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Novel synthesis of a hindered trisubstituted dehydroalanine derivative and its copolymerization with methyl acrylate

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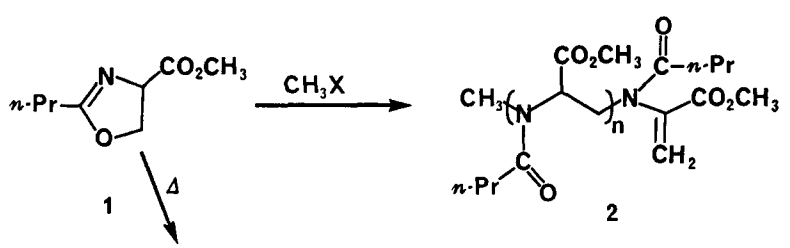
Summary

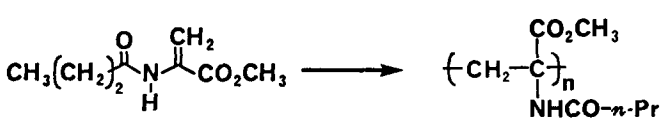
The new monomer N-methyl-N-butyryldehydroalanine methyl ester was obtained in good yield by N-methylation and base catalyzed ring opening of racemic 2-propyl-4-methoxycarbonyl-2-oxazoline. The oxazoline was prepared in high yield from (R,S)-serine methyl ester hydrochloride and ethyl butyroimidate. Attempted radical and anionic homopolymerization of purified monomer failed. Radical copolymerization with methyl methacrylate was also unsuccessful, although copolymerization with the less hindered methyl acrylate did produce copolymer as determined by high resolution ^{13}C NMR. Unsubstituted N-butyryldehydroalanine methyl ester was prepared by an alternative route and was shown to spontaneously homopolymerize to high polymer. Space-filling models of the monomers indicate steric hindrance for approach of the N-methylated monomer to the active chain end, consistent with difficult homopolymerization.

Introduction

Recently, we discovered two unusual side reactions in the cationic ring-opening polymerization of 2-propyl-4-methoxycarbonyl-2-oxazoline **1** (2):



1 **2**



3 **4**

[1] See Reference 1

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In some cases, polymerization produced either an unsaturated endgroup on the low molecular weight polyethylenimine derivative (2, Mn 1600), or vinyl polymer 4 derived from the dehydroalanine derivative 3 (3). It was proposed that similar mechanisms were involved in the isomerization of the oxazoline monomer (leading to formation of N-butyryldehydroalanine methyl ester 3) and formation of the dehydroalanine-like terminal group of the polyethylenimine oligomer.

Based on this mechanism, we have synthesized the previously mentioned (4) N-methyl derivative of a typical dehydroalanine monomer which is analogous to the unsaturated chain-end. Polymerization of this monomer would provide support for both the termination reaction proposed for the ring-opening polymerization of 1, and the use of the unsaturated oligomers thus obtained as macromonomers.

Experimental

The oxazoline and N-butyryldehydroalanine methyl ester were prepared as described previously (2). Spectra were obtained using a Nicolet 5DX FTIR, and Varian EM360, Jeol FX90Q, and Bruker MSL-200 NMRs. Vazo-67 is a DuPont azo initiator.

N-methyl-N-butyryldehydroalanine methyl ester 6

A 200 mL round bottom flask was immersed in an ice bath and charged with racemic 2-propyl-4-methoxycarbonyl2-oxazoline (8.56 g, 0.005 mole, 97% pure by GC), 80 mL dichloromethane, and a teflon stirbar. Dimethyl sulfate (5.2 mL, 0.055 mole) was added slowly over a period of 10 minutes. The mixture was allowed to react at room temperature overnight, then cooled to ice temperature. Triethylamine (7.7 mL, 0.055 mole) was slowly added to this mixture. After 6 hours, GC analysis confirmed a 50-50 mixture of starting material and product. An additional aliquot of dimethyl sulfate (6.0 mL, 0.063 mole) was slowly added to effect complete reaction as shown by GC, and additional triethylamine (5 mL, 0.036 mole) was then added. The exothermic reaction was controlled by cooling in the ice bath. The reaction was complete within 5 hours. The organic phase was extracted with 0.1N HCl (2 X 50 mL), 0.1N Na_2CO_3 (30 mL), and water (50 mL). The organic phase was filtered through a short column of silica gel to remove slight impurities and water. Solvent was removed under vacuum at 45°C to obtain a light orange liquid in 78% crude yield. The overall yield was reduced to 53% after removing low molecular weight substances under high vacuum. Pure compound was obtained by vacuum distillation (10mm Hg) with pot and vapor temperatures of 164°C and 93°C, respectively. The final product was a colorless liquid found to be 99% pure by GLC.

Copolymerization of 6 and methyl acrylate

An oven dried test tube was charged with methyl acrylate (0.2336 g, 2.7 mmole), N-methyl-N-butyryldehydroalanine methyl

ester (0.500 g, 2.7 mmole), and Vazo-67 (0.0305 g, 0.16 mmole). A rubber septum was used to seal the tube before two freeze-thaw cycles were performed under high vacuum at -80°C. The tube was pressurized with nitrogen and immersed in a 60°C bath for three days. The slightly viscous material was dissolved in dichloromethane and precipitated into a 40-fold excess of ice cold petroleum ether. The polymer was dried at 70°C with a yield of 0.24 g (33%).

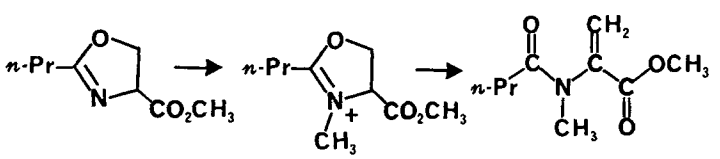
Homopolymerization of N-butyryldehydroalanine methyl ester 3

High polymer was obtained spontaneously during the preparation of one batch of monomer ($[\eta]$=2.19 dL/g, methanol at 25°C). Another portion of monomer was prepared and polymerized in 90% yield in hexane-methanol (95:5) using Vazo-67 at 60°C. The solution-polymerized sample was of considerably lower molecular weight ($[\eta]$=0.64 dL/g) and was used for NMR comparisons.

Results and Discussion

Monomer synthesis and characterization

The synthesis of 6 employed the same reagent used as initiator in the ring-opening polymerization of 1, although excess dimethyl sulfate and low reaction temperatures were required. The intermediate 5 was not isolated but converted directly to product with excess triethylamine. While typical dehydroalanine monomers will undergo spontaneous polymerization even at -5°C, 6 was readily distilled at high temperatures.



1 5 6

The infrared spectra of N-butyryldehydroalanine methyl ester 3 and the N-methyl substituted derivative 6 both show characteristic carbonyl peaks for the methyl ester and the amide groups, although they are shifted in the N-methyl compound 10 cm^{-1} higher and 20 cm^{-1} lower, respectively. The vinylidene absorption is clearly visible in each compound at 1636 and 1633 cm^{-1}. The strong amide II peak at 1518 found in the former compound is absent in the N-methyl derivative as would be expected for a tertiary amide.

The ^{1}H NMR spectra of the two monomers are shown in Figure 1. The two large singlets seen for **6** at 3.1 and 3.8 ppm are due to the N-methyl and methyl ester groups, respectively. The alkyl protons have the splitting patterns normally found for a propyl group. The two singlets at 5.7 and 6.3 ppm are the vinylidene protons. The N-H peak found in the spectrum of **3** at 7.9 ppm is clearly absent in the trisusbstituted derivative.

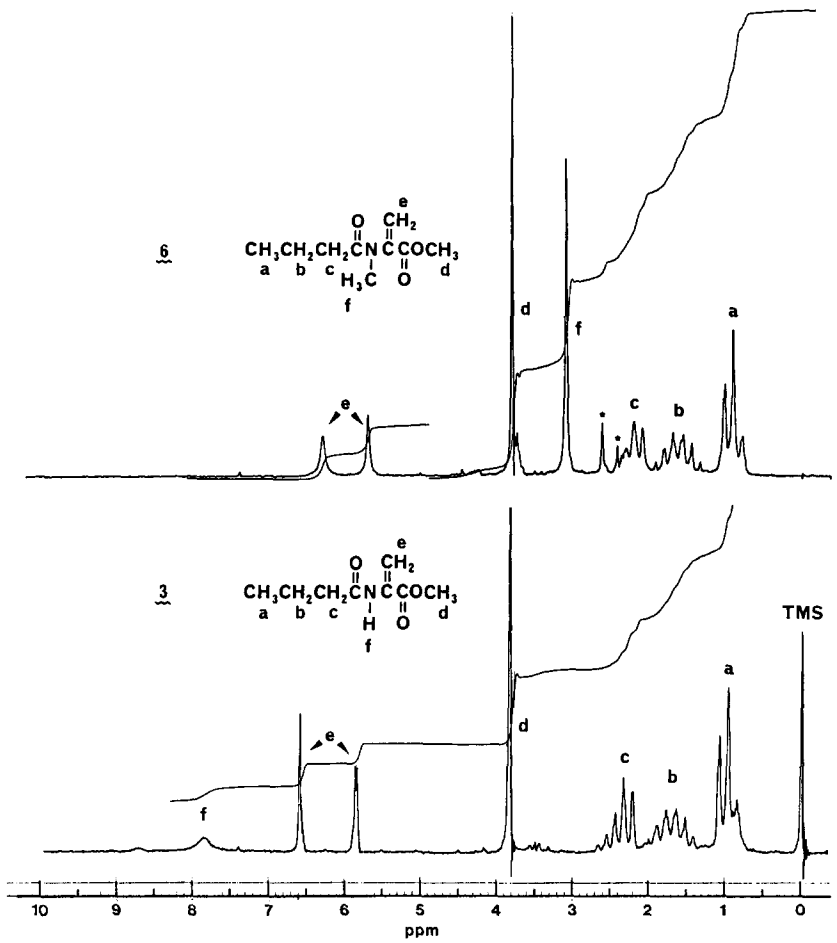


Figure 1. ^{1}H NMR of N-butyryl- (3) and N-methyl-N-butyryldehydroalanine (6) methyl esters.

The ^{13}C NMR spectra of **3** and **6** are given in Figure 2. The N-methyl peak of the latter is barely visible under that of the carbon α to the amide carbonyl. This peak is shifted slightly upfield while both carbonyls are deshielded slightly in **6**. What is most surprising are the ca. 8 and 16 ppm downfield shifts for the alkene peaks of **6** compared to **3**. Perhaps the steric bulk of the added methyl group decreases carbonyl coplanarity with the alkene π-bond, thus decreasing conjugation and putting these carbons in a more deshielding region of the adjacent carbonyl π-cloud.

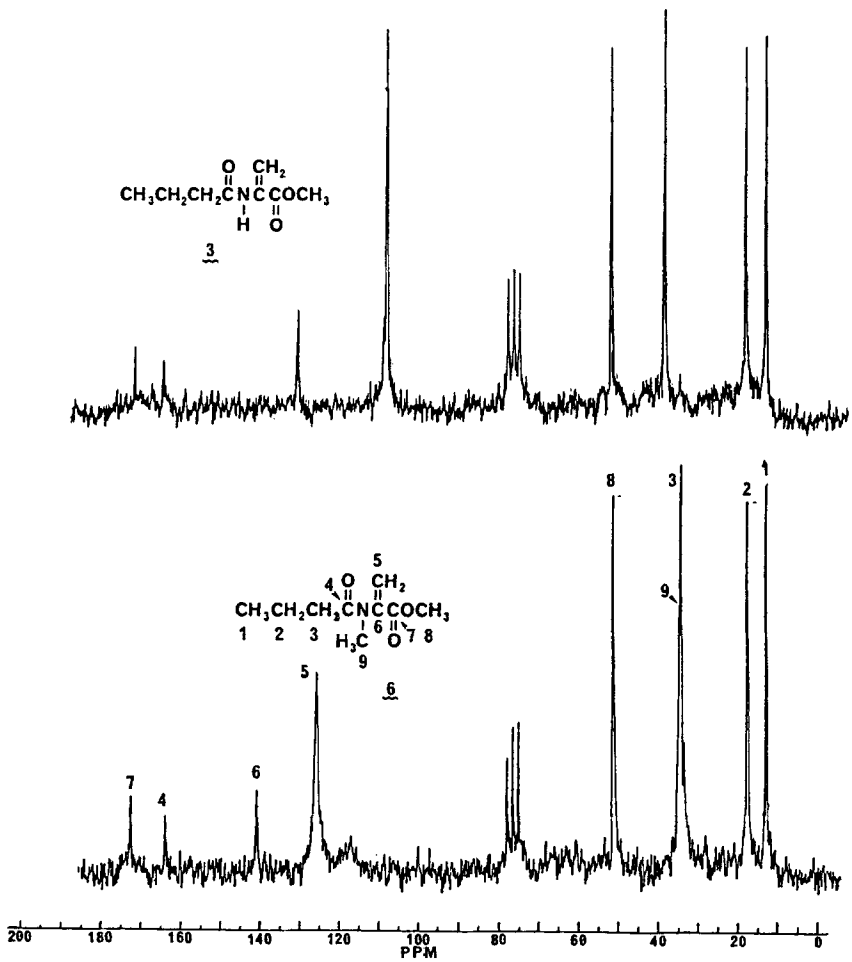


Figure 2. ^{13}C NMR of N-butyryl- (3) and N-methyl-N-butyryldehydroalanine (6) methyl esters.

Polymerization results

Repeated efforts to homopolymerize monomer **6** failed with both free radical and anionic initiators. While this may be due in part to decreased resonance stablization of the reactive chain ends formed from this monomer through decreased coplanarity, it seems more reasonable to suspect the N-methyl group of sterically shielding the terminal position and blocking the approach of incoming monomer. It is known, however, that N-vinylamides containing an extra methyl, ethyl or propyl substituent on the amide nitrogen homopolymerize (5). Thus, it must be the combination of the amide substituent with the adjacent ester group which inhibits homopolymerization.

Copolymerization with less bulky comonomers seemed to offer a possible alternative for polymer formation. While methyl methacrylate gave no copolymer, an equimolar mixture of **6** and methyl acrylate slowly gave a product with a 3-to-1 ratio of acrylate to dehydroalanine units.

The ^{13}C NMR spectrum of the copolymer is given in Figure 3 along with that of a homopolymer of monomer **3**.

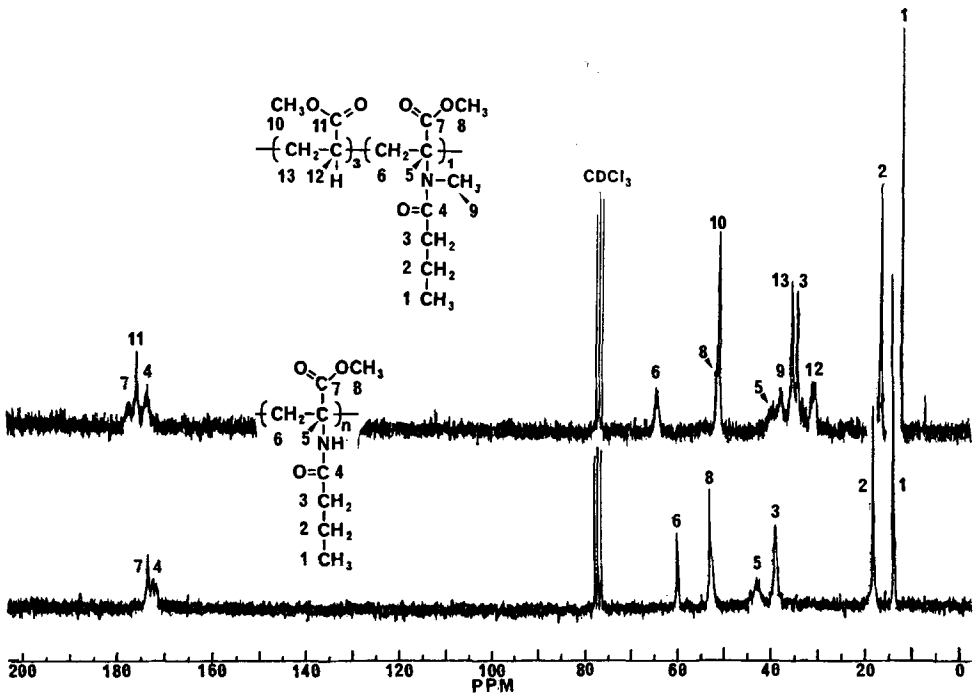


Figure 3. ^{13}C NMR spectra of homopolymer 3 and the 3-to-1 copolymer of methyl acrylate and 6.

Good correlation is seen for peaks of monomer **6** units with homopolymer **3**. In addition, peaks for the acrylate units are almost identical with those of the homopolymer (not shown). Low incorporation of the dehydroalanine groups and slow conversion to copolymer is consistent with formation of a relatively stable captodative radical (6) from monomer **6** which undergoes sterically difficult addition of the acrylate monomer. It is assumed that this copolymer consists of isolated dehydroalanine moieties between short blocks of acrylate units.

Conclusions

These results lead to the following observations and conslusions.

1. Monomer **6** and a variety of analogs are readily available in two steps from the methyl ester of serine.
2. Monomer **6** does not undergo homopolymerization. This would explain why the analogous terminal groups observed previously in oligomer **2** do not radically polymerize to give comb polymers during the oxazoline polymerization.
3. Copolymerization of **6** is possible although it is a sluggish comonomer. This supports the possibility that **2** could also be incorporated as comb units in copolymers but only under forcing conditions and with selected monomers.

Acknowledgements

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