Catalytic Asymmetric Cyanohydrin Synthesis with Synthetic Optically Active Polymer. I. Synthesis of Benzaldehyde Cyanohydrin

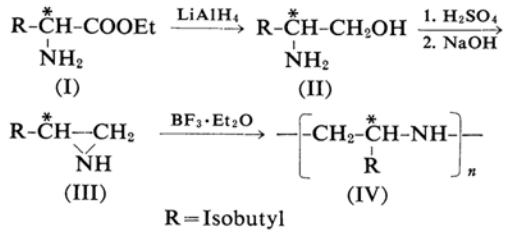
By Sei TSUBOYAMA

(Received November 29, 1961)

Catalytic asymmetric synthesis with optically active substances has been studied by several investigators[1-6], however, no attempts with synthesized polymer. The present author used a synthesized optically active polymer with amino groups as functional group for asymmetric synthesis of benzaldehyde cyanohydrin. This study is of interest for the subject is an enzyme model of biological asymmetric synthesis.

Recently, Minoura et al.[7] reported that, in the polymerization of R- and S-propylenimine, asymmetry of the obtained polymer was well retained. This process was considered available for the synthesis of an optically active polymer with functional groups. In the present work, S-isobutyl-ethylenimine (III), synthesized from L-leucine, was polymerized to an optically active linear polymer IV with ring opening.

1) L. Rosenthaler, *Biochem. Z.*, **14**, 238 (1908); **19**, 186 (1909); **239**, 227 (1931).
2) G. Bredig et al., ibid., **46**, 7 (1912); **249**, 241 (1932); **250**, 414 (1932); **282**, 88 (1935).
3) H. and E. Albers, *Z. Naturforsch.*, **9b**, 122, 133 (1954).
4) V. Prelog and M. Wilhelm, *Helv. Chim. Acta*, **37**, 1634 (1954).
5) H. Pracejus, *Ann.*, **622**, 10 (1959); **634**, 9 (1960).
6) V. K. Krieble and W. A. Wieland, *J. Am. Chem. Soc.*, **43**, 164 (1921).
7) Y. Minoura et al., ibid., **81**, 4689 (1959).



This polymer is solid, softening at about 56°C. Its molecular weight is 4000~6000, and the sign of optical rotation is opposite to that of the monomer, similar to poly-s-propylenimine. An insoluble polymer could not so far be obtained by common cross-linking reagents except tolylene-diisocyanate.

In carrying out the asymmetric cyanohydrin synthesis, styrene-divinylbenzene copolymer containing methyl-D-glucosamide, diethylaminoethyl cellulose, L-leucinol, quinine and Amberlite IR-4B were also employed as catalysts for reference. The results are listed in Table V.

Experimental

Preparation of s-Isobutyl-ethylenimine Polymer (IV, IEI-Polymer).—*L-Leucinol (II).* — The amino alcohol was prepared as described by Karrer[8]. L-Leucine ethyl ester[9] (I) (20 g., 0.125 mol.; b. p. 74°C/7 mmHg, n_D^{20} 1.4289) in ether (150 ml.) was added dropwise with stirring to lithium aluminum hydride (7.6 g., 0.2 mol.) in ether (170 ml.). After the mixture was stirred for 15 min., diluting with ether, water (10 ml.) was added with vigorous stirring. The ether solution was decanted from the precipitate, which was extracted with ether and then with alcohol. These extracts were combined with the first ether solution. The mixture was dried and fractionated under reduced pressure, this gave 10~12 g. (69~82%) of L-leucinol, 78.5°C/2 mmHg, 83°C/4 mmHg, n_D^{27} 1.4470.

s-Isobutyl-ethylenimine (III). — The imine was obtained by a modified procedure of Campbell[10]. A cold mixture of sulfuric acid (11 g., 0.11 mol.) and water (20 ml.) was added with shaking to a solution of L-leucinol (11.7 g., 0.1 mol.) and water (20 ml.). The mixture was distilled at atmospheric pressure until the temperature of the contents reached 115°C. The distillation was continued under reduced pressure while the bath temperature was gradually raised to 180°C. The contents, when solidified, were left as it was for one hour. A cold solution of 40% sodium hydroxide (25 g., 0.25 mol.) was added to the cooled solidified product. The mixture was distilled and the distillate at 94~101°C was collected and saturated with potassium hydroxide. The organic layer formed was separated and was dried with potassium hydroxide pellets and finally with sodium. Distillation gave 4.5 g. (45%) of colorless liquid of ammoniacal odor, b. p. 130~131°C, d_{28}^{28} 0.8123, n_D^{28} 1.4242, $[\alpha]_D^{28}$ −15.39° (original liquid), $[\alpha]_D^{32}$ −24.60° (*c* 1.828 in benzene).

Found: C, 72.58; H, 13.12; N, 13.72%; MR_D, 31.172. Calcd. for $C_6H_{13}N$: C, 72.66; H, 13.21; N, 14.12%; MR_D, 31.307.

The infrared spectrum of the imine III is shown in Fig. 1.

Polymerization of the Imine III.—The polymerization was carried out according to Minoura's procedure. s-Isobutyl-ethylenimine was placed in a dry nitrogen-filled hard glass tube which was

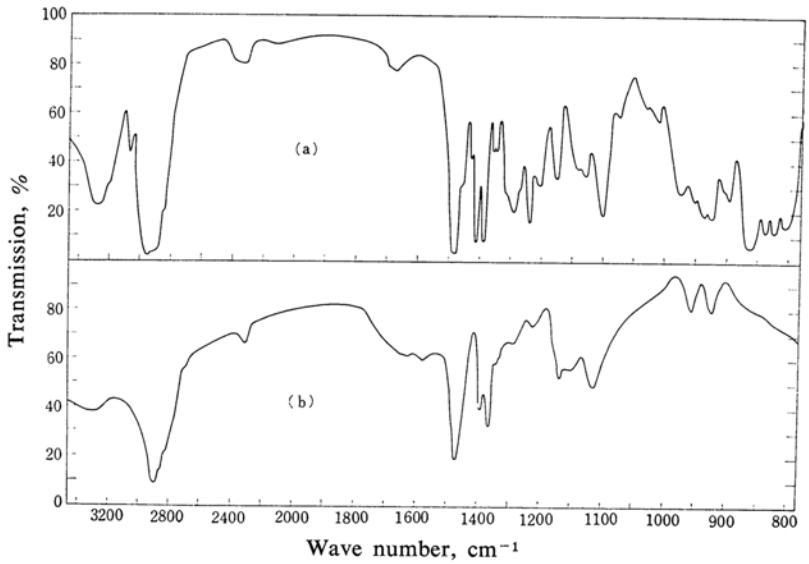


Fig. 1. Infrared absorption spectra of s-isobutyl-ethylenimine (a) and its polymer (b).

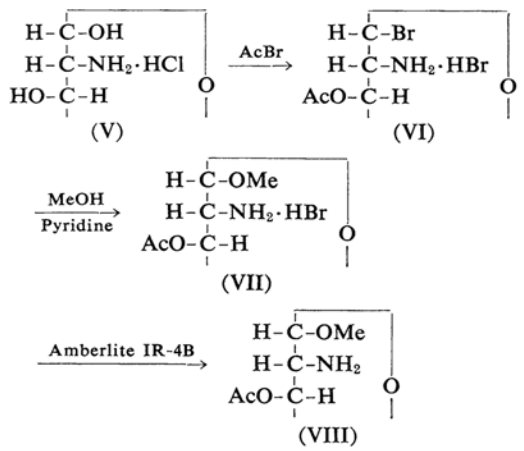
8) P. Karrer et al., *Helv. Chim. Acta*, **31**, 1617 (1948).
9) E. Fischer, *Ber.*, **34**, 442 (1901).
10) K. N. Campbell et al., "Organic Syntheses", Coll. Vol. III (1955), p. 148; T. L. Cairns, *J. Am. Chem. Soc.*, **63**, 871 (1941).

TABLE I. POLYMERIZATION OF S-ISOBUTYL-ETHYLENIMINE*1

Temp. °C	Time hr.	Catalyst		Yield of polymer g.	Mol. wt.	Softening point °C	$[\alpha]_D^{20}$ in C_6H_6	$[\alpha]_D^{20}$ in EtOH
80	20	$BF_3 \cdot Et_2O$	0.2 ml.	2.36			62.6	
80	24	$BF_3 \cdot Et_2O$	0.2 ml.	2.41			66.3	
100	48	$BF_3 \cdot Et_2O$	0.2 ml.	2.40	4000～5000	55	60.6	50.8
25～90*2	53 days	$BF_3 \cdot Et_2O$	0.2 ml.	2.15	4000～6000*3	56	66.7	
150	24	Conc. HCl	0.2 ml.		1020*4			37.5
80	24	Camphor sulfonic acid	0.05 g.			53		

*1 The used imine was 2.5 g.
*2 The temperature was raised gradually.
*3 The polymer was used in the asymmetric synthesis. Found: C, 72.12; H, 12.65; N, 13.69. Calcd. for $(C_6H_{13}N)_n$: C, 72.66; H, 13.22; N, 14.12%.
*4 Found: C, 71.55; H, 12.98; N, 13.34%.

cooled in a dry ice-methanol bath, and when cooled, boron trifluoride-etherate was added to the imine. The tube, after flushed again with nitrogen and sealed, was placed in a constant temperature bath (see Table I). After the required reaction time, the reaction mixture was dissolved in benzene and washed with 10% sodium hydroxide solution to remove the catalyst. The pale yellow benzene solution of the polymer was then washed with deionized water until the washings became neutral and was dried with anhydrous sodium sulfate. The benzene was then removed from the solution in vacuo at room temperature (freez-dry technique was always unsuccessful with this polymer). The obtained polymer was tacky, it solidified when cooled in a dry ice bath. The pale yellow glassy polymer softened at about 56°C. The softened polymer did not vitrify at room temperature unless cooled again in a dry ice bath. The polymer was soluble in common organic solvents, slightly soluble in dimethyl formamide, and insoluble in water. Its molecular weight was measured by cryoscopic method in benzene. For the polymerization, hydrochloric acid and camphor-sulfonic acid were also used as catalysts in place of boron trifluoride as shown in Table I. The infrared spectrum of the linear polymer is given in Fig. 1. From the spectra, it is found that characteristic absorption of ethylenimine, 3070 cm^{-1}, disappeared in spectrum of the polymer.



Polymer Containing Methyl-D-glucosamide (GA-Resin). — Generally, methyl glucoside of amino sugar is said to be very resistant to acid hydrolysis on account of its positive charge of amino group or betain structure, especially, methyl-D-glucosamide is known to be extremely stable to alkali[11,12]. For that reason, methyl-D-glucosamide is available as a functional group for anion exchange resin. Moreover, the amine has many hydroxy groups and many asymmetric carbons. The amine was introduced into chloromethylated styrene-divinylbenzene copolymer.

3,4,6-Triacetyl-methyl-D-glucosamide (VIII). — The amine was prepared from D-glucosamine hydrochloride (V) via bromotriacetyl-D-glucosamine hydrobromide (VI) and triacetyl-methyl-D-glucosamide hydrobromide (VII)[11]. A methanol solution of glucosamide hydrobromide (VII) was passed through a column of free form of Amberlite IR-4B to remove bromine anion. In this procedure, α- and β-methyl-D-glucosamide mixture is supposed to be produced. Recrystallizations from methanol-ether gave free glucosamide (VIII) of m. p. 139～140°C, $[\alpha]_D^{14}$ −20° (*c* 1; methanol).

TABLE II. CAPACITIES OF AcO-GA-RESIN AND GA-RESIN

Amination Temp. °C	Amination Time hr.	Capacities (meq./g.) AcO-GA-Resin HCl	AcO-GA-Resin MA*	GA-Resin HCl	GA-Resin MA*
70	5	1.20	1.84		
85	15	1.83	2.48	2.21	2.68**
90	20	1.60			
100	15	1.55	2.10	1.88	1.96

* MA: Mandelic acid.
** Nitrogen contents: AcO-GA-resin, 2.83; GA-resin, 3.13%. Calculated capacities from the nitrogen contents: AcO-GA-resin, 2.02; GA-resin, 2.24 meq./g. 83% of chlorine in chloromethylated polymer was exchanged by the glucosamide. For the asymmetric synthesis the resin was used.

11) J. C. Irvine et al., *J. Chem. Soc.*, **99**, 250 (1911).
12) R. C. G. Moggridge and A. Neuberger, ibid., **1938**, 745.

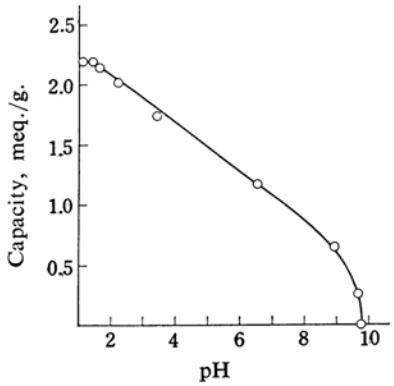


Fig. 2. Titration curve of methyl-D-glucosamide polymer (GA-resin).

Amination.—Styrene-divinylbenzene copolymer (2% crosslinked, 80~100 mesh) was chloromethylated for 48 hr. at 25°C by Pepper's procedure[13]. After the chloromethylated copolymer (10 g.; chlorine content, 16.5%) was allowed to stand overnight in dioxane, the acetylated glucosamide (VIII) (15 g.), dioxane (35 g.), and a trace of methanol were added and the mixture was placed in a bath at constant temperature for appropriate time listed in Table II. The product was washed by cycling with 1 N hydrochloric acid and 1 N sodium hydroxide to remove soluble materials.

The exchange capacity of the resin was fairly high in spite of a bulky group. The resin exhibited an abnormal behavior for adsorption to mandelic acid as shown in Table II. The polymer containing acetyl-glucosamide (VIII) (AcO-GA-resin) was then treated by a barium hydroxide solution for 45 min. to remove the acetyl group. The obtained deacetylated polymer (GA-resin) swelled in alcohol and shrank with acetone and acetic acid. In this respect, acetylated resin was opposite to GA-resin. A titration curve of the resin was typical of weak basic resin.

Diethylaminoethyl Cellulose (DEAE-Cellulose).—This ion-exchange cellulose was prepared from cotton or wood cellulose powder (Toyo Roshi Co., Ltd.) and 2-chlorotriethylamine hydrochloride as described by Peterson and Sober[14]. The exchange capacities of cotton cellulose (nitrogen content, 1.02%) and wood cellulose (nitrogen content, 0.79%) were 0.6 and 0.4 meq./g. respectively.

Asymmetric Synthesis and Analysis of Benzaldehyde Cyanohydrin.—The catalysts used in the cyanohydrin synthesis are very different from one another in chemical, physical and kinetic properties. Since it is essentially difficult to apply the same condition to those catalysts the reaction was carried out under similar conditions as for mole ratio of reagents, reaction time, reaction temperature and solvent.

To a solution of refined benzaldehyde (10.0 ml.) and anhydrous hydrogen cyanide (4.0 ml.), catalyst (0.1~1.0 mmol.) was added and the mixture was made up to 50 ml. with benzene. The solution of benzene was allowed to stand at 20°C for 20 hr. with stirring. The catalyst was filtered off and the filtrate was distilled under reduced pressure to remove unreacted hydrogen cyanide and again was made up to 50 ml. with benzene. Optical rotation of the solution was measured by a polarimeter (Hitachi Ltd.) in 2 dm. tube. A sample of given volume was pipetted from the benzene solution and, after dilution with water, it was treated with 0.1 N potassium hydroxide until pH ca. 11 and was titrated with 0.1 N silver nitrate by means of the potentiometric method[15]. As shown in Fig. 3, the titration curves of benzaldehyde cyanohydrin (fresh distilled, b. p. 118~119°C/0.25 mmHg, 124~126°C/1mmHg[16]), potassium cyanide and several samples from the reaction product mixture were almost of the same form and their end points were very sharp. The titration value of fresh distilled cyanohydrin in benzene

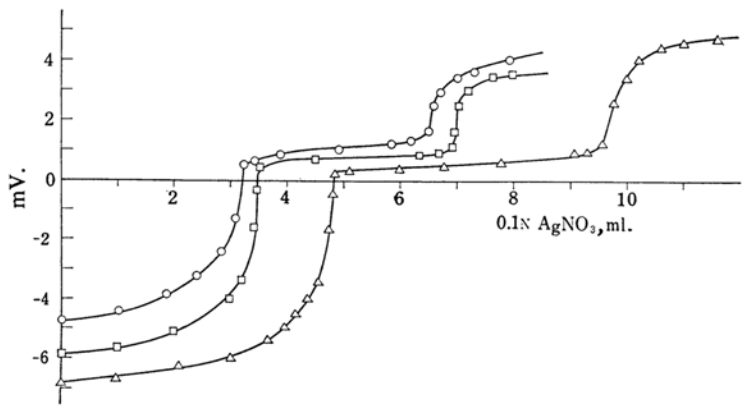


Fig. 3. Titration curve of potassium cyanide and benzaldehyde cyanohydrin.
-○- Reaction mixture
-△- Benzaldehyde cyanohydrin, 0.1302 g. (0.978 mmol.)
-□- 0.07 N KCN, 10 ml.

13) K. W. Pepper et al., ibid., **1953**, 4093.
14) E. A. Peterson and H. S. Sober, *J. Am. Chem. Soc.*, **78**, 751 (1956).
15) J. E. Ricci, *Anal. Chem.*, **25**, 1650 (1953).
16) K. Freudenberg and H. Biller, *Ann.*, **510**, 239 (1934), reported b. p. 115~116°C/0.1 mmHg.

TABLE III. VARIATION OF P% IN EXISTENCE OF CATALYST

	Yield %	α_D	$[\alpha]_D$	P%
When 100 mg. of catalyst was used:				
Containing catalyst	51.5	−2.28	−8.57	19.6
Distilled cyanohydrin*1			−8.20	18.7
When 50 mg. of catalyst was used:				
Containing catalyst	44.5	−1.42	−6.26	14.2
Catalyst removed*2	43.0	−1.30	−5.86	13.3
After a week:				
Containing catalyst	42.7	−1.20	−5.73	13.1
Catalyst removed*2	42.0	−1.20	−5.53	12.6
Distilled cyanohydrin*3			−5.21	11.5

*1 Distilled at 118~119°C/0.25 mmHg under presence of one drop of conc. H_3PO_4. n_D^{20} 1.5308.
*2 Diluted sulfuric acid was used.
*3 Distilled at 123~124°C/1 mmHg, n_D^{25} 1.5221.

TABLE IV. VARIATION OF ROTATION OF IEI-POLYMER UNDER VARIOUS CONDITIONS
(Used: 21.5 mg. of the polymer in 10 ml. of benzene)

	α_D*
IEI-Polymer	+0.14
When D,L-cyanohydrin (37.2 mg.) added	+0.30
In 10 hr.	+0.21
In 20 hr.	+0.13

* Measured with 1 dm. tube.

solution with benzaldehyde agreed throughly with that of equal quantity of the same cyanohydrin used alone. For the calculation of cyanohydrin concentration, the value of the first inflection point in the titration curve was doubled. IEI-polymer, dissolved in benzene solution, may be removed by shaking with sulfuric acid but this process gives rise to various troubles. Furthermore, Amberlite IR-120 or Dowex-50·X-1 (low crosslinked) did not adsorb the polymer even if it is low molecular weight. From Tables III and IV we see that the value of optical rotation of the product with catalyst still in it should be considered satisfactory with the accuracy of 1% or less in error if the correction is made for optical rotation of the polymer itself. Therefore, the optical rotation of cyanohydrin was measured regardless of the polymer content. The optical yield, "P%", expresses the ratio of specific rotation of the product to the absolute value of rotation of optically pure cyanohydrin in benzene, $[\alpha]_D^{25}$ 43.75 (2 dm., *c* 5.006)[17].

Results and Discussion

As regards P% in the last column of Table V, IEI-polymer gives considerably good results presumably because of steric hindrance of bulky isobutyl group adjacent to a functional group and large influences of structural regularity of optically active polymer on the asymmetric synthesis of cyanohydrin. In the regularity of the polymer, a helical conformation may be existent to some extent in dilute benzene or toluene solution. If we could make an IEI-polymer of higher molecular weight, we could expect a better result because of enhanced stereo-regularity.

With GA-resin, the yield and P% are both poor. The resin hardly swelled in benzene and, therefore, the reaction velocity was very slow. Even if satisfactorily swelled, the aldehyde group could not approach the amino group of the catalyst, for the functional amino group is sandwhiched between the polymer skeleton and the bulky glucoside ring. Furthermore, the resin has no asymmetric carbon in the polymer main chain. In spite of many optically active carbons that are in side chains, reagents may be receiving just a slight chance of steric control in transition state.

Concerning DEAE-celluloses, wood cellulose is inferior to cotton cellulose both in yield and in P%, for which lower crystallinity of original wood cellulose powder and intermingled impurities seem responsible. But, what is most unaccountable about wood cellulose is, that the signs of optical rotations of the two reaction produdts are reversed, notwithstanding the two celluloses, one obtained on the market, the other synthesized in the laboratory, being of the same structure (see Table V). It may have been due to differences of the synthetic methods of the DEAE-celluloses or of their

17) I. A. Smith, *Ber.*, **64**, 427 (1931).

TABLE V. ASYMMETRIC SYNTHESES OF BENZALDEHYDE CYANOHYDRIN WITH OPTICALLY ACTIVE POLYMERS

Catalyst	Cata. mg.	Yield %	α_D	$[\alpha]_D$	P%
IEI-Polymer*1	100	51.5	−2.28	−8.57	19.6
	100*2	40.0	−1.86	−9.13	20.8
	100*3	50.0	−1.81	−7.07	16.1
	50*3	44.5	−1.42	−6.26	14.2
	10	8.8	−0.62	−6.80	15.5
GA-Resin	500	23.4	+0.06	+0.50	1.1
	100	13.9	+0.07	+0.98	2.2
DEAE-Cellulose (Cotton)	500	84.4	−1.29	−2.96	6.8
	1670	80.2	−0.84	−2.25	5.2
DEAE-Cellulose (Wood)	500	48.8	−0.32	−1.01	2.3
	500*4	52.0	+0.17	+0.75	1.7
L-Leucinol	117	6.9	(±)	0	0
Quinine	324	74.3	+0.28	+0.73	1.7
Amberlite IR-4B	500	28.8	0	0	0
	100	11.3	0	0	0

*1 $[\alpha]_D$ are the values corrected for the rotation of the polymer.
*2 Catalyst polymerized with camphor sulfonic acid was used; softening point, 53°C.
*3 Molecular weight of the catalyst, 1020. In other cases, molecular weight is 4000～6000.
*4 DEAE-Cellulose of Type 20 (Brown Co.) was used (nitrogen content, 1.10%; exchange capacity, 0.7 meq./g.).

fine structure of the cellulose part. Previously, Bredig et al.[2] found that when diethylamino cellulose was used in the studies of asymmetric cyanohydrin synthesis, the optical yield of the product was 22% as mandelic acid. In comparison with this, the results shown in Table V are too small, which is attributable to the difference between amination processes and the difference in distance between the cellulose part and the amino group.

L-Leucinol, regarded as monomer of IEI-polymer, did not catalize in the asymmetric cyanohydrin synthesis and the cyanohydrin was obtained in a poor yield.

The result with quinine is similar to the results obtained by other workers[2-4].

Amberlite IR-4B does not swell easily in solvent, hence, the reaction velocity is slow and, as expected, stereo-specific reaction did not occur.

Behavior of IEI-Polymer under Various Conditions.—Rate of cyanohydrin formation with IEI-polymer is shown in Fig. 4 (A mixture of 20 ml. of benzaldehyde, 8 ml. of hydrogen cyanide, and 200 mg. of polymer was made up to 100 ml. with benzene. Five milliliters of this reaction mixture was used for every analysis.). Variation of P% vs. reaction time is similar to that in Bredig's case[2] of diethylamino cellulose; it is accompanied with slow racemization. Specific rotation of the polymer is affected a little by the temperature of toluene solution (Fig. 5). Curve of P% vs. reaction temperature is shown in Fig. 5; it has a

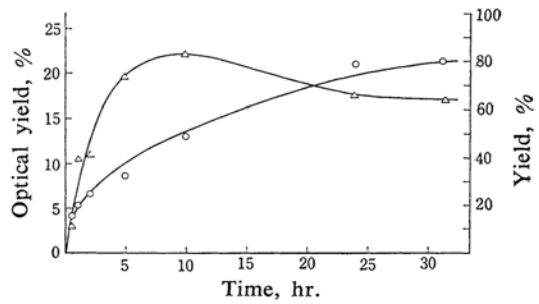


Fig. 4. Time dependence of yield (-○-) and optical yield (-△-) of benzaldehyde cyanohydrin with IEI-polymer.

maximum near −10°C at which temperature the ratio of (−)-cyanohydrin to (+)-isomer is 65:35. It is of interest to note that the existence P% maximum in the range of reaction temperature resembles the enzyme action which becomes powerful within limited ranges of temperature and pH.

In cyanohydrin synthesis, it is well known that carbonium ion of the carbonyl group is more unstable than negatively polarized oxygen, hence, the first step of the reaction is the nucleophilic attack. The reaction is therefore accelerated by the base.

In this asymmetric synthesis, we consider that either the conformation of the transition state is fixed by the steric effect of isobutyl group of the polymer when the carbonyl group approaches the nitrogen of the catalyst or cyanide ion weakly bonded with the amino

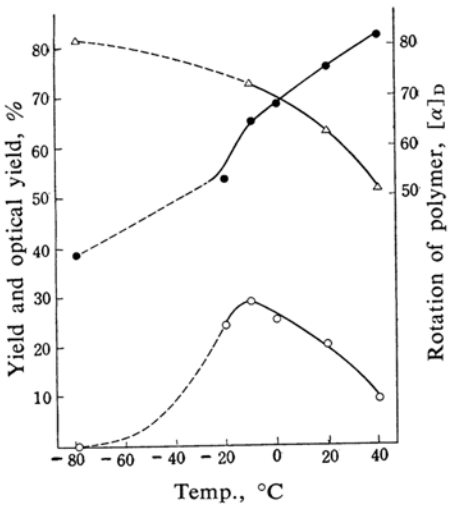


Fig. 5. Temperature dependence of yield (-●-) and optical yield (-○-) of benzaldehyde cyanohydrin and specific rotation (-△-) of IEI-polymer.

group of the polymer attacks the carbonyl group only from a definite direction on account of the isobutyl group. In any case, the spiral structure of the polymer, too, is presumed to give rise to a promoting effect on the asymmetric synthesis.

Summary

Poly-s-isobutyl-ethylenimine was synthesized and with it asymmetric synthesis of benzaldehyde cyanohydrin was carried out with good results: P% is 20%.

This is ascribable to (1) the steric effect of the isobutyl group adjacent to the amino group in the polymer, (2) the stereo-regularity of the polymer, and presence of an asymmetric center and functional group in the main chain of the polymer, and (3) the spiral structure, if it exists, of the polymer enhancing its stereo-regularity effect.

The author wishes to thank Dr. Masaya Yanagita for his many valuable suggestions and constant encouragement throughout the course of this study.

Laboratory of Polymer Chemistry
The Institute of Physical
and Chemical Research
Komagome, Bunkyo-ku, Tokyo