POLY(N-DECANOYLDEDEHYDROALANINE METHYL ESTER) [POLY(METHYL-2-DECANAMIDOPROPENOATE)]

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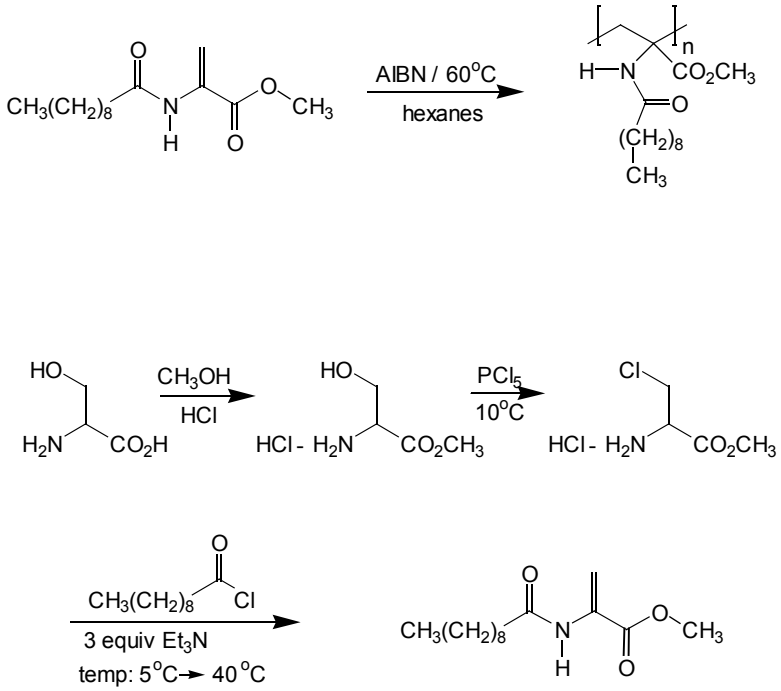
Checked by: C.G. Overberger, R. Bloodworth and A. Tsuei[2]



1. Procedure

a. Monomer Synthesis

Caution! These operations should be carried out in a well-ventilated hood. Benzene and 2-nitropropane are cancer-suspect agents. Decanoyl chloride and PCl_5 are noxious materials. A 500 ml round bottom flask is charged with 3-chloroalanine methyl ester-HCl (8.70 g, 50 mmol, Note 1) and 200 ml hexene, and equipped with a magnetic stirbar and serum stopper. The suspension is stirred in an ice bath while triethylamine (7.0 ml, 50 mmol) is added using an oven-dried syringe. After 15 min, small portions of triethylamine (7.0 ml total volume) and decanoyl chloride (10.5 ml, 50 mmol) are added alternately over 1 h. The reaction temperature is held below 10°C for an additional hour before slowly adding a final equivalent of triethylamine (7.0 ml) to effect the dehydrohalogenation step. The stirred suspension is placed in a 40°C water bath for 2 h, and then refrigerated overnight. The cold suspension is filtered through a coarse fritted-glass funnel to remove the triethylamine-HCl salt. The filtrate is washed twice (500 ml separatory funnel) with 50 ml portions of 0.1N HCl and twice with 50 ml water. The light yellow organic layer is rotary evaporated below 40°C to obtain a yellow oil; crude yield 97% (Note 2). A white crystalline product is obtained from mixed hexanes at -15°C; mp 10.3-11.5°C (Note 3). The checkers suggest that flash chromatography is an effective method of purification for this monomer as well (Note 4).

b. Polymerization

An oven-dried test tube is charged with monomer (1.0 g, 4 mmol), 6 ml hexanes, and 2,2N-azobis(isobutyronitrile) (AIBN) initiator (5-50 mg). The tube is closed with a septum and purged with dry nitrogen for 5 min before suspending it in a 60°C oil bath. Gelation occurs within 4 h although the polymerization is continued for up to 20 h. Some solvent is usually lost by evaporation/diffusion through the septum. The clear polymer gel is dissolved in 5 ml tetrahydrofuran and precipitated into stirring ice-cold methanol (10-fold excess). The polymer mass is removed with forceps and oven dried at 70-80°C overnight; yd >65%.

2. Characterization

The FTIR spectra of monomer and polymer are shown in Figure 1. The vinyl absorption at 1635 cm^{-1} is clearly visible in the monomer while it is absent in the polymer. The C=0 stretch of both the methyl ester and amide functional groups are evident in both spectra (monomer: 1726, 1692 cm^{-1}, polymer: 1739, 1682 cm^{-1}) along with the amide II band at 1515 cm^{-1}.

The ^{13}C NMR spectra are compared in Figure 2. Peak assignments are based on calculated chemical shifts and comparison to model compounds. Monomer vinyl peaks at 130.5 and 109.1 ppm have clearly been converted to polymer backbone carbons observed at 43.0 and 62.0 ppm, respectively. The polymer sample was analyzed by NMR at 80°C to sharpen the backbone and carbonyl carbon peaks, and was found to be essentially atactic by high resolution ^{13}C NMR.

The polymer side-chain crystallinity is shown by both WAXS and DSC. The DSC trace displays a slight endotherm at 70°C (side-chain melting) with a backbone melting endotherm at 190°C.

Polymers have been obtained with molecular weights ranging from 100,000 to 3.6 million.[3] Dilute solution viscosity measurements were made in THF at 25°C using a #50 Cannon-Ubbelohde viscometer. Light scattering (LALLS) data was obtained using a Chromatix KMX-6 spectrophotometer. The Mark-Houwink relationship between intrinsic viscosity [0] (dl/g) and weight-average molecular weight M_w is given below.

$$[0] = 2.63 \times 10^{-4} M_w^{0.63}$$

The polymer is soluble in many organic solvents such as chloroform, methylene chloride and benzene, but only swells in petroleum ether, acetic acid, DMAc, DMF, and methanol. The polymer is insoluble in acetonitrile, DMSO, water, and ethanol.

3. Notes

1. Methyl 2-amino-3-chloropropanoate-HCl or 3-chloroalanine methyl ester-HCl[3] is prepared from commercial D,L-serine methyl ester-HCl. A 1 l reaction kettle is equipped with a mechanical stirrer and charged with 300 ml 2-nitropropane and phosphorous pentachloride (230 g, 1.1 mol). The suspension is stirred in an ice bath while D,L-serine methyl ester-HCl powder (155.6 g, 1.0 mol) is added in small portions over a period of 2 h. The mixture is left at ice temperature overnight. The semi-solid mass is filtered through a fritted glass funnel under nitrogen purge. The white crystalline product is recrystallized from hot absolute methanol, filtered, and rinsed with methylene chloride, and then acetone. The fine white crystalline product is vacuum dried and stored in a refrigerated desiccator; yield >76%; mp 137.9-138.3°C (lit.[4] mp 134-136°C). Chloroform, carbon tetrachloride and methylene chloride have also been used as reaction solvents but were found to give unpredictable yields and a mixture of products.
2. The method described here has been used as a general preparation of alkylamidodehydroalanine methyl esters with carbon chain lengths of 2-18.[5]
3. The purified monomer is very reactive in the liquid state, and care should be taken to reduce time spent at room temperature. We observed one sample spontaneously polymerize to very high molecular weight ([0] = 8.8 dl/g, M_w = ca 15 million) at ca 0°C.
4. Crude monomer (150 mg) is isolated by flash chromatography on silica gel (50 x 130 mm column, 10:1 hexane/ethyl acetate, 40 ml fractions) to afford 75 mg of pure monomer as a colorless oil; TLC R_f = 0.19 (10:1 hexane/ethyl acetate). The purified monomer can be stored under nitrogen for more than one week at 0-5°C.

4. Method of Preparation

Dehydroalanine (Dha), the vinyl analogue of alanine (Ala), is a component of many naturally occurring peptides which exhibit antibiotic properties. These antibacterial polypeptides have been isolated from numerous sources and contain as many as eight dehydroalanine residues. This fact, coupled with the search for new synthetic antibiotics, generated much interest in the preparation of peptides containing biologically active dehydroalanine residues. A review of dehydroamino acids, including dehydroalanine-containing peptides, appeared in 1979.[6]

Many synthetic methods have been established for the introduction of the dehydroalanine residue into peptides. Indirect routes include base-catalyzed elimination reactions on substituted residues of *N*-hydroxy-,[7] *N*_chloro-,[8] and 3-chloroalanine;[9,10,11] ester elimination from 2-acetoxyamino acids,[12] and tosyl esters of serine (Ser)[13] and threonine;[14] and Hofmann elimination from 2,3-diamino acids.[15] Other methods have recently been reported and include direct elimination from cysteine using silver carbonate[16] and the dehydration of serine residues using isoureas,[17] carbodiimides,[18] and a triphenylphosphine-azidodicarboxylate complex.[19] Simpler analogs have been prepared by the direct condensation of pyruvic acid with various amides to produce N-substituted derivatives of dehydroalanine.[20,21] In fact, *N*-acetyldehydroalanine [2-acetamidoacrylic acid] is currently available commercially.[22]

Synthetic polymers have been prepared from various *N*-substituted derivatives of dehydroalanine and are the subject of numerous patents and publications. British (1946)[21] and US (1949)[23] patents describe the bulk and solution polymerization of *N*-acetyldehydroalanine methyl ester [methyl 2-acetamidoacrylate] to produce a clear, water-soluble homopolymer. Copolymers with acrylonitrile, methyl methacrylate, and styrene were also described. We have applied the methyl ester amide synthesis to isocyanates rather than acid chlorides.[24] *N*-alkyl and *N*-aryl urea monomers are obtained which show excellent radical polymerizability.[25]

5. References

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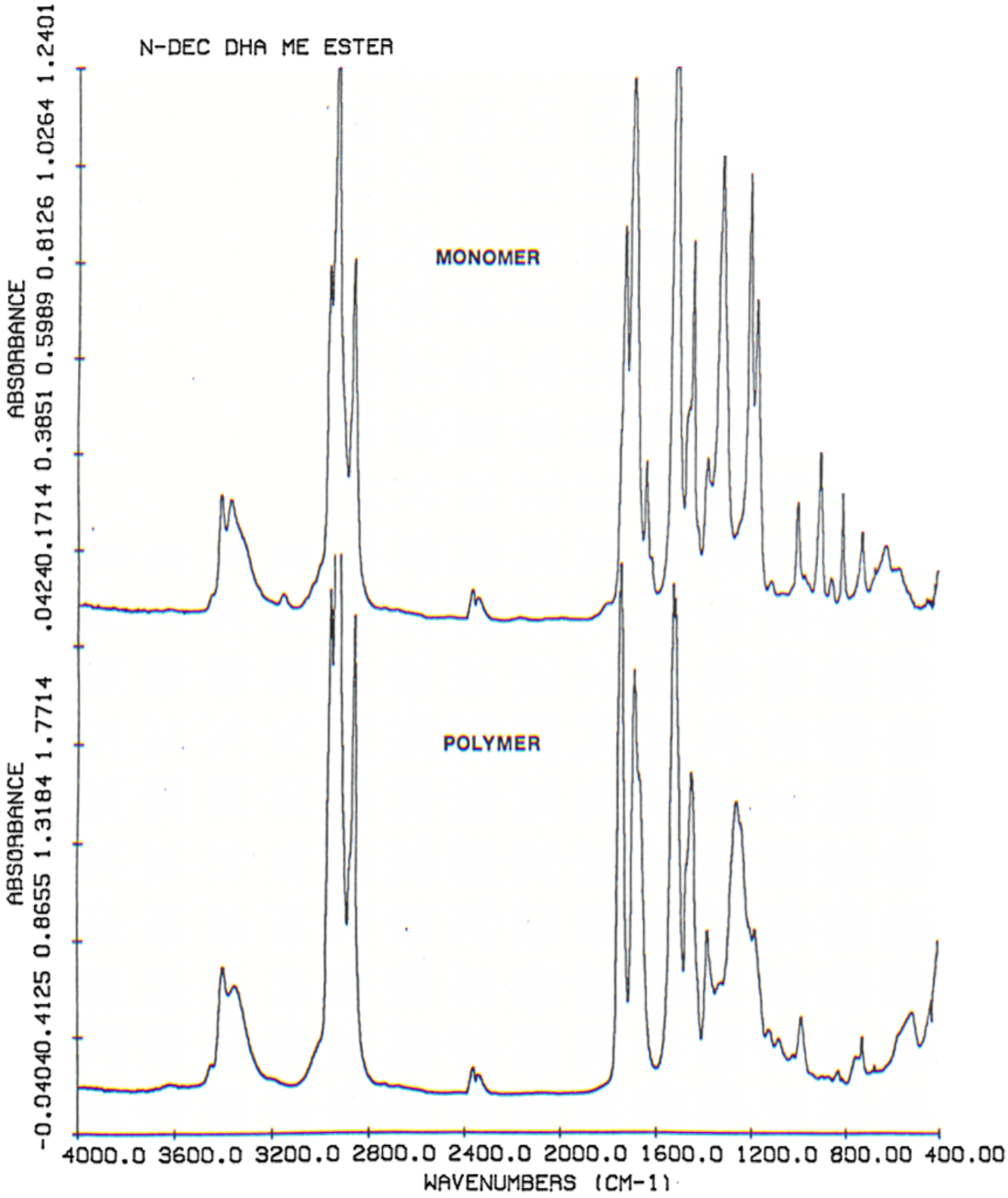
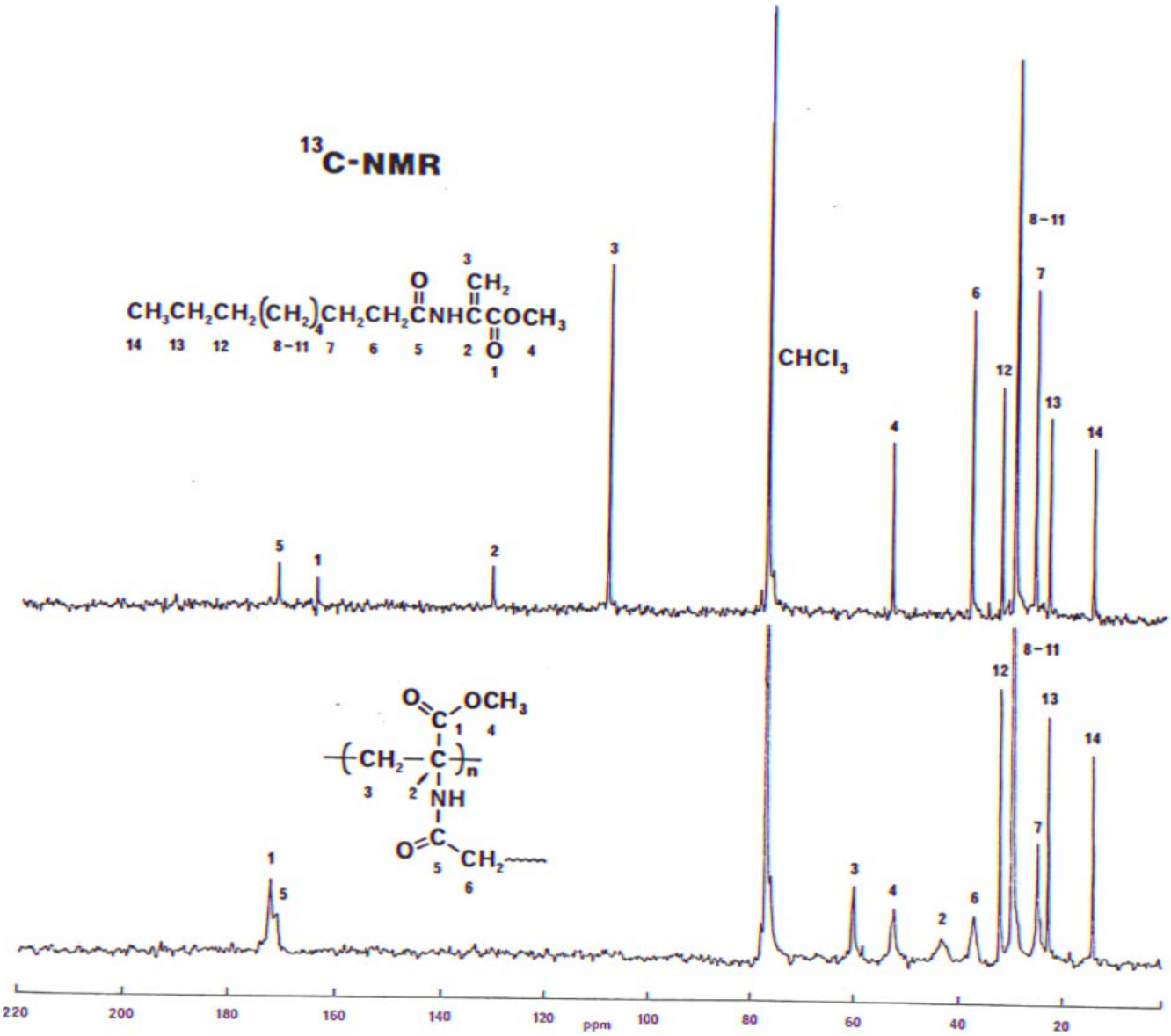

N-DEC DHA ME ESTER
MONOMER
POLYMER
ABSORBANCE
-0.0404 0.4125 0.8655 1.3184 1.7714
ABSORBANCE
.0424 0.1714 0.3851 0.5989 0.8126 1.0264 1.2401
4000.0 3600.0 3200.0 2800.0 2400.0 2000.0 1600.0 1200.0 800.00 400.00
WAVENUMBERS (CM-1)

Figure 1


13C-NMR
CHCl3
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180
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120
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80
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Figure 2