backbone and is monodisperse with respect to molecular weight.

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Stereoelective Polymerization of DL-Amino Acid *N*-Carboxyanhydrides by Nickel *d*-2-Methylbutyrate–Tri-*n*-butylphosphine Catalyst System

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ABSTRACT: The polymerization of *N*-carboxyanhydride of γ-benzyl DL-glutamate or of DL-alanine by the nickel *d*-2-methylbutyrate–tri-*n*-butylphosphine catalyst system proceeded stereoelectively to give an optically active polymer of high molecular weight. The monomer whose absolute configuration is identical with that of the asymmetric carbon in the acyloxy group of the catalyst system was polymerized preferentially.

The characteristic behavior of the $Ni(OAc)_2 \cdot 4H_2O$-*n*-Bu_3P catalyst system exhibited in the polymerization of γ-benzyl L-glutamate NCA (L-BG-NCA) was ascribed to the active participation of the nickel salt in the propagation step.[2] This interpretation was subsequently substantiated by experimental results which indicated that the DL-copolymerizations of mixtures composed of various ratios of L- and DL-BG-NCA by the (*dl*-$C_2H_5(CH_3)CHCOO)_2Ni$-*n*-Bu_3P catalyst system (*dl*-Ni catalyst) were controlled stereochemically more effectively than by the simple amine catalyst.[3] In fact, the stereoregularity of the DL-copolymer prepared by the former catalyst, which was determined by the regular helix content, was far higher than that by the latter one.[3] Kinetic analysis of the polymerization process of DL-BG-NCA or DL-alanine NCA (DL-Ala-NCA) by the *dl*-Ni catalyst also revealed that these polymerization reactions proceeded stereospecifically.[3]

As a logical extention of these experiments, the stereoelective polymerization was applied to DL-BG-NCA having a rather long side chain or DL-Ala-NCA having the shortest side chain. The polymerization of a DL-NCA with the optically active Ni catalyst was suggested to give an optically active polymer. In fact, this expectation was found to give satisfactory results in our work. This paper deals with these experimental results.

The stereoelective polymerization of DL-Ala-NCA or DL-leucine NCA was reported by other workers with the $AlEt_3$–borneol catalyst system[4,5] or optically active amines,[6] but unfortunately specific rotations and molecular weights of their polymers were not sufficiently high values.

Experimental Section

Materials. NCAs, nickel carboxylates, and other reagents were prepared and/or purified by the methods described in preceding papers.[2,3]

Nickel *d*-2-methylbutyrate was prepared as follows. *d*-2-Methylbutyric acid was prepared by oxidizing optically active amyl alcohol (2-methylbutanol) in basic solution[7] and was purified by fractional distillation using Tokyokagakuseiki Model HSB-805E Spinning Band Rectifier: bp 175–177°; $[\alpha]^{20}{}_{\mathrm{D}}$ +17.2° (neat) (lit. $[\alpha]_{\mathrm{D}}$ +19.33°).[8] *d*-2-Methylbutyric acid was transformed to nickel *d*-2-methylbutyrate in the same manner as described for nickel *dl*-2-methylbutyrate:[3] $[\alpha]^{20}{}_{577}$ +4.4° (dichloroacetic acid (DCA), *c* 2.71 g/100 ml), $[\alpha]^{20}{}_{546}$ +6.8° (DCA, *c* 2.71 g/100 ml), $[\alpha]^{20}{}_{577}$ −1.8° (THF, *c* 6.76 g/100 ml), $[\alpha]^{20}{}_{546}$ −2.2° (THF, *c* 6.76 g/100 ml). *Anal.* Calcd for $C_{10}H_8O_4Ni$: C, 45.9: H, 6.90. Found: C, 45.81; H, 6.26.

Solvents. Anisole was refluxed over CaH_2 for 24 hr, refluxed over metallic sodium for 24 hr, and then distilled under an anhydrous argon atmosphere (bp 155°). Other solvents were purified by the methods described in preceding papers.[2,3]

Polymerization. Polymerizations were carried out by the methods described in preceding papers.[2,3] The polymerization of DL-BG- or of DL-Ala-NCA was terminated by adding 100 ml of ethanol to 10 ml of the polymerization medium. By this treatment, unreacted NCA and catalyst system were almost completely removed from the polymer. The yield of polymer was determined gravimetrically. The polymer obtained was washed twice with 100 ml of diethyl ether and dried at 80° for 12 hr *in vacuo*. To remove the free amino acid, catalyst system, and other optically active substances as completely as possible from the polymer, poly(γ-benzyl glutamate) (P-BG) was reprecipitated twice from dioxane (20 ml)–diethyl ether (200 ml) or poly(alanine) (P-Ala) was reprecipitated twice from DCA (5 ml)–diethyl ether (200 ml).

Kinetic Measurements. Polymerization reaction was followed by measuring the intensity of the infrared absorption band at 1850 cm^{-1}, which is assigned to the 2-carbonyl group in the NCA ring, using a JASCO Model DS-402 spectrometer in a 0.1 mm thickness of KBr in a liquid cell under an argon atmosphere. Weak absorption bands due to the solvent (THF) were compensated for using the reference cell. $[M_0]/[M_t]$ is referred to the monomer concentration at the time zero and *t*. v_0 represents the rate of monomer consumption, which is calculated by the equation $-d[M]/dt$.

Characterization of the Polymer. ORD of the polymer was measured in 20- or in 50-mm cells using a Yanagimoto ORD Model 185 or a JASCO Model J10 Automatic Polarimeter. Specific rota-

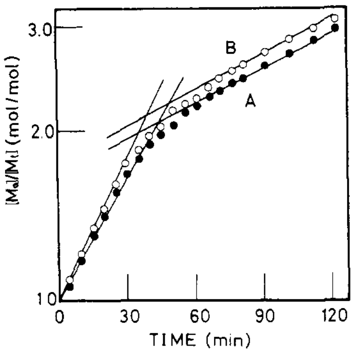

Figure 1. Polymerization of DL- and L-Ala-NCA by *dl*-Ni catalyst: A, L-Ala-NCA; B, DL-Ala-NCA. Polymerization condition; NCA, 0.2 mol/l. in THF; NCA/Ni (mol/mol) = 2; Ni/*n*-Bu$_3$P (mol/mol) = ½; temperature, 25°. Catalyst was aged at 30° for 80 min prior to mixing it with monomer.

Table I
Initial Rate (v_0) of Reaction between Ala-NCA and Ni-Catalyst System

Run	Monomer	Catalyst	$v_0 \times 10^3$, mol/min[a]
A	L-Ala-NCA	*dl*-Ni catalyst	1.80
B	DL-Ala-NCA	*dl*-Ni catalyst	1.87
C	L-Ala-NCA	*d*-Ni catalyst	2.95
D	DL-Ala-NCA	*d*-Ni catalyst	1.67

[a] See Experimental Section.

tion of the polymer was determined from the value at 589 nm in the ORD chart using a JASCO DIP-SL Automatic Polarimeter (20-mm cell).

The ir spectrum was recorded using a JASCO Model DS-402G spectrometer for the thin film prepared by casting from chloroform solution (P-BG) or DCA solution (P-Ala).

The viscosity of solution was measured in DCA (P-BG) or trifluoroacetic acid (TFA) (P-Ala) at 25.0 ± 0.1°. The molecular weight of P-BG was calculated from intrinsic viscosity, $[\eta]$, using the equation:[9] $[\eta] = 2.78 \times 10^{-5}\,\bar{M}_w^{0.87}$.

Results and Discussion

1. Polymerization of DL-Alanine *N*-Carboxyanhydride (DL-Ala-NCA) by the *d*-Ni Catalyst. Rates of conversion of Ala-NCA by Ni catalyst were measured by ir spectroscopy for four pairs, both racemic and optically active compounds, under identical conditions (Figures 1 and 2). L-Ala-NCA by *dl*-Ni catalyst followed a similar curve to DL-Ala-NCA by *dl*-Ni catalyst, except for the time required to reach an intercepting point being slightly longer for L-Ala-NCA than for DL-Ala-NCA (Figure 1). Similar curves were obtained for *d*-Ni catalyst, but the time required for reaching an intersecting point was longer for DL-Ala-NCA than for L-Ala-NCA (Figure 2). Initial rates of polymerization (v_0) measured from these data seem to show that *d*-Ni catalyst has a preferential reactivity toward L-Ala-NCA by *d*-Ni catalyst (Table I). Since nickel *d*-2-methylbutyrate is *S* form and L-alanine is also *S* form, the conclusion can be drawn that the Ni catalyst reacts preferentially with Ala-NCA whose absolute configuration is the same as that of the acyloxy group of the catalyst.

Polymerization of DL-Ala-NCA proceeded smoothly in 2% anisole solution by the *d*-Ni catalyst at 30°. Optically active or inactive polymer was obtained depending on the catalyst preparation method (Table II). An optically active polymer was obtained in a 17% yield. Specific rotation of the polymer, $[\alpha]^{20}\mathrm{D}$, was −24.7° in DCA and −28.3° in TFA (Table II). These values of optically pure polymer (P-L-Ala) are +35.1° in DCA and −158.1° in TFA. Hence, the optical yield of this synthetic P-Ala was 18% in TFA (approximated random-coil solvent).[10] The value of b_0 calculated from the ORD curve in DCA was −42.8 which was recorded in DCA (helix solvent)[10] in the range of 300 to 700 nm (Figure 3). This value seems to be the same as that of the polymer obtained by the DL-copolymerization of Ala-NCA containing 65% of L-Ala-NCA by *n*-hexylamine. The ORD curve recorded for TFA solution follows a simple curve (Figure 4) in the range of 350 to 700 nm. It may be concluded from this result that the optically active polymer can be obtained from DL-Ala-NCA and that the catalyst system containing *S* form of the 2-methylbutyrate (= *d*-2-methylbutyrate) reacts preferentially with the *S* form (= L-form) of the monomer.

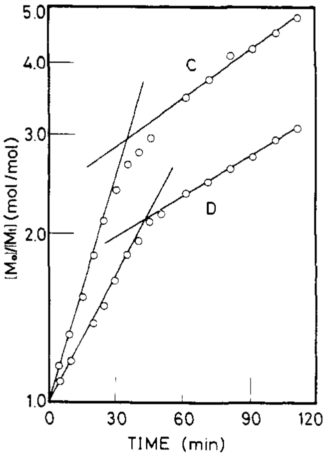

Figure 2. Polymerization of DL- and L-Ala-NCA by *d*-Ni catalyst: C, L-Ala-NCA; D, DL-Ala-NCA. (Polymerization condition, see Figure 1.)

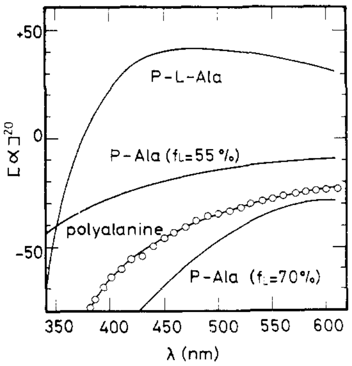

Figure 3. ORD curves of polyalanines in DCA at 20°. (Polymerization condition, see Figure 1.)

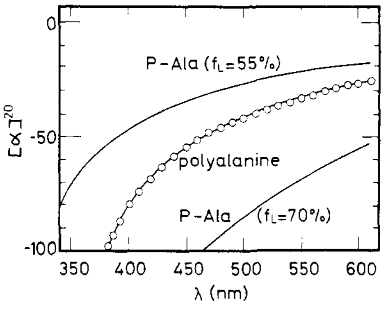

Figure 4. ORD curves of polyalanines in TFA at 20°. (Polymerization condition, see Figure 1.)

2. Polymerization of DL-BG-NCA. DL-BG-NCA was polymerized in 5% dioxane solution at 30° by a 0.01 molar amount of the *d*-Ni catalyst, which was prepared from

Table II
Polymerization of DL-Alanine NCA by the *d*-Ni Catalyst[a]

Run	PBu_3/*d*-Ni, mol/mol	Polymerization time, hr	Yield, %	$[\alpha]^{20}D$[b] DCA, deg	TFA, deg	η_{sp}/c[c] TFA
d-1	2.0	12.0	16.9	−24.7	−28.3	0.165
d-2	4.0	15.4	24.2	0.0	0.0	0.139
d-3	6.0	1.8	18.3	0.0	0.0	0.113

[a] NCA, 1.0 g; anisole 50 ml; NCA/Ni (mol/mol) = 100:1; Ni-P aging, 80 min at 30°. [b] Specific rotation of polymer was measured in DCA and TFA (*c* 0.2 g/100 ml). [c] Viscosity was measured in TFA (*c* = 0.2 g /100 ml) at 25.0 ± 0.1°.

Table III
Stereoelective Polymerization of DL-BG-NCA by *d*-Ni Catalyst[a]

	Yield, %	$F_L/(F_L + F_D)$,[b] %	$[\alpha]^{20}D$ (DCA), deg	Optical yield, %	$\bar{M}_v$[c]	R[d]
P-BG(A)	1.9	87.7	−12.82	75	6.8×10^4	7.29
P-BG(B)	10.4	73.8	−8.09	48	7.0×10^4	2.97
P-BG(C)	23.5	70.4	−6.94	41	7.6×10^4	2.78
P-BG(D)	28.0	67.1	−5.81	34	7.9×10^4	2.31

[a] Polymerization condition: DL-BG-NCA 0.500 g (1.91 mmol); molar ratio, DL-BG-NCA:n-Bu_3P:$(d\text{-}C_2H_5(CH_3)CHCO_2)_2Ni$ = 100:6:1; solvent, dioxane 10 ml; temperature, 30°. Catalyst was aged at 30° for 50 min before mixed with monomer. [b] Calculated from specific rotation value, which was measured in DCA (*c* 0.2 g/100 ml). [c] Viscosity was measured in TFA at 25.0 ± 0.1° and $\bar{M}_v$ was calculated by equation $[\eta] = 2.78 \times 10^{-5}\bar{M}_w0^{0.87}$.[9] [d] Calculated with the equation, $R = \ln(1 - px - x)/\ln(1 + px - x)$, proposed by Bührer and Elias[6] in which $p = ([P_L] - [P_D])/([P_L] + [P_D])$, *i.e.*, optical yield (%) = 100 × p, and 100 × X is a conversion (%).

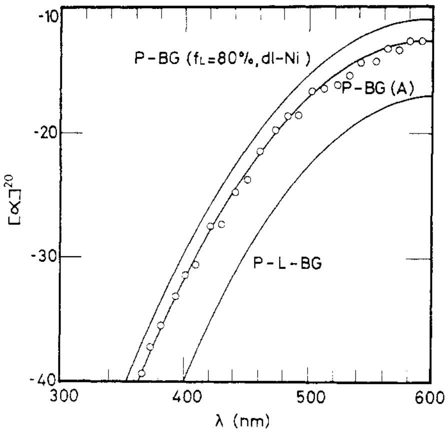

Figure 5. ORD curve of P-BG and P-L-BG measured in DCA at 20°. (Polymerization condition, see Table III.)

nickel *d*-2-methylbutyrate and *n*-Bu_3P in a molar ratio of 1:6 and was aged for 50 min at 30°. The negative value of the specific rotation in DCA solution of the polymer indicates that poly(γ-benzyl glutamate) (P-BG) is, as expected, rich in L-residue content (Table III). Optical yield of P-BG varied from 75 to 34% depending on polymer yield.

The structure of P-BG was studied with ir and ORD. Specific rotation (Table II) and ORD (Figure 5) of P-BG(A) indicate that the content of L-residue in P-BG corresponds to that of P-BG prepared by the DL-copolymerization of BG-NCA containing *ca.* 80% of L-BG-NCA by the *dl*-Ni catalyst. Regular helix content of *ca.* 50% in P-BG(B) determined by the ir spectrum (Figure 6) corresponds to that of P-BG prepared independently by the DL-copolymerization of BG-NCA containing *ca.* 70% of L-BG-NCA by the *dl*-Ni catalyst. Thus, the *d*-Ni catalyst containing *S*-2-methylbutyrate (= *d*-2-methylbutyrate) reacts preferentially with *S*-BG-NCA (= L-BG-NCA) to give *S* residue rich P-BG, in agreement with the results of the polymerization of DL-Ala-NCA by the *d*-Ni catalyst.

The value of specific rotation of the P-BG measured in DCA solution decreased with the increase in the yield (Figure 7). The specific rotation of P-BG was measured in DCA (random-coil solvent).[11] The contents of L and D residue in P-BG calculated from observed values of $[\alpha]^{20}D$ are shown in Figure 8. The D content in P-BG increased progressively with the polymerization time. This result is due to the following reasons: the content of the D monomer in the polymerizing medium increased progressively due to the formation of L residue-rich oligomer and polymer, and hence the apparent stereoelectivity of the catalyst lowers progressively with the polymerization time.

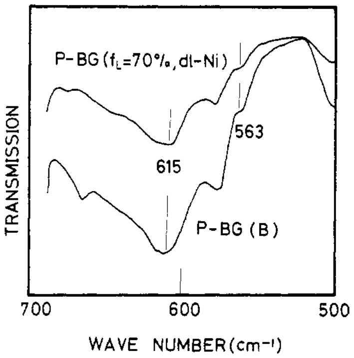

Figure 6. Ir spectra of P-BG. (Polymerization condition, see Table III.)

The value of R[6] of P-BG shown in Table III is very high, especially in a low yield. Since R, a measure of asymmetric synthesis,[6] is parallel to d[L]/d[R], the high value of R observed in our case means that the polymerization is highly asymmetric, compared to the reports of other workers.[4-6]

3. Effect of Preparation Method, Especially of Catalyst System, on Stereoselective and Stereoelective Polymerization. The regular helix content of P-BG prepared in the DL-copolymerization of DL- and L-BG-NCA by the *dl*-Ni catalyst was found to be profoundly influenced depending on the preparation method, especially on the aging time, of the catalyst system.[3]

In the stereoelective polymerization of DL-Ala-NCA by the *d*-Ni catalyst, specific rotation of the polymer was found to depend remarkably on the method of catalyst preparation (Table II and III). For example, the catalyst system was prepared by reacting Ni(d-$C_2H_5(CH_3)CHCOO)_2$ with *n*-Bu_3P in a molar ratio of 1:2 at 30° for 80 min and was used in a concentration of 1 mol

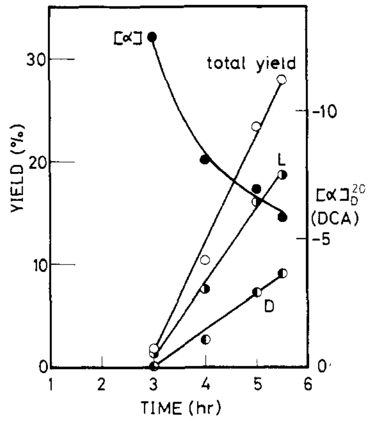

Figure 7. Stereoelective polymerization of DL-BG-NCA by *d*-Ni catalyst: ○, total yield of polymer; ◑ and ◐, calculated content of L and D residues in polymer; ●, specific rotation of polymer in DCA. (Polymerization condition, see Table III.)

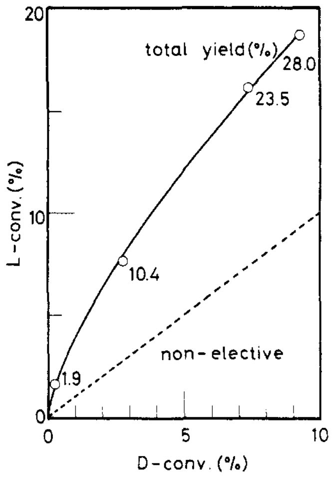

Figure 8. Contents of L and D residues in P-BG. (Polymerization condition, see Figure 1.)

% to the monomer. The most suitable aging time for obtaining the optically active polymer was found to depend on the molar ratio of the nickel salt to the phosphine and the reaction temperature: the lower the ratio and the lower the temperature, the shorter the optimum aging time. Further refinement of the catalyst preparation method is expected to be able to increase stereospecificity and/or stereoelectivity of polymerization.

4. On the Active Species for Stereoselective or Stereoelective Polymerization. The difference in the stereoregularity of polymers observed in DL-copolymerization of varying L/D ratios of BG- or Ala-NCA by the *dl*-Ni catalyst could be interpreted by assuming that either *d* or *l* species in the *dl*-Ni catalyst is more reactive toward D-NCA than toward L-NCA.[3] The polymerization of DL-BG- or DL-Ala-NCA by the *d*-Ni catalyst gave the corresponding optically active polymers. This stereoelective polymerization shows that our proposed mechanism deduced from the stereoselective polymerization is valid. In fact, the configuration of the asymmetric carbon atom in the acyloxy group of the *d*-Ni catalyst plays an important role in the preferential selection of an enantiomeric monomer having an identical absolute configuration among racemic monomers, when the catalyst system is used in an appropriate manner.

The reaction sequence occurring in the catalyst forming reaction, especially in the aging time, was followed by uv and ir spectroscopy together with its catalytic activity.[12] Unfortunately, the reaction course was found to be able to lead to an unambiguous identification of stereoselective (or optically inactive) or a stereoelective (or optically active) catalyst species. A reaction sequence deduced from these experimental data[12] seems to show that the catalyst system is usually composed of several kinds of nickel complexes, which are formed in a consecutive and/or competitive reaction occurring between nickel 2-methylbutyrate and tri-*n*-butylphosphine.

This type of interpretation explains the active participation of the nature, amount, and temperature of the metal atom, the carboxyl group of nickel carboxylate, and the alkyl group or the phosphorus atom of phosphine for exhibiting these kinds of catalytic actions of the specified monomeric NCA. The search for a catalytically active site is considered to be opened up by this interpretation for further studies.

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