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Stereoselective and Asymmetric-Selective Polymerization of α-Amino Acid N-Carboxyanhydride

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Stereoselective and Asymmetric-Selective Polymerization of α-Amino Acid N-Carboxyanhydride

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ABSTRACT

The enantiomer selectivity in the propagation reaction of NCA was investigated by using suitable model reactions. Contrary to the assumption usually made, the enantiomer selectivity in the nucleophilic addition of chiral amines to NCA depended strongly on the structure of amine or NCA and the solvent. In the polymerization by an activated-NCA mechanism, the addition of activated NCA to NCA was found for the first time to be enantiomer-selective. In addition to this, the chiral penultimate unit was found to participate in the enantiomer selection. Structures of the transition states leading to the different types of enantiomer selection were proposed.

GENERAL ASPECTS OF STEREOSPECIFIC POLYMERIZATION OF α-AMINO ACID N-CARBOXYANHYDRIDE

Poly(α-amino acids) have been used as the structural model for proteins. Recently, the use of poly(α-amino acids) as functional

polymers such as the enzyme-model catalyst and the biomedical materials has become increasingly important. Synthesis of poly(α-amino acid) by the polymerization of α-amino acid N-carboxyanhydride (NCA) is most efficient and has been used most frequently. In the polymerization of NCA the stereoselectivity or the asymmetric selectivity is involved, because both of the interacting species, the growing chain and the monomer, are chiral. In this regard, the stereoselective or the asymmetric-selective polymerization of NCA could be considered as the model for the enantiomer selection in enzyme reactions.

Factors influencing the stereoselectivity or the asymmetric selectivity in the NCA polymerization can be classified as follows: (1) catalyst control: enantiomer selection by counterions produced from chiral initiators; (2) terminal-unit control: enantiomer selection by the chiral active end of the growing chain; (3) penultimate-unit control: enantiomer selection by the chiral penultimate unit in the growing chain; (4) conformation control: enantiomer selection by the chiral conformation of growing chain such as α-helical or β-extended conformation.

With regard to the stereospecific polymerization of α-amino acid NCA, review articles have been published by Tsuruta [1] and Inoue [2]. A number of investigations included in those articles have been concerned with the overall aspects of the stereospecific polymerization of NCA, and very few investigations have dealt with the enantiomer selection in each elementary step of the propagation reaction.

With respect to the enantiomer selection according to the catalyst-control mechanism, Suzuoki and his co-workers [3, 4] investigated polymerization initiated by chiral quaternary ammonium hydroxides as initiators, and Tani and his co-workers [5, 6] used chiral Ni compounds as initiators; the latter workers discussed the observed asymmetric selectivity on the basis of the catalyst-control mechanism. Inoue and his co-workers [7-9] reported that some organometallic compounds and chiral NCA form a chiral catalytic site which selects one of the enantiomeric NCAs in the propagation reaction. However, the mechanism of propagation reaction has remained unclear in these polymerizations initiated by "peculiar" initiating systems. As far as the overall stereospecificity in the bulk of the polymerization is considered, contributions from factors other than the catalyst-control mechanism may be involved.

The terminal-unit control has been invoked most frequently to explain the stereoselectivity or the asymmetric selectivity in NCA polymerizations. Surprisingly, this has been made without firm experimental evidence which could be easily obtained in model reactions. Elias and his co-workers [10] digested poly(α-amino acid) produced from racemic NCA with chiral initiators by an enzyme, carboxypeptidase A, and concluded that stereoselection occurred

according to the terminal-unit control. However, to explain the results of the enzyme digestion, they had to assume perfect stereoselection. The same conclusion was obtained by Bührer and Elias [11] from the kinetic treatment of the optical yield of polymer produced from DL copolymerization initiated by chiral amines. Perfect enantiomer selection is hardly believable from our experience.

As far as we are aware, no systematic investigation of penultimate-unit control in NCA polymerizations has been carried out.

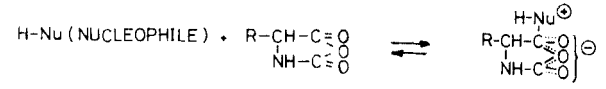
Since Doty and his co-workers [12-15] and Idelson and Blout [16, 17] proposed an apparently interesting explanation of the autoacceleration and the asymmetric selection in the NCA polymerization on the basis of the conformation-control mechanism, many people have employed this mechanism to explain their stereoselectivity or asymmetric selectivity. Inoue and his co-workers [18, 19] verified the existence of α-helix control by the kinetic treatment of the optical rotation during the polymerization. They continued investigating the correlation between the stereospecificity and the secondary structure of the growing chain by spectroscopy [20-23] but the mechanism of enantiomer selection does not seem to be correlated satisfactorily with the secondary structure of the growing chain. The α-helix-control mechanism has been criticized severely by Bamford and his co-workers [24-26], Williams and his co-workers [27-30], and recently by Elias and his co-workers [31]. The most difficult point of the conformation-control mechanism is that it usually accompanies several different stereocontrol mechanisms, because when the growing chain assumes some specified conformation, both the penultimate and the terminal units are necessarily chiral and participate in the enantiomer selection. Without overcoming this difficulty, the conformation-control mechanism cannot be established.

To discuss the stereoselectivity and the asymmetric selectivity in the NCA polymerizations, we employed several model reactions in which the factors (1) to (4) can be considered separately. More importantly, we considered that each factor would appear differently according to the mechanism of propagation reaction. Hence we investigated each factor for either a nucleophilic-addition-type propagation or an activated-NCA-type propagation. We will describe subsequently our recent experimental results mainly concerning the stereocontrol mechanisms (2) and (3).

STEREOSELECTIVE AND ASYMMETRIC-SELECTIVE POLYMERIZATION ACCORDING TO TERMINAL-UNIT CONTROL

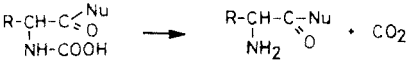
Asymmetric Selection in Nucleophilic-Addition-Type Propagation

The propagation reaction according to the nucleophilic-addition-type mechanism can be represented as shown in Eqs. (1)-(3) [32].



(1)

(2)



(3)

In the polymerization of Sar NCA step (2), in which the ring opening of the primary adduct and the intramolecular proton transfer are involved, is rate-determining. In the polymerization of common α-amino acid NCAs such as Phe, Leu, and Glu(OBzl) NCAs, step (1) is rate-determining; the stereospecificity in the propagation reaction must be determined in the step (1). Many people explained the observed asymmetric selectivity by assuming a preferential reaction between the same enantiomorphic species. However, no firm experimental evidence for this has been obtained. Furthermore, perfect selection between the same enantiomorphic species (the rate constants of crosspropagation reactions $k_{DL} = k_{LD} = 0$) has been assumed, irrespective of the polymerization conditions. This is highly suspicious, however.

We employed optically active amines (mainly α-amino acid esters) as the model compound for the propagating amine (H-Nu), and investigated the asymmetric selectivity in the nucleophilic addition of these amines to NCA [33]. The amine-to-NCA molar ratio was kept between 1 and 2 so that the measured reaction rate should reflect the reaction between amines and NCAs (very little polymerization follows). The nucleophilic addition of optically active amines to D(R)- or L(S)-Phe NCA was effected in m-$(MeO)_2$Ph at 25°C. From the time-conversion curve and the first-order plot, the respective second-order rate constant $k_{D(R)}$ and $k_{L(S)}$ were determined. The extent of asymmetric selection was judged by the deviation of $k_{D(R)}/k_{L(S)}$ or $k_{L(S)}/k_{D(R)}$ from unity. The experimental results are shown in Table 1. Under the experimental conditions, further addition to Phe NCA of phenylalanine amide which resulted from the reaction between an amine and an NCA might occur to some extent. To avoid the complexity occurring as a result of a reaction of this type, the nucleophilic addition to D(R)- or L(S)-N-MePhe NCA of some optically

TABLE 1. Asymmetric Selection of Enantiomorphic Phe NCAs and N-MePhe NCAs by Optically Active Amines in m-$(MeO)_2$Ph at 25°C[a]

No.	Amine	Phe NCA			N-MePhe NCA		
		$k_{L(S)}$	$k_{R(D)}$	$k_{D(R)}/k_{L(S)}$	$k_{L(S)}$	$k_{D(R)}$	$k_{D(R)}/k_{L(S)}$
1	$Et_2N-\overset{\overset{O}{\|\|}}{C}-CH_2NHMe$	157	184	1.18	5.72	5.54	1.04
2	$EtO-\overset{\overset{O}{\|\|}}{C}-CH_2NH_2$	98.2	106	1.08			
3	(S)-$EtO-\overset{\overset{O}{\|\|}}{C}-\underset{\underset{Me}{\|}}{CH}-NH_2$	6.65	6.44	0.97	0.934	1.80	1.93
4	(S)-$EtO-\overset{\overset{O}{\|\|}}{C}-\underset{\underset{CH_2Ph}{\|}}{CH}-NH_2$	1.49	2.19	1.47			
5	(S)-$EtO-\overset{\overset{O}{\|\|}}{C}-\underset{\underset{On\ Bu}{\|}}{CH}-NH_2$	3.74	5.45	1.46			
6	(S)-$EtO-\overset{\overset{O}{\|\|}}{C}-\underset{\underset{iBu}{\|}}{CH}-NH_2$	2.81	5.37	1.91	0.205	1.15	5.61
7	(S)-$EtO-\overset{\overset{O}{\|\|}}{C}-\underset{\underset{iPr}{\|}}{CH}-NH_2$	1.79	4.24	2.37	0.107	0.798	7.46

(continued)

TABLE 1 (continued)

No.	Amine	Phe NCA			N-MePhe NCA		
		$k_{L(S)}$	$k_{R(D)}$	$k_{D(R)}/k_{L(S)}$	$k_{L(S)}$	$k_{D(R)}$	$k_{D(R)}/k_{L(S)}$
8	(S)–EtO–C(=O)–CH(CH$_2$–COOEt)–NH$_2$	1.13	1.02	0.90			
9	(R)–EtO–C(=O)–CH(Ph)–NH$_2$	2.24	2.37	1.06			
10	(S)–EtO–C(=O)–CH(–CH$_2$–CH$_2$–)–NH	1.64	1.48	0.90	73.2	24.2	0.331
11	(S)–Me–CH(Ph)–NH$_2$	5.12	2.39	0.47	2.81	1.75	0.623
12	(R)–Me–CH(nHex)–NH$_2$	1.58	2.09	1.33			

[a] [NCA] = 50 mmole/liter; [Amine] = 50 ~ 100 mmole/liter; all $k \times 10^{-3}$ liter/mole-sec.

active amines was investigated in m-$(MeO)_2$Ph. It has been confirmed by us that the reaction between an amine and an NCA is the only reaction under this condition. The experimental results for N-MePhe NCA are shown in Table 1.

Inspection of Table 1 leads to the following conclusions. The presence and the extent of asymmetric selection, and the nature of the preferred enantiomer are strongly dependent on the reaction conditions. Usual L(S)-α-amino acid esters as nucleophilic amines react preferentially with D(R)-Phe NCA, except for proline ethyl ester, which reacts preferentially with L(S)-Phe NCA; that is, the reaction between the species having the opposite steric configuration takes place preferentially. The asymmetric selectivity of these amino acid esters is enhanced by the N-methylation of Phe NCA, which indicates the possible regulation of the steric course of the reaction by the nitrogen or the N-substituent of NCA. The extent of asymmetric selectivity by these amino acid esters is increased with increasing bulkiness of the C_α-substituent of amines. Other optically active amines such as α-phenylethylamine and 2-octylamine behave differently; that is, they select NCA having the same steric configuration. Furthermore the asymmetric selectivity in these reactions is lowered by the N-methylation of Phe NCA.

From the above observations, a transition-state model for the reaction of α-amino acid esters with Phe NCA or N-MePhe NCA in m-$(MeO)_2$Ph was proposed as depicted in Fig. 1. This transition-state model was depicted under the following considerations. The orientation of the C_α-substituent in Phe NCA or N-MePhe NCA was determined on the basis of the 100 MHz NMR spectra of the NCAs in $CDCl_3$ and $PhNO_2$-d_5. Amines approach NCAs from the opposite side of the five-membered ring accommodating the C_α-substituent. The access should realize the most efficient overlapping of the lone-pair electrons of the amine and the orbital of C=O bond of the NCA. There is some interaction between the nitrogen of NCA and the C=O group of approaching amine.

The transition-state model of Fig. 1 can be viewed as a substituted cyclohexane. In the reaction between an L(S)-amine and a D(R)-NCA, the substituents assume a stable 1,4-diequatorial arrangement, hence the preference for species having the opposite steric configuration emerges. It is very probable that under the present conditions the amide-aromatic interaction, aromatic-aromatic interaction, and hydrogen bonding operate among amine, NCA, and solvent, and they affect the steric course of the reaction. We are now investigating the solvent effect on the asymmetric selectivity.

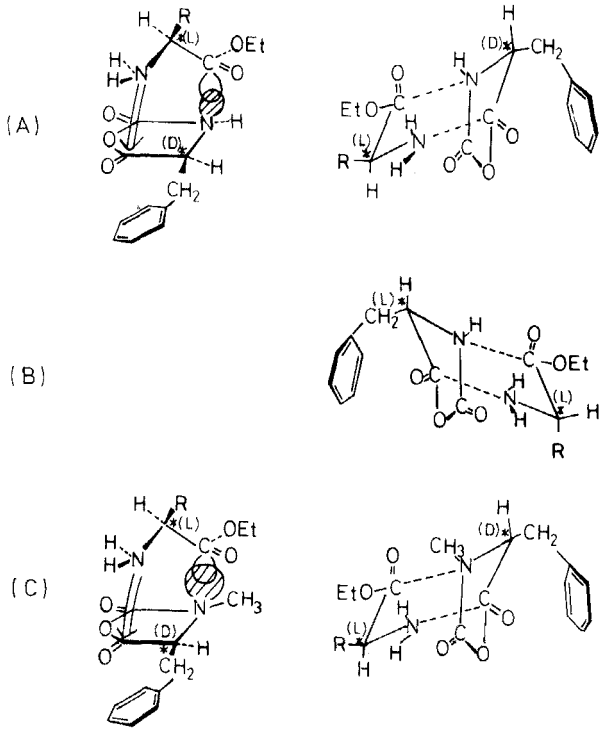


FIG. 1. Transition-state model for reaction of α-amino acid esters with Phe NCA or N-MePhe NCA.

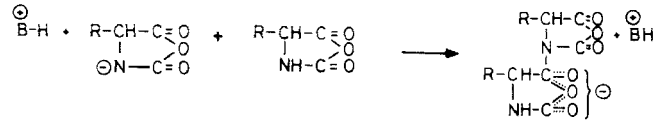
Stereoselection in Activated-NCA-Type Propagation

The propagation reaction according to the activated-NCA-type mechanism can be represented as shown in Eqs. (4)-(6) [34].

The stereoselectivity in the propagation reaction of this type may arise in step (5), where an adduct is formed between an activated NCA (NCA anion) and an NCA. Little care has been taken of the stereoselectivity in the propagation reaction according to the activated-NCA-type mechanism. We have observed this type of stereoselectivity in the polymerizations of Phe NCA initiated by certain secondary amines.

When Phe NCA was polymerized in $PhNO_2$ by poly-N-methyl-L-alanine as initiator, which is optically active and takes a specific secondary structure, L(S)- and D(R)-Phe NCAs polymerized at the

(4)



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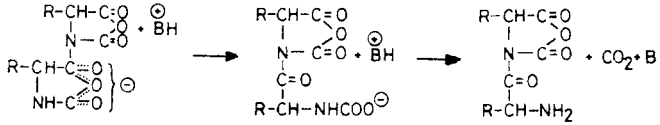


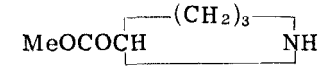
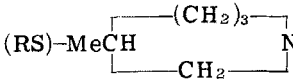
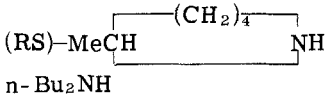
(6)

same rate, which was about twice as large as that of racemic (RS)-Rhe NCA [35]. Obviously, this stereoselectivity arises from the preferential reaction of a chiral growing chain with the same enantiomorphic NCA. The stereoselectivity was observed also in the polymerization initiated by small secondary amines such as N-methyl-L-alanine diethylamide [35]. Therefore, the present type of stereoselectivity is not explained in terms of the conformation-control mechanism. The stereoselectivity was equally observed in the polymerization initiated by racemic amines having an asymmetric carbon atom (N-methyl-DL-alanine diethylamide, etc.) and by amines without asymmetric carbon atoms (sarcosine diethylamide, etc.) [36]. Therefore, the stereoselectivity is not due to the catalyst control. Furthermore, the terminal unit of the growing chain of L(S)-Phe NCA was found not to select noticeably the enantiomorphic NCAs [36]. L(S)-Phenylalanine ethyl ester as the terminal-unit model was found to select the oppositely enantiomorphic NCA only weakly (see Table 1). Therefore, the stereoselectivity observed in the polymerization of Phe NCA cannot be explained in terms of the conventional terminal-unit control mechanism.

In contrast to conventional ideas on the stereospecific polymerization of NCA, the stereoselectivity observed in the present polymerizations seemed to appear in a specific mode of propagation reaction. The effects on the stereoselectivity of initiator amines, α-amino acid NCAs, and solvents were therefore investigated.

With regard to the effect of the structure of initiator amines on

TABLE 2. Stereoselectivity in the Polymerization of Phe NCA by Various Amines[a]

Amine	Selectivity
n-$HexNH_2$	0
$Me_2NCOCH_2NH_2$	0
(S)–$Me_2NCOCH(Bz)NH_2$	0
Me_2NCOCH_2NHMe	±
$Me_2NCO(CH_2)_2NHMe$	+
$Me_2NCO(CH_2)_3NHMe$	+
	0
(RS)–$Et_2NCOCH(Me)NHMe$	+
(S)–$Et_2NCOCH(Me)NHMe$	+
	0
	0
	±
	+
n-Bu_2NH	+
$PhCH_2NHMe$[c]	0
(RS)–PhCH(Me)NHMe[c]	+
$PhCH_2NHEt$[c]	+
n-Bu_3N[c]	+

[a] 25°C, $PhNO_2$ solvent, [NCA]/[Amine] = 20.
[b] (+) stereoselective; (0) nonstereoselective; (±) weakly stereoselective.
[c] [NCA]/[amine] = 10.

the stereoselectivity in the polymerization of Phe NCA in $PhNO_2$, the experimental results listed in Table 2 were obtained [37]. The important conclusion drawn from the experimental results is that strongly basic and bulky amines which do not easily undergo a nucleophilic addition to NCA induce the stereoselective polymerization. It seems that the stereoselective polymerization of Phe NCA is attained in the activated-NCA-type polymerization.

Next, six kinds of α-amino acid NCAs which have different structural characteristics were polymerized by certain kinds of amines in $PhNO_2$ [38]. The stereoselectivity in these polymerizations is summarized in Table 3. It is evident that primary amines induce non-stereoselective polymerization of all NCAs and tertiary amines induce stereoselective polymerization of all NCAs. On the other hand, N-methyl-L-alanine diethylamide, a secondary amine, induced the stereoselective polymerization of NCAs, provided that the proton abstraction by the amine from NCA is not sterically obstacled. It is nearly established that the stereoselective NCA polymerization occurs in the activated-NCA-type polymerization.

The polymerization of Phe NCA by certain kinds of secondary amines were further investigated in different solvents [39]. The occurrence of stereoselective polymerization under these conditions is summarized in Table 4. It is clear from these data that the stereoselectivity appears in dipolar solvents in which the proton abstraction by amines from Phe NCA is favored. All these experimental results indicate that the enantiomer selection is performed in the addition of NCA anion to the N-acylated oxazolidine-2,5-dione terminal in the activated-NCA-type polymerization.

To explain the enantiomer selection in the reaction of two chiral cyclic compounds, a transition-state model as depicted in Fig. 2 was assumed. In the presentation of the transition-state model, the following factors were taken into account. The activated NCA approaches to the carbonyl group of the terminal NCA ring from the opposite side of the NCA plane on which the C_α-substituent resides. Two dipolar acid anhydride groups keep themselves as remote as possible. The electron clouds of NCA anion should overlap most efficiently with the orbital of the carbonyl group of the terminal NCA ring. It is understandable from Fig. 2 that a severe steric crowding exists in the access of the C_α-substituent of activated NCA having L(S)-configuration toward the 5-carbonyl group of the terminal NCA ring having D(R)-configuration or vice versa, thus leading to the preferred reaction between the species having the same steric configuration.

To the stereoselectivity in the activated-NCA-type propagation, the chirality of the penultimate unit and the chain conformation contribute to some extent as well as the enantiomer selection between chiral cyclic compounds as described above. We first investigated the

TABLE 3. Stereoselectivity in the Polymerization of Six α-Amino Acid NCAs by Different Amines at 25°C in $PhNO_2$

α-Amino acid	Stereoselectivity					
	n-$HexNH_2$	$PhCH_2NHMe$	Et_2NCOCH_2NHMe	(S)-$Et_2NCOCH(Me)NHMe$	n-Bu_2NH	n-Bu_3N
Phe	0	0	±	+	+	+
Glu(OEt)	0[b]	0	0	+		
Ala	0	0	0	+		+
Leu		0	0	+		
Val	0	0	0	0	0	+
Ile			0	0[c]	0	+

[a](+) stereoselective; (0) nonstereoselective; (±) weakly stereoselective.
[b]n-$OctNH_2$ was used.
[c](RS)-$Et_2NCOCH(Me)NHMe$ was used.

TABLE 4. Stereoselectivity in the Polymerization of Phe NCA in Different Solvents at 25°C

	Stereoselectivity		
Amine	m-$(MeO)_2$Ph	$PhNO_2$	$HCONEt_2$
(RS)-$Me_2NCOCH(Me)NHMe$	0	+	+
Me_2NCOCH_2NHMe	0	±	+
$Me_2NCO(CH_2)_2NHMe$	0	+	+
$PhCH_2NHMe$	0	0	+
$Me_2NCOCH_2NH_2$		0	0

[a](+) stereoselective; (0) nonstereoselective; (±) weakly stereoselective.

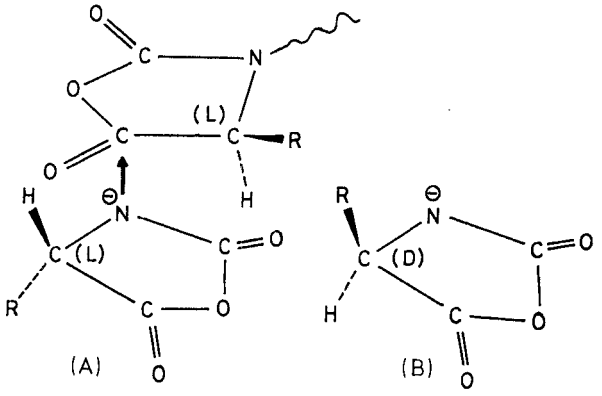
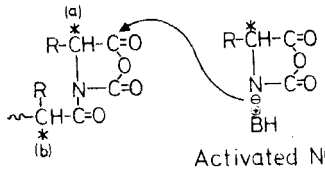
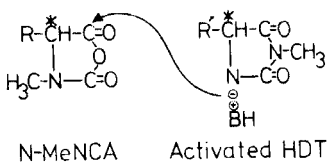


FIG. 2. Transition-state model of enantiomer selection in reaction of two chiral compounds.

addition to N-methyl amino acid NCA of 3-methyl-5-substituted hydantoins (HDT) activated by tertiary amines. This reaction models very well the propagation reaction of the activated-NCA type as shown below. Substituted HDT compounds do not homopolymerize. Therefore, the reaction of the activated HDT with the N-methyl NCA is free from the complexities arising from the penultimate unit and the chain





conformation. This reaction will give us precise information about the stereoselectivity of the reaction of the activated NCA with the terminal NCA ring in the polymerization.

The addition reactions to N-MeAla NCA (R=CH_3) of various substituted HDTs activated by n-Bu_3N were investigated at 25°C in $PhNO_2$ as a solvent [40]. No reaction occurred between n-Bu_3N and N-MeAla NCA and between substituted HDT and N-MeAla NCA. It was also confirmed that the racemization of HDT does not take place during the reaction. The experimental results are shown in Table 5. For all combinations of the reactants, the reaction rate between the activated L(S)-HDT and L(S)-NCA was larger than that between the activated L(S)-HDT and DL(RS)-NCA. In particular, in the reactions of activated Ala HDT, the rate decreased in the order: L(S) ~ L(S) > L(S) ~ DL(RS) = D(R) ~ DL(RS) > L(S) ~ D(R). These experimental results clearly demonstrate that activated HDTs react preferentially with N-MeAla NCA having the same steric configuration.

When N-MeAla NCA is used, the secondary amine resulting from the addition of activated HDT may add slowly to another N-MeAla NCA. In the latter reaction, the problem of stereoselectivity is not concerned. Therefore, this reaction does not interfere with the stereoselectivity in the addition of activated HDT to N-MeAla NCA. However, the extent of enantiomer excess will be affected by this reaction, which is calculated on the basis of the optical rotation of HDT remaining unreacted at a certain conversion of NCA. From

TABLE 5. Reaction Rate of N-MeAla NCA and 3-Methyl-5-Alkyl HDTs of Various Configurations and C_5 Substitution Activated by n-Bu_3N in $PhNO_2$ at 25°C[a]

	Reaction rate × 10^3 (mole/liter-hr)			
NCA	L(S)-Me	D(R)-Me	L(S)-Bzl	L(S)-iPro
L(S)-N-MeAla	7.8	4.2	6.6	3.2
DL(RS)-N-MeAla	5.2	5.4	3.0	2.1

[a] $[NCA]_0$ = 0.1 mole/liter; $[HDT]_0$ = $[n\text{-}Bu_3N]_0$ = 0.05 mole/liter.

TABLE 6. Reaction Rate of L(S)-N-MePhe NCA and 3-Methyl-5-Alkyl HDTs Activated by Et_3N in $HCONMe_2$ at 30°C[a]

Configuration of C_5 of HDT	Reaction rate $\times 10^{-4}$ (mole/liter-min)		
	Me	Bzl	iPro
L(S)	2.6	2.2	1.9
D(R)	1.6	1.4	1.1

[a] $[NCA]_0 = 0.1$ mole/liter; $[HDT]_0 = 0.2$ mole/liter; $[Et_3N]_0 = 1.42$ mole/liter.

these considerations, the use of NCA without homopolymerizability is desirable. In the following, the reaction of activated HDT and N-MePhe NCA was investigated.

The addition reactions to L(S)-N-MePhe NCA of L(S)- or D(R)-HDT activated by Et_3N were investigated at 30°C in $HCONMe_2$ as a solvent [40]. The reaction rates for the different pairs of reactants are shown in Table 6. For all reactions between activated HDT and N-MePhe NCA, L(S)-NCA reacted with activated L(S)-HDTs rapidly, that is, the selectivity for the species having the same steric configuration was observed. The kinetic relationship in this reaction was investigated. The rate of NCA consumption was first-order with respect to the NCA and the HDT concentrations and nearly independent of the Et_3N concentration. This kinetic pattern is explained by assuming that the adduct formation between an activated HDT and an NCA is the rate-determining step.

The racemic (RS)-HDT was activated by Et_3N at 30°C in $HCONMe_2$ as a solvent and added to L(S)-NMePhe NCA [40]. When 60-70% of NCA initially present had been consumed, unreacted HDT was recovered and the optical rotation was measured. The enantiomer excess of the recovered HDT was calculated on the basis of the optical rotation of the optically pure HDT as the standard. In any of the reactions, the recovered HDT contained more D(R)-HDT, that is, the optical resolution was performed during the reaction as the result of the faster consumption of L(S)-HDT with L(S)-N-MePhe NCA. The enantiomer excess was a function of the C_5-substituent of HDT and decreased in the order $CH_3 > C_6H_5CH_2 > (CH_3)_2CH$. The enantiomer excess was found to increase with increasing conversion. At a conversion of 20%, the excess of enantiomer observed was about 1/3-1/10 as small as that calculated on assuming a perfect enantiomer selection. For the blank experiment, D(R)-HDT/L(S)-HDT mixtures having various compositions were mixed with L(S)-N-MePhe NCA and the HDT was recovered from the mixture by the same procedure.

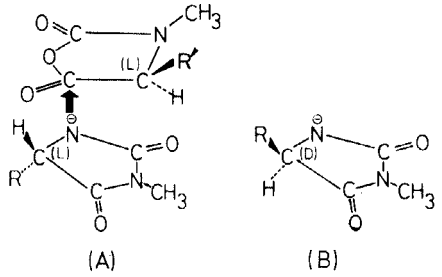


FIG. 3. Mechanism of enantiomer selectivity of activated HDT.

The optical composition of the recovered HDT agreed well with that of the starting material within the experimental error. This proves that optical resolution does not occur during the recovery of unreacted HDT.

Since a very similar behavior was observed both in the addition reaction of activated HDT to NCA and in the addition reaction of activated NCA to the terminal NCA ring of a growing chain, the enantiomer selectivity of activated HDT may be explained by a similar mechanism shown in Fig. 3 (see also Fig. 2). In other words, the mechanism of stereoselection in the activated-NCA-type propagation (Fig. 2) was confirmed to be valid. It should be noted that the enantiomer selection in the activated-NCA-type propagation is three to ten times as severe as that in the addition of activated HDT to N-MePhe NCA. For reasons of the difference, the contributions from the chiral penultimate unit and the chiral secondary conformation of the growing chain, in addition to the terminal-unit control, should be taken into account.

ASYMMETRIC-SELECTIVE POLYMERIZATION ACCORDING TO PENULTIMATE-UNIT CONTROL

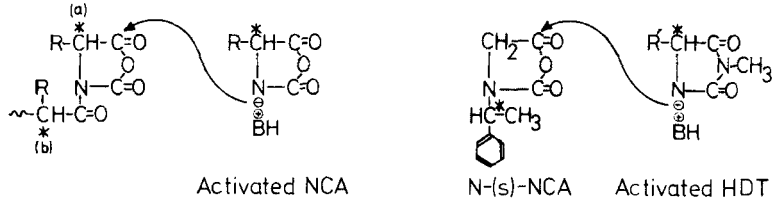
Neither in the nucleophilic-addition-type propagation nor in the activated-NCA-type propagation, the control of the enantiomer selection by the chiral penultimate unit has been investigated. In the concluding part of the preceding section, the contribution from the chiral penultimate unit to the enantiomer selection in the activated-NCA-type polymerization was implied. In order to test this possibility, activated HDT was reacted with N-(S)-α-phenylethylglycine NCA [N-(S)-NCA], an N-substituted NCA carrying an asymmetric center in the N-substituent, and the stereoselectivity was investigated.

TABLE 7. Reaction Rate and Enantiomer Selectivity in the Reaction of N-(S)-α-Phenylethylglycine NCA and 3-Methyl-5-Alkyl HDTs Activated by Tertiary Amines at 25°C

Solvent (ε)	Rate and selectivity	Reaction rate × 10^{-4} (mole/liter-min)		
		Me	iPro	Bzl
$PhNO_2$	R_D	2.44[b]	1.13	1.69
(34.6)	R_L	1.98[b]	0.63	0.92
	R_D/R_L	1.23	1.79	1.83
MeCN[c]	R_D	19.3	3.29	21.4
(37.5)	R_L	12.0	3.50	17.7
	R_D/R_L	1.61	0.94	1.21
$HCONMe_2$[c]	R_L	11.2	3.45	7.77
(37.6)	R_D	9.21	2.76	6.10
	R_L/R_D	1.21	1.25	1.28

[a] $[N\text{-(S)-NCA}]_0 = 0.1$ mole/liter; $[HDT]_0 = 0.05$ mole/liter, $[n\text{-}Bu_3N]_0 = 0.05$ mole/liter.
[b] $[HDT]_0 = 0.1$ mole/liter.
[c] $[HDT]_0 = 0.2$ mole/liter, $[Et_3N]_0 = 0.032$ mole/liter.

It is clear in the scheme shown that this sort of addition reaction models very well the enantiomer selection by the chiral penultimate unit in the activated-NCA-type propagation.



Three different kinds of HDTs [L(S)- and D(R)-HDT for each of them] activated by n-Bu_3N or Et_3N were reacted with N-(S)-NCA in such different solvents as $PhNO_2$, MeCN, and $HCONMe_2$ at 25°C [41]. N-(S)-NCA is susceptible to nucleophilic amines but does not

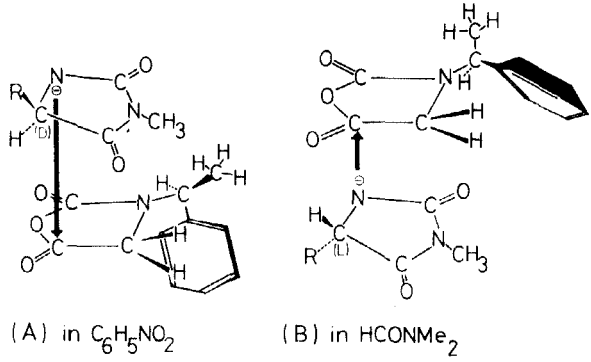


FIG. 4. Transition-state model for the addition of activated HDT to N-(S)-NCA in $PhNO_2$ and $HCONMe_2$.

homopolymerize. It does not react with tertiary amines without HDT added. Therefore, in the present reaction system, an equimolar reaction between an activated HDT and an N-(S)-NCA is strictly dealt with. The experimental results concerning the stereoselectivity are summarized in Table 7. The conclusions drawn from the data are as follows. The addition of activated HDT to N-(S)-NCA is stereoselective. The stereoselectivity is not specifically related with the bulkiness of the C_5-substituent, but varies strongly with the nature of solvent. In $PhNO_2$ and MeCN an activated D(R)-HDT reacts preferentially, but in $HCONMe_2$ an activated L(S)-HDT reacts preferentially. It is an important discovery that a chiral center involved in the N-substituent affects the enantiomer selection in the activated-NCA-type propagation. The degree of stereoregulation by the chiral N-substituent is nearly equal to or a little less than that by the chiral C_α-atom in the NCA ring. It is therefore probable that both the chiral penultimate unit and the chiral terminal unit participate in the enantiomer selection and lead to a large stereospecificity in the activated-NCA-type propagation.

As described above, in the reaction of activated HDT and N-(S)-NCA, the preferable reaction between the species having the opposite steric configuration took place in $PhNO_2$ and MeCN, but between those having the same steric configuration in $HCONMe_2$. Solvents may affect the orientation of N-α-phenylethyl group of the NCA with respect to the NCA plane. 100 MHz NMR spectra of N-(S)-NCA were measured in $PhNO_2$-d_5 and $HCONMe_2$, and the orientation of the phenyl group with respect to the NCA plane was determined on the basis of the upfield shift of $C_\alpha H_2$ signal due to the ring-current effect of the phenyl

group, $C_\alpha H_2$ signal of Sar NCA being taken as the standard. On the basis of the NMR measurements, the transition-state model (Fig. 4) was proposed for the addition of activated HDT to N-(S)-NCA in $PhNO_2$ and in $HCONMe_2$.

The transition-state model of Fig. 4 was presented on taking the following points into account. With respect to the orientation of the phenyl group, a folded conformation prevails in $PhNO_2$ but an extended conformation in $HCONMe_2$. The activated HDT approaches the N-(S)-NCA from the opposite side of the phenyl group. The activated HDT and N-(S)-NCA are so arranged that the most efficient overlapping between the nitrogen anion and the orbital of the carbonyl group is attained and the dipolar acid-anhydride groups are placed as far away from each other as possible. From the models in Fig. 4, the preferred reactions of N-(S)-NCA with activated D(R)-HDT occurring in $PhNO_2$ and those with activated L(S)-HDT occurring in $HCONMe_2$ are easily understandable.

We are now investigating the enantiomer selection by the penultimate-unit control in the nucleophilic-addition-type propagation.

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