Catalytic Asymmetric Benzaldehyde Cyanohydrin Synthesis with Synthetic Optically Active Polymer. II. Cross-linked Poly-(s)-isobutylethylenimine

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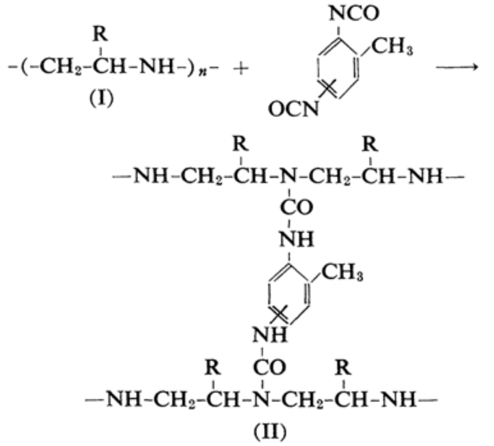
In the previous paper,[1] an asymmetric synthesis of benzaldehyde cyanohydrin performed in the presence of the basic catalyst of several optically active polymers was described. With poly-(s)-isobutylethylenimine (I), the optical yield of the produced (−)-cyanohydrin was relatively high, about 20%. In the present work, an insoluble polymer, obtained from poly-(s)-isobutylethylenimine by cross-linking with tolylene diisocyanate (TDI), was used. The insoluble polymer catalyst can be separated from the reaction mixture containing unstable and viscous compounds and reused. Besides, the cross-linking seems to stabilize the conformation.



(R=Isobutyl)

TABLE I. CROSS-LINKING OF POLY-(S)-ISOBUTYLETHYLENIMINE WITH TOLYLENE DIISOCYANATE

Sample No.	TDI weight mg./polymer g.	-NCO/=NH	Capacity meq./g.
1	150	0.17	3.68
2	174	0.20	3.00*
3	261	0.30	2.71
4	348	0.40	2.18
5	700	0.80	1.70
6	280	0.32	3.57**

* Found: C, 67.83; H, 10.65; N, 13.10. Calcd. for $(C_6H_{13}N)\cdot(C_9H_6N_2O_2)_{0.20/2}$: C, 71.09; H, 11.76; N, 14.42%.

** Molecular weight of the original polymer is 3300, the others are 1050. Analytical data as hydrochloride; Found: C, 58.90; H, 9.66; N, 11.67; Cl, 11.55. Calcd. for $(C_6H_{13}N)\cdot(C_9H_6N_2O_2)_{0.32/2}\cdot(HCl)_{1-0.32}$: C, 58.85; H, 9.72; N, 12.18; Cl, 15.88%.

The Cross-linking of Poly-(s)-isobutylethylenimine.—Among the cross-linking agents tested so far, only TDI gave an insoluble product from the polymer I, while with the others the polymer did not even gelatinize. The TDI cross-linked polymer (II) swells in benzene or toluene, but it repels water in spite of the presence of hydrophilic amino groups; this property seems to be useful for a catalyst in organic solvents. The exchange capacities of the cross-linked polymers are listed in Table I. The infrared spectrum of the polymer reveals the presence of a –NH–CO–N= group by absorptions at 1655 cm^{-1} and at 1525 cm^{-1} as similar to that of phenyl isocyanate-modified polymer (Fig. 1).

Benzaldehyde Cyanohydrin Synthesis with Cross-linked Polymer.—The asymmetric synthesis and analysis of the product were carried out in a similar way to those described in the previous paper.[1]

The data in Table II show that the product with the cross-linked polymer and that with the original linear polymer are completely reversed in the sign of the optical rotation. This reversal of sign is independent of whether or not the reaction system is homogeneous, for we observe the same result when a solvent-soluble catalyst partly modified with phenyl or methyl isocyanate is used instead of TDI. Since *symm-n*-butylphenylurea had no catalytic activity for cyanohydrin formation in a benzene solution, the –NH–CO–N= groups themselves may not be related directly to this reversal.

The Contribution of –NH–CO–N= Groups to the Asymmetric Synthesis.—In order to elucidate the reversal of sign, several polymers

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[1] S. Tsuboyama, This Bulletin, 35, 1004 (1962).

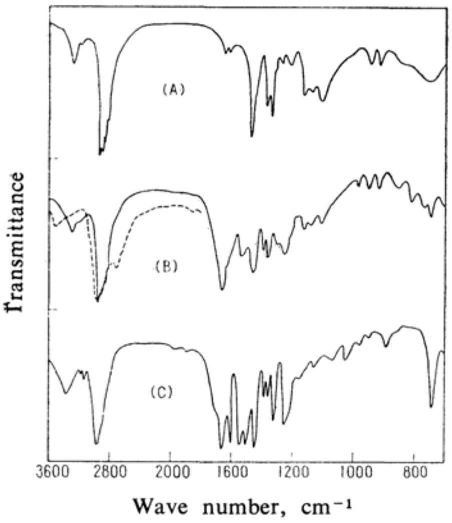


Fig. 1. Infrared absorption spectra: (A) poly-(s)-isobutylethylenimine (I), (B) solid line; TDI cross-linked polymer (II), dotted line; its HCl salt, (C) phenyl isocyanate modified polymer.

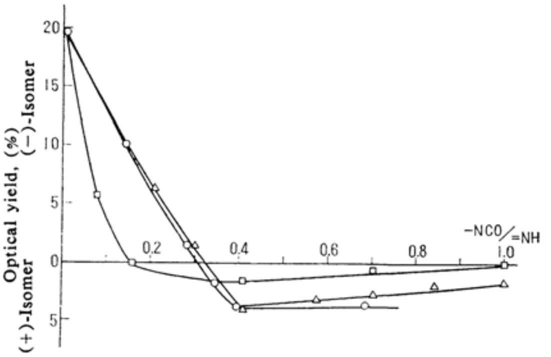


Fig. 2. Effect of introducing -NH-CO-N= group into the polymer I on the optical yield of the asymmetric synthesis.
—○— Tolylene diisocyanate
—△— Phenyl isocyanate
—□— Methyl isocyanate

containing R-NH-CO-N= groups in various ratios were prepared by the addition of TDI, phenyl or methyl isocyanate to the linear polymer, and the asymmetric cyanohydrin formation was carried out with each of them as a catalyst. The optical yields of the product obtained with various modified polymers as catalysts are given in Table III and illustrated in Fig. 2. In the figure, the optical yield is plotted against the mole ratio of the isocyanate group to the amino group, -NCO/=NH, on the assumption that the added isocyanate had reacted stoichiometrically. It may be seen from the results that: (1) with respect to the TDI series, the optical yield decreases continuously with the additional amount of isocyanate, and the sign of the optical rotation of the product changes from negative to positive. The curve shows that the optical yield reaches a maximum at approximately the ratio of 0.4 and that thereafter it is independent of the ratio, suggesting that TDI reacts with the linear polymer to some extent but not further, for its taking part in the reaction seems to be hindered by the net work structure formed. The benzene solution of the polymer emulsifies near 0.34 and is gelatinized at the ratio of 0.40 (Table III); (2) the curve concerning phenyl isocyanate is similar to that of TDI at values lower than 0.4, but at values over this ratio, the optical yield of the (+)-isomer decreases with the increase in the ratio. As the polymer modified with phenyl isocyanate has no net work, phenyl isocyanate seems to be introduced more easily than TDI into the polymer. However, even when the ratio is 1, the minor amino groups, which are capable of catalyzing, are still likely to remain in the polymer. In any case, both these polymers have almost identical efficiencies for the steric course of the asymmetric reaction, regardless of the reaction phase; (3) in the methyl isocyanate series, the cross-over point of

TABLE II. ASYMMETRIC SYNTHESIS WITH CROSS-LINKED POLY-(S)-ISOBUTYLETHYLENIMINE*

Catalyst	Catalyst wt. mg.	Cyanohydrin Yield, %	α_D**	$[\alpha]_D$	P%***
Polymer I	100	51.5	−2.15	−8.34	19.0
1	270	86.0	+0.30	+0.68	1.5
3	400	65.0	+0.15	+0.45	1.0
3	40	24.5	+0.30	+2.41	5.5
5	500	64.1	+0.42	+1.29	2.9
6	300	84.4	+0.62	+1.42	3.3

* These reactions were performed with benzaldehyde (0.1 mol.) and hydrogen cyanide (0.1 mol.) in the presence of the polymer catalyst (1 mmol.) in benzene at 20°C for 20 hr.

** c 1—4, 2 dm. tube.

*** Optical yield; percentage of specific rotation of the product to the absolute value of the rotation of optically pure cyanohydrin in benzene, $[\alpha]_D^{25}+43.75$ (c 5.006).

Table III. Asymmetric synthesis with poly-(s)-isobutylethylenimine modifide by several isocyanates

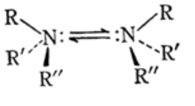
-NCO/=NH	Apparent reaction phase	Polymer α_D*	Cyanohydrin		
			α_D**	$[\alpha]_D$	P%
Tolylene diisocyanate					
0.136	Homogeneous	+0.32	−1.30	−4.42	10.0
0.273	Homogeneous	+0.07	−0.20	−0.68	1.6
0.340	Emulsive		+0.20	+0.78	1.8
0.395	Gelatinous		+0.30	+1.67	3.8
0.682	Heterogeneous		+0.30	+1.68	3.8
Phenyl isocyanate					
0.200	Homogeneous		−1.40	−2.89	6.6
0.286	Homogeneous	+0.14	−0.22	−0.65	1.5
0.400	Homogeneous		+0.66	+1.79	4.1
0.571	Homogeneous	+0.16	+0.32	+1.32	3.2
0.700	Homogeneous		+0.36	+1.07	2.5
0.840	Homogeneous	+0.22	+0.10	+0.96	1.9
1.000	Homogeneous	+0.28	+0.11	+0.72	1.7
Methyl isocyanate					
0.075	Homogeneous	+0.26	−0.64	−2.55	5.8
0.158	Homogeneous	+0.20	0.00	0.00	0
0.270	Homogeneous	+0.11	+0.12	+0.45	1.0
0.404	Homogeneous	0.00	+0.22	+0.69	1.7
0.700	Homogeneous	−0.20	+0.05	+0.16	0.4
1.000	Homogeneous		0.00	0.00	0

* The optical rotation of the original linear polymer, α_D +0.60.

** *c* 1—4, 2 dm. tube.

the curve comes at a value of the ratio lower than those the cases of the former two, and then P% gradually approaches zero by way of a maximum at about 0.4. If the reversal in the sign of the cyanohydrin produced by these polymers depends on only the size of the introduced group, the first two series must be more effective than the methyl isocyanate series, at least within the range of small values of the ratio, and the curves of the former must be steeper than the curve of the latter. However the result obtained refute this assumption; some other explanation, therefore, should be considered.

One possible interpretation is as follow. Amines, and presumably amine polymers, may be converted at a very high rate and with a very low energy to their enantiomers by a molecular vibration of the type known in NH_3 molecule (as is shown in the scheme).



In this reaction, therefore, when the carbonyl reagent approaches equivalently to either side of the amine which is vibrating, the cyanohydrins produced at the two sides become enantiomers with each other. Consequently, the selectivity of the reaction may not be recognized. Only when the accessibilty of the reagent is different on the two sides of interconverting amine, as a result of a steric requirement, the reaction will be performed asymmetrically. In the steric requirement, even if the absolute configuration of the polymer remains the same, the accessibility of the reagent and even the direction of its approach appear to change as a result of the change produced by the modification in the arrangement at the circumference of the catalytic center. Each conformation of these modified polymers may be very unlike the original one because of such interaction as intra- and inter-molecular hydrogen bonding between introducing groups or between the amino group and the introducing group. To the newly-formed conformation, the approach of the reagent may become easier on the side opposite to what would the approach be originally. In all cases, it seems that the arrangement of these modified polymers changes markedly until the ratio reaches 0.4 but that thereafter the conformation undergoes no appreciable change. Although the conformation of these polymers has not yet been analyzed, it should be noted that the configuration and the optical yield of the product in the asymmetric synthesis are not always controlled by the absolute configuration of the catalyst but by the conformation of the circumference of the catalytic center.

Experimental

Cross-linking of Poly-(s)-isobutylethylenimine with Tolylene Diisocyanate.—To an ice-cooled solution of 1.0 g. of the linear polymer I in 25 ml. of toluene was added dropwise a known volume of toluene solution containing 1% of tolylene diisocyanate* with vigorous stirring. The viscous or opaque jelly-like solution formed was then stirred for about 5 hr. at 60°C and allowed to stand overnight at room temperature. The insoluble polymer was filtered off and washed with hot toluene, benzene, ethanol and ether. The pale yellow solid obtained was then ground and screened to 20—40 mesh. To regenerate it, the dried polymer was made to swell thoroughly with benzene and then washed with ethanol, N hydrochloric acid, 4% ammonium hydroxide and finally with deionized water. The exchange capacity was measured for the wet polymer in the presence of N/10 hydrochloric acid and N sodium chloride (Table I).

Other cross-linking agents for the amine polymer, such as ethylene dichloride[2] epichlorohydrine,[3] formaldehyde, tetra- and pentamethylene dibromide, *symm*-dichloroacetone, *p*-xylylene dichloride, and their various combinations, were applied under various conditions. Every mixture of the linear polymer and an agent was heated in a sealed glass tube at 100—180°C for 24—72 hr., but no insoluble product was obtained.

Phenyl Isocyanate-modified Polymer.—A solution of a slight excess of phenyl isocyanate in benzene was added with stirring into a solution of the linear I polymer in benzene, and the mixture was left standing overnight at room temperature. The benzene solution was then washed with water to remove the excess of isocyanate. The pale yellow solution obtained was freeze-dried; m. p. 143°C. $[\alpha]_D^{23}+71.01$ (*c* 2.056, benzene).

Found: C, 71.95; H, 8.36; N, 10.84. Calcd. for $(C_{13}H_{18}N_2O)_n$: C, 71.52; H, 8.31; N, 12.83%.

***symm-n*-Butylphenylurea.**—To an ice-cooled solution of 0.7 g. (0.01 mol.) of *n*-butylamine in 5 ml. of heptane, a solution of 1.2 g. (0.01 mol.) of phenyl isocyanate in heptane was added slowly with stirring. The product, *symm-n*-butylphenylurea, separated as needle crystals which weighed 1.7 g. and melted at 129—130°C after recrystallization from ethanol.

Found: C, 68.92; H, 8.12. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39%.

Asymmetric Synthesis with Several Isocyanate-modified Polymers.—To every solution of 50 mg. of the linear polymer in benzene was added an appropriate, known volume of benzene solution containing ca. 1% of one of TDI, phenyl and methyl isocyanate (b. p. 39.5—40.5°C),[4] dropwise, with vigorous stirring, and each solution thus prepared was then filled up to 10 ml. with benzene. After 3 hr., the rotation of each solution was measured, and the asymmetric synthesis and analysis of cyanohydrin were carried out in a way similar to that described in the previous report.[1] For the measurment of the optical rotation, all the samples except the gelatinized ones were purified by distillation.

Summary

Asymmetric benzaldehyde cyanohydrin synthesis with TDI cross-linked poly-(s)-isobutylethylenimine has been studied. The cyanohydrin obtained was (+)-isomer; its sign is opposite to what it is in the case of the linear polymer. With the linear and soluble polymer which contains some –NH–CO–N= groups, the (+)-isomer was also found to be produced. These results suggest that (1) the reversal of the sign is independent of the reaction phase, and (2) the configuration of the product is not always controlled by the configuration of the asymmetric carbon in the catalyst but by the conformation of the catalytic center.

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* Hodogaya Chem. Co., Ltd., 2,4-isomer: 2,6-isomer = 80:20. distilled at 97—97.5°C/3 mmHg, n_D^{28} 1.5634.

2) F. J. Shepherd and J. A. Kitchener, *J. Chem. Soc.*, **1957**, 86.

3) G. Manecke and K. F. Bonhoffer., *Z. Electrochem.*, **55**, 475 (1951).

4) J. Colucci, *Can. J. Research*, **23B**, 111 (1945).