.8\times10^4$ (from light scattering measurement) was obtained based on ricinoleic acid and sebacic acid. The use of light scattering in measurement of molecular weight of polyanhydrides hasn't been reported before, so for the first time, the absolute molecular weight (weight average) of polyanhydrides was achieved by means of light scattering with Zimm plotting method.

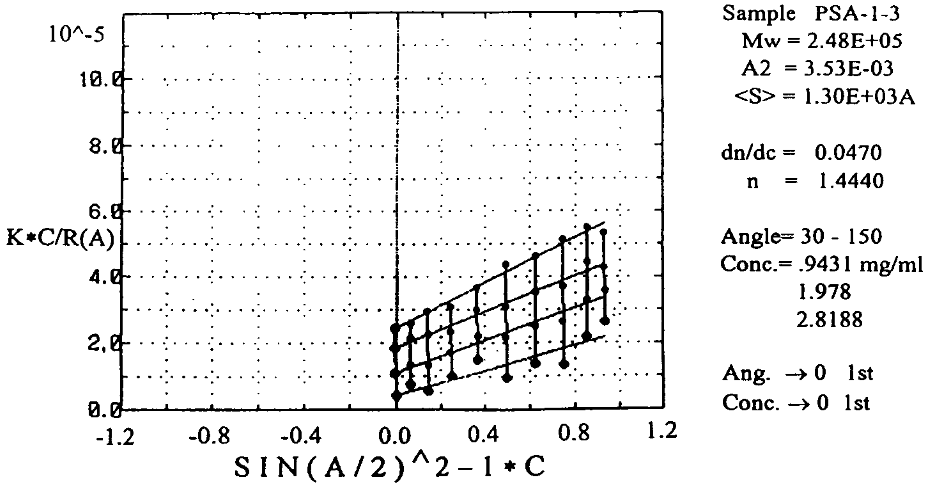


Figure 4. Zimm plot of PSA ($[\eta]=112.5 cm^3/g$) in chloroform (measured at 25 °C)

In order to prevent the degradation of polyanhydride in chloroform solution, the polymer solution was stored at lower temperature (e.g. 0°C) before light scattering measurement.

***Properties of copolyanhydrides***

Crystallinity of several typical polyanhydrides was measured by X-ray diffraction referring to the method reported before[7,12], Fig.5. The results were listed in Table 1. Table 1 showed that copolyanhydrides possessed much lower crystallinity than homopolyanhydrides and that the branched chains in molecular structure affected crystallinity of polymer. Poly(ricinoleic acid-co-adipic acid) displayed lower crystallinity than poly(ricinoleic acid-co-sebacic acid) due to higher density of branched chains.

Table 1. Crystallinity of several typical polyanhydrides measured by X-ray diffraction

| polyanhydride | intrinsic viscosity [η] ($cm^3/g$) | crystallinity $\chi_c$ (%) |
|---|---|---|
| PSA◊ | 112.5 | 72.54 |
| PAA# | 54.3 | 78.95 |
| Poly(ricinoleic acid-co-adipic acid)* | 94.2 | 31.78 |
| Poly(ricinoleic acid-co-sebacic acid)* | 126.0 | 51.43 |

◊PSA: poly(sebacic anhydride).
#PAA: poly(adipic acid)
*Molar ratio of ricinoleic acid and aliphatic diacid was 1/4.

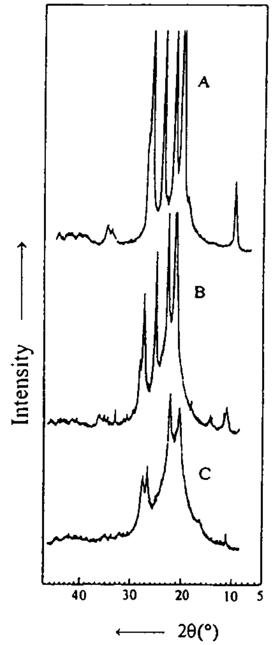
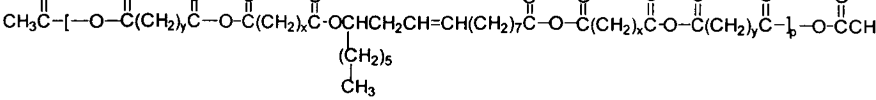


Fig.5. X-ray diffraction curves. A: PSA.
B: Poly(ricinoleic acid-co-sebacic acid).
C: Poly(ricinoleic-co-adipic acid)

Thermal properties of synthesized copolyanhydrides with the following structure were analyzed by DSC. Table 2 and Figure 6.



$$CH_3\overset{O}{\overset{\|}{C}}-[-O-\overset{O}{\overset{\|}{C}}(CH_2)_y\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}(CH_2)_x\overset{O}{\overset{\|}{C}}-O\underset{\underset{CH_3}{|}}{\underset{(CH_2)_5}{\underset{|}{C}}}HCH_2CH=CH(CH_2)_7\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}(CH_2)_x\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}(CH_2)_y\overset{O}{\overset{\|}{C}}-]_p-O-\overset{O}{\overset{\|}{C}}CH_3$$

From Table 2 and Figure 6, the following regularity on the thermal properties of polymers were found:

(1) Because of the higher crystallinity, homopolyanhydrides didn't display obvious glass transition in DSC thermograms, so corresponding glass transition temperatures were not detected.

(2) Copolyanhydrides exhibiting much lower heat of fusion (ΔH) but clearer glass transitions indicated lower crystallinity which was consistent with the results of X-ray diffraction. Meanwhile, it was notable that copolyanhydrides with higher intrinsic viscosity (indicating higher molecular weight) displayed more distinct glass transition, the similar results were also obtained in the DSC measurement of copolyanhydrides based on poly(ethylene glycol) oligomers and sebacic acid[13].

Table 2. Results of DSC analysis on thermal properties of polyanhydrides with different compositions

| sample | composition X | composition Y | [η] (cm$^3$/g) | Tg (°C) | Tpeak (°C) | ΔH (J/g) |
|---|---|---|---|---|---|---|
| A | 4 | 4 | 94.2 | 56.6 | 70.4 | 50.11 |
| B | 4 | 8 | 83.4 | 46.5 | 57.5 | 34.73 |
| C | 8 | 2 | 71.2 | not found | 64.3 | 37.79 |
| D | 8 | 2 | 96.4 | 54.9 | 70.6 | 45.23 |
| E | 8 | 4 | 64.2 | not found | 51.3 | 43.97 |
| F | 8 | 4 | 79.8 | 49.2 | 65.6 | 52.25 |
| G | 8 | 8 | 82.3 | not found | 70.1 | 53.27 |
| H | 8 | 8 | 109.4 | 46.6 | 73.7 | 43.24 |
| I | 8 | 8 | 126.0 | 48.0 | 75.3 | 60.07 |
| PSA | | | 112.5 | not found | 86.0 | 134.5 |
| PAA | | | 54.3 | not found | 79.0 | 83.86 |

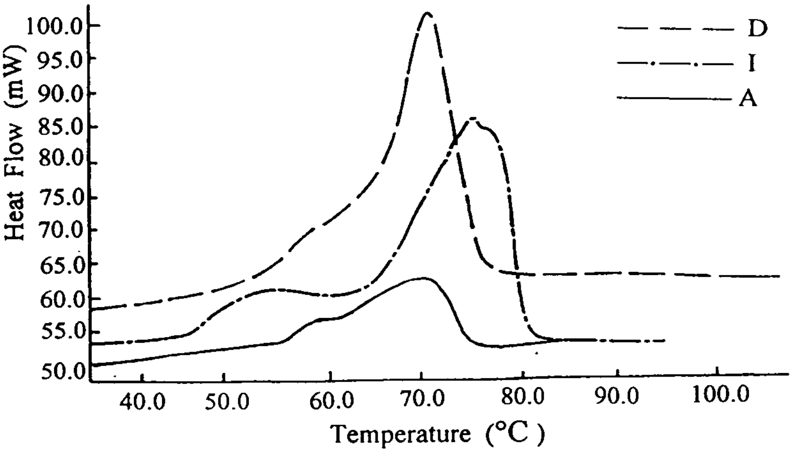


Figure 6. DSC thermogram for several typical copolyanhydrides

## Conclusion

Novel route to aliphatic copolyanhydrides from intermediate diacids based on ricinoleic acid has been developed. Aliphatic copolyanhydride with high molecular weight up to 1.38×10$^5$ (weight average) was prepared by melt polycondensation in optimized reaction conditions. The synthesized copolyanhydrides displayed better mechanical properties than aliphatic homopolyanhydrides[14] due to the introduction of fatty branched chain into their molecular structure lowering the polymer crystallinity. Remarkable improvement of thermal properties of copolyanhydride in comparison with the homopolyanhydride has been of benefit for thermal processing of copolymers.

**Acknowledgment:** the authous are grateful to Prof.Lingxiang Tian, Ms.Xiaoqin Wang and Mr.Zhendong Wang for DSC measurement and other help.

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