Syntheses and Reactions of Optically Active Polymers. I. Syntheses and Polymerizations of *N*-Vinylbenzyl-L-amino Acid Derivatives

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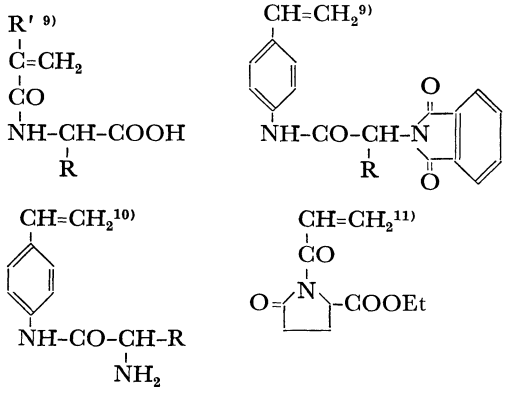
N-Vinylbenzyl-L-amino acids were synthesized by the reaction of L-amino acids with formylstyrenes and the subsequent reduction of the condensation products with sodium borohydride. The procedure was performed without protection of the various functional groups of amino acids and racemization was not accompanied by the above process. The method is useful for the synthesis of optically active vinyl monomers containing various amino acids with their intact functionality. As a representative L-amino acid, a variety of *N*-vinylbenzyl-L-leucine derivatives such as *N*-methyl-L-leucine, L-leucine ethyl ester, L-leucinol and *N*-formyl-L-leucine ethyl ester were prepared by means of chemical transformation. These optically active monomers of leucine derivatives were polymerized to optically active polymers.

Though considerable attempts were made to carry out asymmetric syntheses using optically active polymers as catalysts or reagents,[1–5] no clear asymmetric courses, as usually seen in the formation of low optically active products, have been established. Steric regulation for asymmetric induction would be better achieved by proper selection of a functional group responsible for the asymmetry in the reaction course.

We previously reported on the use of polymers as chemical reagents in amide group formation.[6] To extend the utility of reagents of this type, we have undertaken the investigation of syntheses and reactions of polymers containing optically active groups.

The groups of our primary concern are those derived from α-amino acids, which contain one asymmetric carbon and various functional groups. Some devices have been worked out for the preparation of synthetic polymers possessing α-amino acid residues. Most polymers were synthesized through polymer reactions by which α-amino acids were introduced into reactive polymers, such as chloromethylated polystyrene[7] polymethacroyl chloride.[8] A few polymers have also been obtained by polymerizations of vinyl monomers containing α-amino acids as shown below.[9–11]



In polymer reactions, undesirable side reactions are sometimes inevitable. As to the monomers hitherto prepared, either amino- or carboxyl-group was transformed into amide for introduction of the vinyl group.

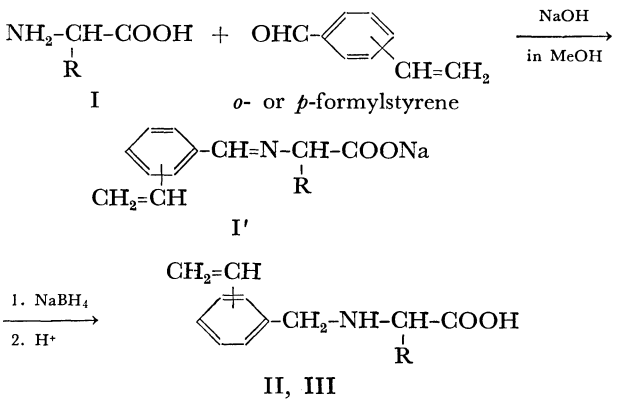
In order to use optically active polymers as chiral components for asymmetric reactions, it is desirable that they are prepared by polymerization of optically active monomers. This paper describes a new convenient synthesis and polymerization of vinyl monomers which contain an optically active α-amino acid moiety.

Results and Discussion

Syntheses of N-*Vinylbenzyl-*L-*amino Acids.* Quitt *et al.*[12] reported a synthetic procedure of *N*-benzyl-L-amino acids, in which L-amino acids were allowed to react with benzaldehyde and be reduced subsequently with sodium borohydride.

This procedure was applied and a variety of *N*-vinylbenzyl-L-amino acids were prepared by the reaction of L-amino acids with *o*- or *p*-formylstyrene according to Scheme 1.

The reaction of sodium salt of L-amino acids, glycine, valine, leucine, tyrosine, histidine and glutamine, was carried out in methanol at room temperature. Intermediate (I′) formed was not isolated but was reduced with sodium borohydride under cooling conditions to give *N*-vinylbenzyl-L-amino acids (II or III) as crystals after acidification of the reaction mixture. Vinyl monomers II and III were obtained in good yield without protection of the functional groups. The physical data of the monomers synthesized by the above procedure



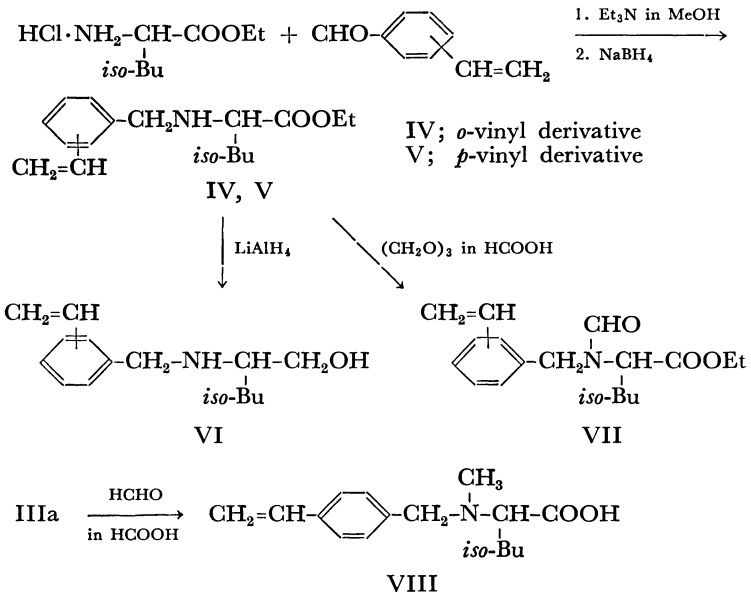
II; *o*-vinyl derivatives, III; *p*-vinyl derivatives
R; IIa=H, IIb=*iso*-Pro, IIc=*iso*-Bu,
IId=CH_2-(C$_6$H$_4$)-OH, IIe=CH_2-(imidazole), IIf=$CH_2CH_2CONH_2$
IIIa=*iso*-Bu, IIIb=$CH_2CH_2CONH_2$

Scheme 1.

TABLE 1. PHYSICAL DATA OF *N*-VINYLBENZYL-L-AMINO ACIDS

Product (Formula)	Yield (%)	Mp (°C)	Recrystallization Solvent	$[\alpha]_D^{23}$	Anal. (Calcd) (%) C	H	N
IIa ($C_{11}H_{13}O_2N$)	48	202 (dec.)	Water		68.72 (69.09	6.83 6.85	7.39 7.33)
IIb ($C_{14}H_{19}O_2N$)	62	224 (dec.)	Water-DMF[a)]	+39.5[b)]	71.56 (72.07	8.28 8.21	6.20 6.20)
IIc ($C_{15}H_{21}O_2N$)	76	196 (dec.)	Water-Acetic acid	+27.5[b)]	73.28 (72.84	8.76 8.56	5.78 5.66)
IId ($C_{18}H_{19}O_3N$)	83	235 (dec.)	DMF	+ 3.5[c)]	72.01 (72.70	6.51 6.44	4.99 4.71)
IIe ($C_{15}H_{17}O_2N_3$)	66	113 (dec.)	Water	−12.0[b)]	66.37 (66.40	6.54 6.32	15.06 15.49)
IIf ($C_{14}H_{18}O_3N_2$)	58	164 (dec.)	Water	+ 9.5[b)]	64.07 (64.10	7.00 6.92	10.65 10.68)
IIIa ($C_{15}H_{21}O_2N$)	80	208 (dec.)	d)	+11.0[c)]	72.58 (72.84	8.59 8.56	5.46 5.66)
IIIb ($C_{14}H_{18}O_3N_2$)	83	188 (dec.)	Water	+24.0	63.95 (64.10	6.89 6.92	10.54 10.68)

a) DMF; *N*,*N*-dimethylformamide. b) $c=2.0$, in acetic acid. c) $c=2.0$, formic acid. d) The compound was purified by reprecipitation twice from formic acid into water.



Scheme 2.

are given in Table 1. These amino acid derivatives are optically active and are insoluble in non-polar organic solvents. *o*-Vinyl derivatives are more soluble than *p*-vinyl derivatives in acetic acid, trifluoroacetic acid and formic acid.

Hydrogenolysis of compounds IIb and IIc with palladium-carbon catalyst produced the starting amino acids, L-valine and L-leucine. Optical rotations of the hydrogenolysis products coincided with those of the starting L-amino acids, indicating that the reactions according to Scheme 1 proceed without recemization.

Syntheses of N-*Vinylbenzyl-*L-*leucine Derivatives.* L-Leucine was selected as a representative, and several vinyl monomers carrying the derivatives of this amino acid were prepared according to Scheme 2.

The reaction of L-leucine ethyl ester with formylstyrenes gave *N*-vinylbenzyl-L-leucine ethyl esters IV and V. The reduction of IV with lithium aluminium hydride yielded *N*-*o*-vinylbenzyl-L-leucinol (VI). The reaction of IV with trioxane in formic acid did not give the *N*-methylated product but *N*-formyl-*N*-*o*-vinylbenzyl-L-leucine ethyl ester (VII). *N*-methylation of IIIa was carried out with formalin in formic acid to give *N*-methyl-*N*-*p*-vinyl-benzyl-L-leucine (VIII). The results are summarized in Table 2. The L-leucine derivatives are optically active. Vinyl monomers IV, V, VI and VII are easily soluble in almost all organic solvents, while the *N*-methylated amino acid(VIII) is soluble in acetone, methanol, chloroform and other polar solvents.

Optically active vinyl monomers containing various functional groups derived from α-amino acids were

Table 2. Physical data of *N*-vinylbenzyl-L-leucine derivatives

Product (Formula)	Yield (%)	Bp (Mp) (°C/mmHg)	$[\alpha]_D^{23}$	Anal. (Calcd) (%) C	H	N
IV ($C_{17}H_{25}O_2N$)	66	129—131/0.5	−39.5[a]	74.45 (74.14	9.36 9.15	4.97 5.09)
V ($C_{17}H_{25}O_2N$)	73	153—155/1	−50.5[a]	73.96 (74.14	8.69 9.15	5.01 5.09)
VI ($C_{15}H_{23}ON$)	70	(57—59 °C)	+22.3[a]	77.27 (77.20	10.22 9.94	6.06 6.00)
VII ($C_{18}H_{25}O_3N$)	59	173—177/1	−17.0[a]	71.39 (71.25	8.16 8.31	4.57 4.62)
VIII ($C_{18}H_{27}O_2N$)	73	(158—160 °C)	+48.5[b]	73.56 (73.53	8.86 8.87	5.30 5.36)

a) $c=2.0$, in abs. ethanol. b) $c=2.0$, in acetic acid.

Table 3. Polymerization of *N*-vinylbenzyl-L-leucine derivatives[a]

Monomer	(g)	AIBN (mg)	Solvent	Polymerization Time (hr)	Product	Yield (g)
			Homopolymerization			
IIIa	2.47	82	Formic acid	60	IX	2.52
V	2.74	164	Bulk	40	X	2.24
VIII	2.61	82	Acetic acid	40	XI	2.54
			Copolymerization with Styrene[b]			
IIc	2.47	328	Acetic acid	40	XII	3.66
V	4.11	492	Bulk	40	XIII	8.31
V	2.74	328	Benzene	60	XIV	5.10
VIII	2.61	328	Acetic acid	40	XV	5.64
			Cross-linking Polymerization[c]			
IIc	2.47	328	Acetic acid	20	XVI	5.81
V	5.48	492	Benzene	20	XVII	12.85
VIII	2.61	328	Acetic acid	20	XVIII	6.19

a) Polymerization conditions; solvent 10 ml, temperature 75—80 °C, in sealed tube. b) Mole ratios of initial mixture; leucine derivative: styrene = 1 : 3. c) Mole ratios of initial mixture; leucine derivatives : styrene : divinylbenzene = 2 : 5 : 1.7.

prepared easily without protection of the functional groups (Schemes 1 and 2).

Polymerization of N-*Vinylbenzyl*-L-*leucine Derivatives.* Homo- and co-polymerizations of *N*-vinylbenzyl-L-leucine derivatives were carried out with the use of azobisisobutyronitrile (AIBN) as an initiator at 75—80 °C. The results are summarized in Tables 3 and 4.

Homopolymerization of IIIa in formic acid gave *N*-formylated homopolymer (IX). Homopolymer of V was gummy and became insoluble after a few weeks. Copolymerization of IIc, V, and VIII with styrene gave the corresponding copolymers, whose compositions coincided with mole ratios of the initial monomer mixtures. The inherent viscosities of copolymers were low, but the infrared absorption bands at 990 and 910 cm^{-1} (–CH=CH_2) disappeared virtually in the IR spectra of the products. The homo- and co-polymers shown in Table 4, are optically active. Cross-linking polymerization of L-leucine derivatives in the presence of divinylbenzene (DVB) was carried out with an AIBN initiator. Cross-linked insoluble polymers were obtained in good yield. Polymers IX and XI are soluble in formic acid, acetic acid, and trifluoroacetic acid and insoluble in other organic solvents. Polymers XII and XV are soluble in formic acid, trifluoroacetic acid, pyridine, and *N*,*N*-dimethylformamide and insoluble in ether and methanol. Polymers XIII and XIV are soluble in almost all organic solvents except methanol and ethanol.

These optically active functional polymers might be useful as adsorbents for the chromatographic resolution of amino acid racemates, or as chiral components for asymmetric syntheses.

Experimental

The melting points were uncorrected. The IR spectra were obtained as potassium bromide disks with a Jasco Model DS-403G grating infrared spectrophotometer. Optical rotations were determined with a Jasco Model ORD/UV-5 optical rotatory dispersion recorder. Formylstyrenes were prepared by Dale's method.[13]

Preparation of N-*vinylbenzyl*-L-*amino Acids.* The following is an example of the general procedure. L-Leucine, 3.93 g (0.03 mol), was dissolved in 30 ml of methanol containing 1.20 g (0.03 mol) of sodium hydroxide and 1.0 ml of water. To this solution was added 4.20 g (0.032 mol) of *o*-formylstyrene with stirring at room temperature. After 1 hr, 5 ml of water containing 0.75 g (0.02 mol) of sodium borohydride was added dropwise below 20 °C by cooling

TABLE 4. PHYSICAL PROPERTIES OF POLY-*N*-VINYLBENZYL-L-LEUCINE DERIVATIVES

Polymer	Softening Temp. (°C)	$[\alpha]_D^{23}$	$[\eta]$ inh	Anal. (Calcd) (%) C	H	N	Mole-% of Amino acid[a]
			Homopolymer				
IX	>300	−20.0[b]	0.77[c]	69.40 (69.79	7.91 7.69	5.20 5.09)[d]	—
X	—	—	—	73.62 (74.14	9.04 9.15	5.32 5.09)	—
XI	>300	+4.2[b]	0.57[c]	72.81 (73.53	8.80 8.87	5.37 5.36)	—
			Copolymer with Styrene				
XII	95—115	−3.1[e]	0.07[f]	82.80 (83.72	7.99 8.05	2.59 2.50)[g]	26.2
XIII	85— 95	−25.0[e]	0.17[f]	83.61 (84.0	8.37 8.36	2.49 2.39)[g]	26.5
XIV	85— 95	−23.6[e]	0.09[f]	83.50 (84.0	8.32 8.36	2.70 2.39)[g]	29.0
XV	160—170	−11.2[e]	0.11[f]	82.63 (83.70	8.21 8.19	2.77 2.44)[g]	29.9
			Cross-linked Copolymer				
XVI	>300	—	—	84.65	8.14	2.92	32.2
XVII	>300	—	—	85.14	8.47	2.27	22.9
XVIII	>300	—	—	85.25	8.34	2.32	24.4

a) Based on nitrogen analysis. b) $c=2.0$, in formic acid. c) $c=0.5$ g/dl, in formic acid. d) calculated for the *N*-formylated polymer ($C_{16}H_{21}O_3N$). e) $c=2.0$, in tetrahydrofuran. f) $c=0.5$ g/dl, in tetrahydrofuran. g) calculated for the initial copolymerization mixture.

with ice-cold water, and the solution was stirred for 1 hr under cooling. The pH was then adjusted to 5—6 with diluted hydrochloric acid. *N-o*-Vinylbenzyl-L-leucine was precipitated as white crystals and filtered and washed with acetone. The yield was 6.8 g (76%). Recrystallization from water-acetic acid gave a pure material, mp 196 °C (dec.).

N-p-Vinylbenzyl-L-leucine was prepared with *p*-formylstyrene instead of *o*-formylstyrene. The other *N*-vinylbenzyl-L-amino acids were similarly obtained by the reactions of L-amino acids with formylstyrenes. The results are summarized in Table 1.

IR absorption bands common to *N-o*-vinylbenzyl-L-amino acids are as follows: (cm^{-1}), 3200 (NH), 3080—3020 (aromatic CH), 1620—1550 (COO^-), 990, 910 ($-CH=CH_2$), 780 (*o*-substituted benzene), and those for *N-p*-vinylbenzyl-L-amino acids are 3200 (NH), 3080—3030 (aromatic CH), 1620—1550 (COO^{-1}), 990, 910 ($-CH=CH_2$), 850—800 (*p*-substituted benzene).

Hydrogenolyses of compounds (IIb) and (IIc) (1.0 g) with 10% palladium-carbon catalyst (0.5 g) were carried out in acetic acid (20 ml) at 80 °C and 100 atm for 10 hr. Palladium-carbon was filtered off. Acetic acid was then, evaporated under vacuum, and the residue was recrystallized from water. L-Leucine; yield 0.42 g, mp 293 °C (dec.), $[\alpha]_D^{27}$ −11.0 (*c* 2.0, H_2O). L-Valine; yield 0.37 g, mp 300 °C, $[\alpha]_D^{27}$ +6.3 (*c* 4.8, H_2O).

Preparation of N-*Vinylbenzyl-L-leucine Ethyl Ester.* L-Leucine ethyl ester hydrochloride, 19.5 g (0.10 mol), and triethylamine, 10.2 g (0.10 mol), were dissolved in 100 ml of methanol. *o*-Formylstyrene, 13.5 g (0.10 mol), was added to this solution at room temperature. After stirring for 1 hr, 30 ml of water containing 3.8 g (0.10 mol) of sodium borohydride was added dropwise below 20 °C by cooling with ice-cold water and stirring. The solution was stirred for 1 hr under cooling, and then 20 ml of 5% sodium carbonate solution was added. This solution was extracted three times with 150 ml of ether. The ether solution was dried with sodium sulfate, and concentrated. The residue was distilled in the presence of 0.5 g of cuprous chloride under vacuum to yield 18.2 g (66%) of *N-o*-vinylbenzyl-L-leucine ethyl ester, bp 129—131 °C/0.5 mmHg.

N-p-Vinylbenzyl-L-leucine ethyl ester was similarly obtained, bp 153—155 °C/1 mmHg. The yield was 70%.

IR data (cm^{-1}); 3080, 3070 (aromatic CH), 2980, 2880 (isobutyl), 1720 (COOEt), 1625 ($-CH=CH_2$), 1450, 1370 (isobutyl), 1170, 1150 (ester), 990, 910 ($-CH=CH_2$), 825 (*p*-vinyl compound), 775 (*o*-vinyl compound).

Preparation of N-o-*Vinylbenzyl-L-leucinol.* *N-o*-Vinylbenzyl-L-leucine ethyl ester, 16.0 g (0.058 mol), in 70 ml of ether was added dropwise with stirring to lithium aluminium hydride, 3.8 g (0.10 mol) in 80 ml of ether. After the mixture was stirred for 40 min and then diluted with ether, 10 ml of water was added with vigorous stirring. The ether solution was filtered, and the precipitate was washed with ether and with methanol. The washings were combined with the filtrate. The mixture was dried, and concentrated under vacuum to give crystals. Recrystallization from *n*-hexane gave a pure material in 70% (9.4 g) yield, mp 57—59 °C.

IR data (cm^{-1}); 3500 (OH), 3080—3000 (aromatic CH), 2990, 2920, 2880 (isobutyl), 1630 ($-CH=CH_2$), 1590, 1490, 1450 (benzene ring), 1100—1050 (-C-O-) 990, 910 ($-CH=CH_2$), 780 (*o*-substituted benzene).

Reaction of N-o-*Vinylbenzyl-L-leucine Ethyl Ester with Trioxane in Formic Acid.* *N-o*-Vinylbenzyl-L-leucine ethyl ester, 8.0 g, and trioxane, 1.0 g, were dissolved in 5 ml of formic acid. The solution was heated at 95—1000 °C for 2 hr, and then concentrated under vacuum. The residue was distilled under vacuum to give *N-o*-vinylbenzyl-*N*-formyl-L-leucine ethyl ester, bp 173—176 °C/1 mmHg. The yield was 5.1 g.

IR data (cm^{-1}); 3080, 3070 (aromatic CH), 2980, 2970 (isobutyl), 1730 (ester), 1670 (amide), 1625 ($-CH=CH_2$).

Preparation of N-p-*Vinylbenzyl-N-methyl-L-leucine.* *N-p*-Vinylbenzyl-L-leucine, 15.0 g (0.06 mol) was suspended in

the solution of formic acid (12 ml) and 40% formalin (9 ml; *ca.* 0.12 mol) and heated on a water bath for 30 min. *N-p*-Vinylbenzyl-L-leucine was gradually dissolved into the solution with vigorous carbon dioxide evolution. This solution was concentrated under vacuum. Water was added to the residue and then evaporated. The procedure was repeated three times. *N-p*-Vinylbenzyl-*N*-methyl-L-leucine, thus separated, was recrystallized from benzene two times. The yield was 12.2 g, mp 158—160 °C.

IR data (cm^{-1}); 1600 (COO^-), 1370 (CH_3), 990, 910 ($-CH=CH_2$), 845, 825 (*p*-substituted benzene).

Polymerization of N-*Vinylbenzyl-L-leucine Derivatives.* Homo- and co-polymerizations of *N*-vinylbenzyl-L-leucine derivatives were carried out with 5—10 mol% of azobisisobutyronitrile (AIBN) as an initiator at 75—80 °C. The amounts of monomers and solvents used are given in Table 3.

The polymerization tubes were sealed off under vacuum, and heated in a thermostated bath. After polymerization, the polymer solution was poured into a non-solvent and the polymer obtained as precipitates was purified by reprecipitation.

Cross-linked polymers (XVI—XVIII) were similarly prepared by polymerization in the presence of divinylbenzene, purified by washing with benzene and with methanol, respectively, in a Soxhlet extractor for 5 hr.

Non-solvents were acetone for IX, water for X, ether for XI and XV, and methanol for XII, XIII and XIV. Solvents were formic acid for IX and XI, and tetrahydrofuran for X, XII, XIII, XIV and XV.

In the IR spectra of homopolymers, the bands at 990 and 910 cm^{-1} ($-CH=CH_2$) disappeared completely. In the IR spectra of copolymers the bands at 1630, 990 and 910 cm^{-1} ($-CH=CH_2$) disappeared, and those at 1490, 750 and 690 cm^{-1} ($-CH=CH_2$) disappeared, and those at 1490, 750 and 690 cm^{-1} ($-CH_2-CH-C_6H_5$) appeared.

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