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Stereocontrol in DL-Leucine N-Carboxyanhydride Polymerizations

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ABSTRACT

L-Leucine and DL-leucine N-carboxyanhydride were polymerized in 1,4-dioxane at 25°C with either benzylamine or L-α-methylbenzylamine as initiator, using a constant volume reactor for rate studies. A rapid initiation period was followed by two pseudo-first-order propagation periods for the racemic (DL) monomer and by three pseudo-first-order propagation periods for the L-monomer. The ratio of rate constants of the L- to the DL-polymerization is about 2 for any given polymerization period, independent of initiator type. Such a behavior is expected for stereoselective propagations without crossover, leading to blends of isotactic polymers.

INTRODUCTION

Three different types of experiments indicate that the polymerization of racemic DL-leucine N-carboxyanhydride by chiral and non-chiral amines [1] leads to the formation of long stereoblocks if not blends of poly(L-leucine) and poly(D-leucine) molecules [2].

First, the polymerization of these NCA's by chiral compounds can be described by the ideal copolymerization equation

$$\frac{d[L]}{d[D]} = R\frac{[L]}{[D]} \quad (1)$$

where R is independent of monomer conversion but dependent on initiator type, solvent, and temperature [1]. The constant, R, could not be interpreted as ratio of propagation constants, i.e., k_{LL}/k_{DD}, but had to be interpreted as ratio of concentrations of propagating chain ends, i.e., $(k_{LL}/k_{DD})([P_{LL}^*]/[P_{DD}^*]) = [P_{LL}^*]/[P_{DD}^*]$. Such an interpretation assumes the absence of crossover, i.e., $k_{DL} = k_{LD} = 0$, and would thus result in the formation of a blend of L- and D-poly(leucine) molecules [1-3].

Second, the infrared spectrum of the polymer from the racemic DL-leucine NCA agrees with that from poly(L-leucine) [4]. It does not exhibit the extra band at 1643 cm^{-1} which is characteristic for syndiotactic poly(leucine), i.e., a polymer with 100% alternating D- and L-units. The poly(leucine) from DL-leucine NCA must therefore have no or only few D-L-bonds, i.e., a very high percentage of long isotactic poly(leucine) blocks or chains.

Third, the comparison of L-leucine yields from stereosequencing experiments with the stereospecific proteolytic enzyme carboxypeptidase A also points toward the formation of long isotactic leucine blocks [2, 3]. These experiments yielded 98% L-leucine from authentic poly(L-leucine), 0% L-leucine from authentic poly(D-leucine), and L-leucine contents corresponding to 94-98% isotacticity from the polymers of racemic DL-leucine NCA [3].

We now wish to report the results of a fourth type of experiment, also indicating the formation of long isotactic blocks, if not blends, of D- and L-chains from DL-leucine NCA. This experiment is based on the comparison of the propagation rate constants of L- and DL-leucine NCA polymerizations with the primary amines, L-α-methylbenzylamine and benzylamine, as initiators. The former is a chiral primary amine, the latter a nonchiral one. Both initiators led to very highly isotactic poly(leucine)s in previous experiments [3], although the first polymerization is asymmetric-stereoselective and the latter is not.

Polymerizations of mixtures of D- and L-antipodes are copolymerizations. The rate v_p of such copolymerizations is given by

$$-d[M]/dt = k_{LL}[P_L^*][L] + k_{DD}[P_D^*][D] = v_p \quad (2)$$

if crossover reactions are absent ($k_{LD} = k_{DL} = 0$) and monomer is consumed by normal propagation reactions only. $[M]$, $[P_D^*]$, $[P_L^*]$, $[L]$, and $[D]$ are the molar concentrations of total NCA, active chain

ends attached to D- and L-units, and L- and D-NCA's. If in addition the initial monomer mixture is racemic, then

$$[L] = [D] = (\tfrac{1}{2})[M] \tag{3}$$

$$[P_L^*] + [P_D^*] = [P^*] \tag{4}$$

and Eq. (1) becomes

$$v_p = (k_p/2)[P^*][M] \tag{5}$$

because $k_{LL} = k_{DD} = k_p$. The rate of polymerization of racemic NCA's should thus be one-half of the rate of either D- or L-NCA in the absence of crossover [5-7].

EXPERIMENTAL

N-Carboxyanhydrides (NCA's) were prepared by phosgenation of L-leucine and DL-leucine, respectively, in dry 1,4-dioxane using standard methods [8]. The crude NCA's were recrystallized four times from diethyl ether/hexane, dried under vacuum, and finally stored in a deep-freezer at -25°C. Immediately before polymerization, the NCA's were again recrystallized from diethyl ether/hexane in a glove box under nitrogen and then dried under vacuum.

Dioxane for polymerizations was prepared as follows: A mixture of 700 mL dioxane, 70 mL water, and 9.5 mL conc aqueous hydrochloric acid solution (Baker) was heated gently at reflux under a nitrogen atmosphere for 16 h. Potassium hydroxide pellets (Fisher) were added to the stirred mixture until it was strongly basic. The dioxane layer was removed and dried for 4 h over anhydrous calcium sulfate. The dioxane was then distilled over anhydrous calcium hydride.

Benzylamine and L-α-methylbenzylamine were stirred with calcium hydride and subsequently distilled under reduced pressure (see Ref. 4).

Polymerizations were conducted in a Bamford-type constant volume apparatus [9]. A few drops of chlorotrimethylsilane were placed into the polymerization vessels. The vessels were then allowed to stand at room temperature until the walls were covered with a thin layer of condensed vapor. Toluene was added to the flask with swirling. After 30 min the flask was rinsed repeatedly with small portions of toluene and then dried for 48 h at 125°C under reduced pressure.

NCA solutions were prepared in a glove box and placed into the polymerization apparatus where they were stirred for 5-10 min under nitrogen until the manometer reading became constant. The initiator

solution in dioxane was then added in such amounts that the total of initiator and monomer solution was 100 mL. All polymerizations were carried out with monomer concentrations of 0.095 mol NCA/L and initiator concentrations of 0.0019 mol/L at 25°C, i.e., an initial concentration ratio $[NCA]_0/[I]_0 = 50$. This ratio is the same as in our previous experiments [3], but the actual concentrations are lower by a factor of 2 because of the restricted volume of our polymerization apparatus.

Number-average degrees of polymerization were also calculated from monomer conversion y and initial monomer/initiator ratios $[NCA]_0/[I]_0$

$$\langle X_n \rangle = \left(\frac{[NCA]_0}{[I]_0} \right) y \tag{6}$$

Previous experiments with primary amine initiated leucine NCA polymerizations showed that these calculated number-average degrees of polymerization are practically identical with those determined via amine end group titrations [10].

RESULTS AND DISCUSSION

The polymerizations with both benzylamine and L-α- methylbenzylamine as initiator followed the four-stage kinetics observed previously [10] for L-leucine NCA with 1,6-hexanediamine as initiator: a rapid polymerization Stage I is followed by two consecutive pseudo-first-order polymerization Stages II and III (Figs. 1 and 2). An additional pseudo-first-order polymerization Stage IV was observed for the polymerization of L-leucine NCA but not for the racemic DL-leucine NCA. The reason for this apparent discrepancy may, however, be the fact that the polymerization of the DL-NCA was carried out to far lower conversions than that of the L-NCA.

The polymerizations became visibly heterogeneous for the polymerization of L-NCA after 3-4 h and for the DL-NCA after 10 h, independent of the initiator used. The onset of precipitation coincides with the transition from Stage I to Stage II for the L-NCA polymerization whereas no such relation was found for the polymerization of DL-NCA (Figs. 1 and 2). We thus conclude that the change from Stage I to Stage II is not caused by a change of the macroscopic physical state of the polymers in solution. An aggregation of polymer molecules to subvisible structures may, however, precede the precipitation.

The number-average degrees of polymerization are collected in Table 1 for the various transitions between polymerization stages (I→II, II→III, III→IV) and for the intercept from the extrapolation of II back to zero time (t→0). These degrees of polymerization are independent of the initiator type for a given monomer type. They are,

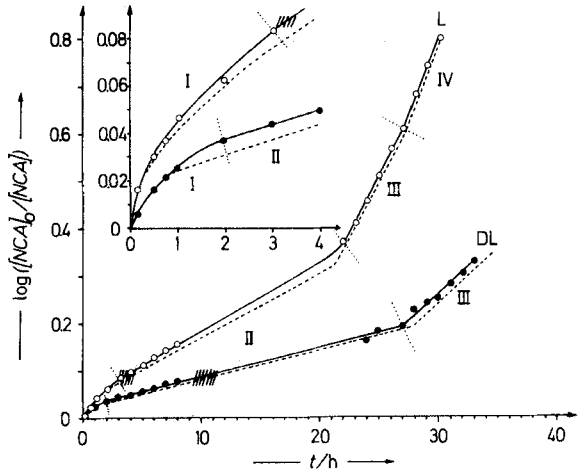

FIG. 1. Polymerization of L- (○) and DL-leucine (●) NCA's by L-α-methylbenzylamine in 1,4-dioxane at 25° C. Broken lines give results with benzylamine for comparison. Dotted lines indicate polymerization stages I-IV. Hatched areas indicate onset of polymer precipitation.

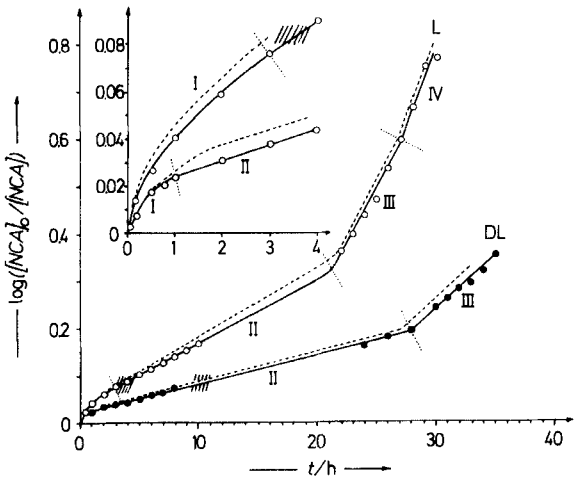

FIG. 2. Polymerization of L- (○) and DL-leucine (●) NCA's by benzylamine in dioxane at 25° C. Broken lines give results with L-α-methylbenzylamine for comparison. Dotted lines indicate polymerization stages I-IV. Hatched areas indicate onset of polymer precipitation.

TABLE 1. Number-Average Degrees of Polymerization, $\langle X \rangle_n$, at Transition Points, as Calculated from Conversion and Initial Concentration Ratios (monomer/initiator)

Monomer	Initiator[a]	$\langle X \rangle_n$ at t→0	I→II	II→III	III→IV
L	L-Me-BA	4.4	8.9	27	36
L	BA	3.9	7.9	25	35
DL	L-Me-BA	2.8	3.6	18	-
DL	BA	1.9	3.1	17	-

[a] L-Me-BA = L-α-methylbenzylamine, BA = benzylamine.

TABLE 2. Propagation Rate Constants k_p of Polymerization Stages II, III, and IV for the Polymerization of L- and DL-Leucine NCA's in Dioxane at 25°C with Benzylamine (BA) or L-α-Methylbenzylamine (L-Me-BA) as Initiator

Monomer	Initiator	$10^3 k_p/(L\ mol^{-1}\ s^{-1})$ for Stage II	III	IV
L	BA	4.35 ± 0.05	14.6 ± 1.0	21.2 ± 1.4
L	L-Me-BA	4.54 ± 0.12	15.5 ± 1.0	-
DL	BA	2.06 ± 0.04	7.4 ± 0.4	19.8 ± 0.3
DL	L-Me-BA	2.10 ± 0.06	7.9 ± 0.8	-

however, always higher for the L-monomer than the DL-monomer. In general, the extrapolated degrees of polymerization are higher than 2. Consequently, the rapid Stage I cannot originate solely from a fast reaction of initiator with one monomer molecule followed by regular propagation steps independent of the degree of polymerization [5]. Also, the degrees of polymerization for the transition II→III, originally attributed to a coil/helix transition [5], are between 17 and 27 and thus much higher than the degrees of polymerization of 6-10 required for helix formation. All these observations agree qualitatively with our previous findings for the polymerization of L-leucine NCA with the bifunctional initiator 1,6-hexanediamine [10].

The propagation rate constants k_p, calculated from Eq. (4) with $[P^*] = [I]_0$ are practically independent of the initiator type for a

TABLE 3. Ratios of Propagation Rate Constants k_p^L/k_p^{DL} for the Two Polymerization Stages II and III

Initiator	k_p^L/k_p^{DL} for Stage II	k_p^L/k_p^{DL} for Stage III
Benzylamine	2.11 ± 0.09	1.97 ± 0.24
L-α-Methylbenzylamine	2.16 ± 0.18	1.96 ± 0.32

given monomer type and polymerization stage (Table 2). They are, however, higher for the L-monomer than the DL-monomer for a given polymerization stage. The ratios $(k_p^L/k_p^{DL})_{II} = 2.14$ and $(k_p^L/k_p^{DL})_{III} = 1.96$ equal 2 within limits of error (Table 3). This is exactly the behavior expected for a stereoselective propagation without crossover steps. In this case, each type of propagating chain end recognizes only its own monomer type and thus only one-half of all monomer molecules.

The study of the polymerization rates of L- and DL-leucine NCA's thus leads to the same conclusion as our previous studies of relative kinetics [1], infrared spectra [4], and enzymatic sequencing [2, 3]: DL-leucine NCA undergoes a stereoselective polymerization to long isotactic blocks, if not blends, with primary amines as initiators, regardless of the chirality of the initiator.

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