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^{13}C-NMR Sequence Analysis. XVIII. Tacticity of Poly(D,L-β-amino Acids)

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^{13}C-NMR Sequence Analysis. XVIII.* Tacticity of Poly(D,L-β-amino Acids)

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ABSTRACT

D,L-Cis-2-aminocyclobutane-1-carboxylic acid NCA, D,L-cis- and trans-2-aminocyclohexane-1-carboxylic acid N-carboxyanhydride (NCA) and D,L-cis-2-aminocyclohexane-1-carboxylic acid NCA were polymerized under various conditions. The ^{13}C-NMR spectra of the resulting β-polyamides measured in trifluoroacetic acid show splittings of all signals reflecting diads and triads. Poly-D,L-3-aminobutyric acid obtained by anionic polymerization of D,L-4-methyl acetidinone does not display tacticity effects in its ^{13}C-NMR spectrum. Hence it is concluded that tacticity effects are observable only if both α- and β-carbons

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have a substituent. Furthermore, it was found that the reaction conditions do not have a strong influence on the stereospecificity of the NCA-polymerization. In all cases nearly random sequences of D and L-units were obtained.

INTRODUCTION

Stereoselective reactions of amino acid derivatives are of general interest because all biochemical reactions involve a high degree of stereospecificity. Furthermore, it is known that isotactic poly-α- or poly-β-amino acids are more suitable for the production of fibers than poly-D,L-amino acids [1]. On the other hand, it must be kept in mind that the synthesis of optically pure enantiomers is more costly than the preparation of racemic monomers. Thus, a stereoselective polymerization of racemic α- and β-amino acid derivatives is highly desirable. In this connection it is necessary to have a reliable and routine analytical method, which allows one to characterize the tacticity of the polypeptides and β-polyamides. In a previous paper we have demonstrated that high resolution ^{13}C-NMR spectroscopy is useful for this purpose for a limited number of polypeptides [2]. In this work it was our intention to clarify whether ^{13}C-NMR spectroscopy can also be applied to analyze the tacticity of poly-D,L-β-amino acids.

EXPERIMENTAL

Materials

Tetrahydrofuran, dioxane, and triethylamine were refluxed and distilled twice over sodium wire; pyridine was refluxed and distilled over freshly powdered calcium hydride and dimethylformamide was distilled over P_4O_{10} in vacuo. The β-amino acid NCA's were synthesized as described previously [3] and used for the polymerizations immediately after isolation.

Polymerizations

A 50-mmole portion of a NCA was dissolved in 80 ml dry solvent and the catalyst was added. The reaction mixture was protected against moisture by a freshly prepared calcium chloride drying tube. The polymers were precipitated from ca. 600 ml ice-cold diethyl ether. After filtration the polymers were dried at $80^\circ C/10^{-2}$ mbar.

Measurements

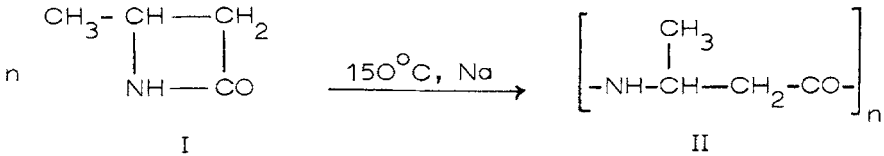
All ^{13}C-NMR spectra were obtained on a Bruker WH-360 FT NMR spectra (8.4 Tesla) at ca. 30°C. A 400 mg portion of polymer dissolved in 2 ml trifluoroacetic acid was measured in 10 mm diameter sample tubes with a coaxial 4 mm tube containing TMS and dioxane-d_8 (1:1 by volume). A pulse width of 12 μs (ca. 40°), 32 K data points on a spectral width of 18,000 Hz and an exponential line-broadening of 0.7 Hz were used.

The viscosities were measured in an Ostwaldt viscometer thermostatted at 20°C.

RESULTS AND DISCUSSION

Poly(D,L-3-aminobutyric Acid) and Poly(D,L-cis-2-aminocyclobutane-1-carboxylic Acid)

Poly(D,L-3-aminobutyric acid)(II) was obtained by anionic polymerization at 150°C from the racemic β-lactam (I). Since under these conditions no stereoselectivity is expected, the NMR signals should display tacticity splittings in the case of sufficient resolution. However, although a FT NMR spectrometer with an 8.4 Tesla magnet was used, no tacticity effects were detectable. This result agrees well with our observation that 90.5 MHz ^{13}C-NMR spectra of poly-D,L-alanine also lack any information on tacticity [2]. Obviously, one small substituent such as a methyl group does not influence the local conformation and the solvation shell sufficiently to cause a resolution of diad or triad peaks in the ^{13}C-NMR spectra. However, it must be emphasized that in the case of polypeptides, even those with larger side chains, such as poly-D,L-phenylalanine and poly-D,L-N^{ϵ}-Z-lysine, do not exhibit tacticity effects in their ^{13}C-NMR spectra when measured at 90.5 MHz [2]. Only monomer units with branched side-chains gave measurable spectroscopic effects [2]. Since in the case of C-α or C-β monosubstituted poly(D,L-β-amino acids) the distance between the chiral centers is still greater than in the case of polypeptides, tacticity effects are not likely to be found in the ^{13}C-NMR spectra, even if the substituents would be more bulky than a methyl group. Thus, the measurement of poly-D,L-aminobutyric acid merely confirmed the conclusion we had drawn from our investigation of poly(D,L-α-amino acids). Since the detection of tacticity in ^{13}C-NMR spectra of poly(D,L-β-amino acids) was more probable in the case of α,β-disubstituted β-amino acid units, various polymers of alcylic D,L-β-amino acids were synthesized. Poly(cis-D,L-2-amino cyclobutane-1-carboxylic acid) (IV), prepared from the previously described [3] NCA III was studied first. The CH_2 groups of the cyclobutane ring are the smallest chemically stable substituents an α-,β-substituted



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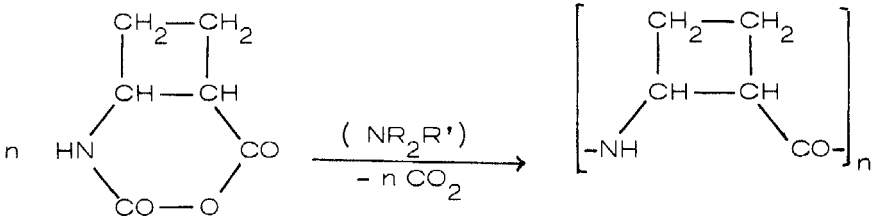


III IV

β-amino acid unit can possess. But even in this relatively unfavorable case, the ^{13}C-NMR spectra clearly display tacticity splittings of all signals (Fig. 1). To check whether the individual peaks of the five signals really stem from diastereometric sequences and not from endgroups or low molecular weight reaction products, polyamide IV was prepared under various conditions (Table 1). The spectra of all samples exhibited the same signal patterns; only the intensity ratios of the individual peaks were slightly different (Fig. 1A and 1B). Furthermore, the signals remained unchanged after reprecipitation of individual samples. Thus, we do not see any reason to doubt the steric origin of the splittings.

The assignment of the signals to the individual carbons is based on the well known substituent effects of amide nitrogens and carbonyl groups [4]. The stronger -I effect of the nitrogen is expected to shift not only the signal of C-2 downfield relative to that of C-1 but also the signal of C-3 relative to C-4. This assignment of C-3 also agrees with the pattern of the signal at 27-28 ppm, since the splitting into two peaks fits well the signal pattern of C-2. The signal at 20 ppm, assigned to C-4, exhibits on the other hand, a triad sensitivity, which agrees well with that of the signal of C-1. However, why two carbons of the cyclobutane ring display diad effects while the other two are sensitive to triads still remains obscure, and we cannot assign the individual diad and triad peaks at the current stage of our investigation. In the case of the carbonyl signal, the two peaks obviously represent the two diastereomeric diads L-L (D-D) and L-D (D-L), since the carbonyl group is located between two chiral centers. A similar spectroscopic behavior as well as an assignment was previously reported for the carbonyl signals of poly-D,L-leucine and poly-D,L-valine

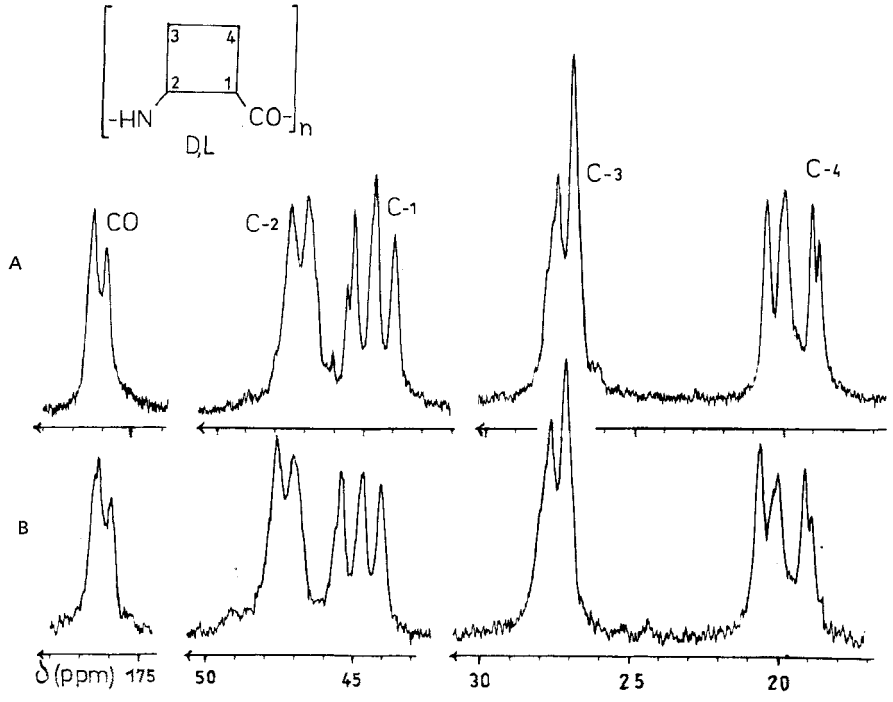


FIG. 1. 90.5 MHz ^{13}C-NMR spectra of poly(D,L-cis-2-aminocyclobutane-1-carboxylic acid) (IV) in TFA: (A) polymer from expt. 2, Table 1; (B) polymer from expt. 7, Table 1.

[2]. Upon comparison of the spectra of all samples obtained according to Table 1 it was found that the intensity ratio of the two carbonyl peaks did not vary greatly. Figues 1A and 1B represent two extreme cases, demonstrating that the intensity ratio of the two carbonyl peaks is near 1:1 in all cases. From these observations we can draw the following interesting conclusions: (1) the sequences of D- and L-units are nearly random in nature; (2) the reaction conditions summarized in Table 1 do not have a substantial influence on the stereospecificity of the polymerization.

Poly(D,L-β-amino Acids) with Six-Membered Rings

In addition to the poly-2-aminocyclobutane carboxylic acid IV, the poly-D,L-β-amino acids V, VI, and VII were prepared from the corresponding β-NCAs (Tables 2 and 3). V is a cis-cyclohexene, VI a cis-cyclohexane, and VII a trans-cyclohexane derivative. Since the

TABLE 1. Reaction Conditions and Results of the Polymerization of D,L-Cis-2-aminocyclobutane-1-carboxylic Acid NCA

No.	Solvent	Catalyst (cocatalyst)	Mole ratio NCA/Cat.	Mole ratio NCA/Cocat.	Temp. (°C)	Time (days)	Yield (%)	η_{sp}/c (cm^3/g)[a]
1	Dimethylformamide	Tert-butylamine	10:1	–	20	5	64	15.0
2	"	"	30:1	–	20	5	74	18.2
3	"	"	60:1	–	20	5	57	16.6
4	Dioxane	"	60:1	–	20	11	94	24.6
5	"	"	60:1	–	100	5	80	16.7
6	Dimethylformamide	Triethylamine	50:1	–	20	5	~1	–
7	Dioxane	"	50:1	–	20	11	88	25.0
8	Pyridine	Pyridine	1:20	–	20	5	92	23.8
9	"	Pyridine (MEC-Gly-NCA)[b]	1:20	50:1	20	5	94	18.3

[a] Measured with c = 10 g/liter in dichloroacetic acid (98%) at 20°C.
[b] N-Methoxycarbonyl glycine-NCA.

TABLE 2. Reaction Conditions and Results of the Polymerization of D,L-Cis-2-aminocyclohexene-1-carboxylic acid NCA (Nos. 1-4) and D,L-Cis-2-aminocyclohexane-1-carboxylic Acid NCA (Nos. 5-9)

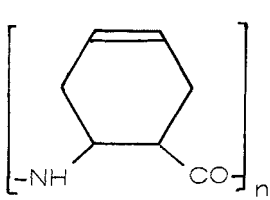
No.	Solvent	Catalyst (cocatalyst)	Mole ratio NCA / Catal.	Mole ratio NCA / Cocat.	Temp. (°C)	Time (days)	Yield (%)	η_{sp}/c (cm^3/g)[a]
1	Dioxane	Tert-butylamine	20:1	–	100	2	80	11.7
2	Dioxane	Tert-butylamine	60:1	–	100	2	99	11.7
3	Dimethylformamide	Tert-butylamine	60:1	–	20	17	95	21.6
4	Dioxane	Triethylamine (MEC-Gly-NCA)[b]	25:1	10:1	20	3	71	12.5
5	Tetrahydrofuran	Benzylamine	40:1	–	60	4	80	17.8
6	Dimethylformamide	Benzylamine	40:1	–	60	4	72	14.5
7	Tetrahydrofuran	Triethylamine (MEC-Gly-NCA)[b]	10:1	20:1	20	2	68	10.4
8	Tetrahydrofuran	Triethylamine (MEC-Gly-NCA)[b]	10:1	60:1	20	2	75	12.7
9	Dimethylformamide	Triethylamine (MEC-Gly-NCA)	40:1	10:1	20	2	11	13.0

[a]Measured with c = 10 g/liter in dichloroacetic acid (98%) at 20°C.
[b]N-Methoxycarbonyl glycine-NCA.

TABLE 3. Reaction Conditions and Results of the Polymerization of D,L-Trans-2-aminocyclohexane-1-carboxylic Acid

No.	Solvent	Catalyst	Mole ratio NCA / Catal.	Temp (°C)	Time (days)	Yield (%)	η_{sp}/c (cm^3/g)[a]
1	Dimethylformamide	Benzylamine	20:1	20	17	96	13.7
2	Dimethylformamide	Benzylamine	40:1	20	17	90	17.3
3	Dimethylformamide	Benzylamine	60:1	20	17	94	20.0
4	Dimethylformamide	Benzylamine	80:1	20	17	88	21.0
5	Dioxane	Triethylamine	50:1	20	12	78	18.4
6	Dimethylformamide	Triethylamine	50:1	20	12	67	18.7
7	Dimethylformamide	Na methanolate	50:1	20	5	69	17.0
8	Pyridine	Pyridine	1:20	20	5	93	13.8

[a]Measured with c = 10 g/liter in dichloroacetic acid (98%) at 20°C.



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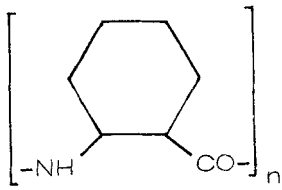

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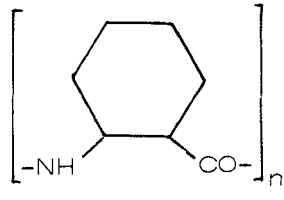

VII

six-membered rings are bulkier substituents than the cyclobutane group, it is not surprising that the ^{13}C-NMR signals of the above poly(D,L-β-amino acids) exhibit splittings and line broadening caused by their tacticity. When the spectra of IV, V, VI, and VII (Figs. 1-4) are compared with each other it is clearly observable the line-width increases in the order IV-VII, while the resolution of the splittings decreases. This relationship is probably a consequence of differences in the conformational freedom of the cyclic substituents. The diastereomeric sequence units L-L (D-D) and L-D (D-L) statistically distributed along the polymer chain not only cause different local conformations of the main chain, but also influence the conformation of the cyclic substituents. A greater variation of the main and side chain conformation is more likely for bulky substituents with higher flexibility. Hence, it is obvious that polyamide IV must show the sharpest signals, since the cyclobutane ring is the smallest and most rigid substituent. The polyamides with cyclohexane rings (VI and VII) represent the opposite extreme, while the C–C double bond of the cyclo hexene ring reduces the flexibility of the substituent in polyamide V.

To prove that the splittings of the ^{13}C-NMR signals result from steric effects and not from low molecular weight amino acid derivatives or endgroups, the polyamides were reprecipitated in several cases and measured again. Furthermore, in the case of VII, a series of products was prepared under similar reaction conditions but with different monomer/initiator ratios (Nos. 1-4, Table 3). The viscosity measurements demonstrate that various polymerization degrees were obtained in this way. Yet the signal patterns of the four samples were nearly identical. This result agrees well with that obtained for polymer IV in experiments 1-3 of Table 1.

The assignment of the ring carbons in polymers V, VI, and VII is based mainly on the different electronegativities of amide nitrogen and carbonyl group in analogy with the cyclobutane ring of IV. An assignment of diad and triad peaks was not possible, because model compounds with well defined steric sequences were not available. However, the signals of C-1 and C-6 in the case of V and C-1 and C-2 in the case VI exhibit a simple splitting into two peaks which probably represent the two diastereomeric diads L-L (D-D) and L-D (D-L) (Figs. 2 and 3). If one accepts this interpretation, then three interesting

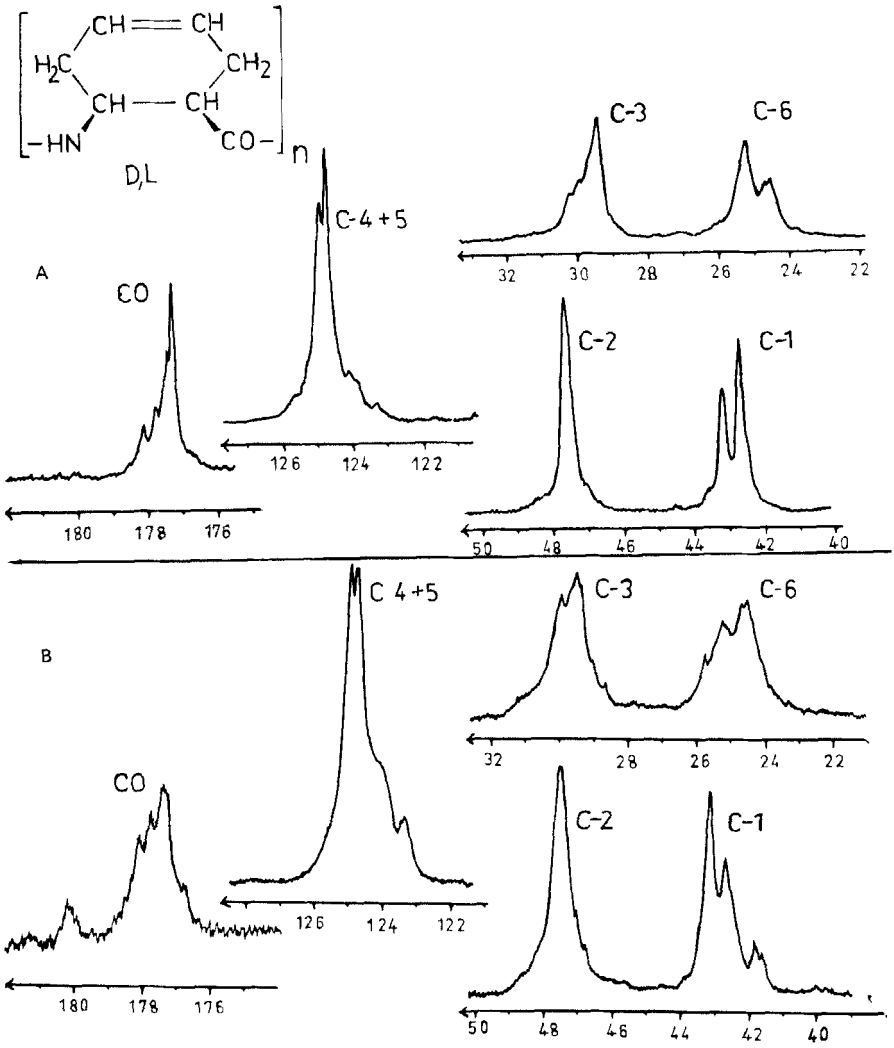

FIG. 2. 90.5 MHz ^{13}C-NMR spectra of poly(D,L-cis-2-amino-cyclohexene-1-carboxylic acid) (V) in TFA: (A) polymer from expt. 3, Table 2; (B) polymer from expt. 2, Table 2.

conclusions can be drawn from the ^{13}C-NMR spectra of polymer V and VI in good agreement with our evaluation of the spectra of Fig. 1.

(1) The ratio of L-L/L-D bonds is within the limits of 0.5-2.0; in other words the stereospecificity of the β-NCA polymerization is low and nearly random sequences of D- and L-units are the result in all experiments of Tables 1-3.

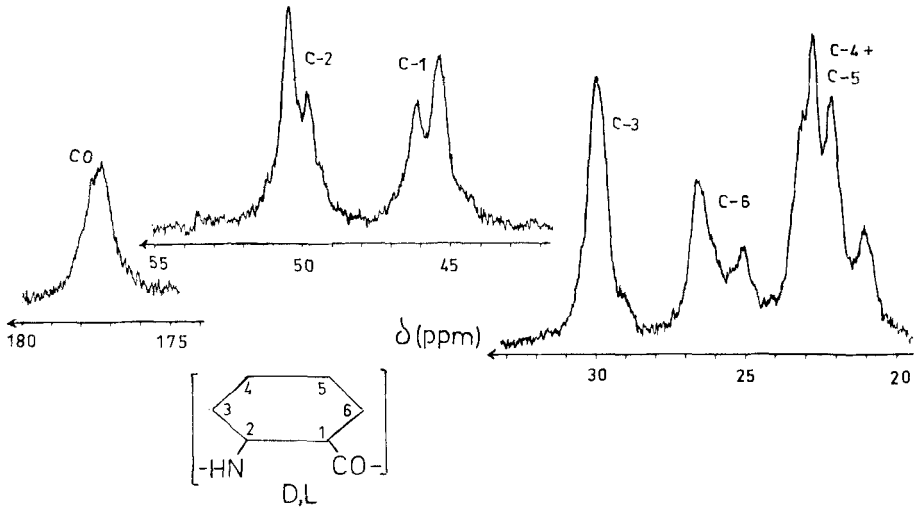

FIG. 3. 90.5 MHz ^{13}C-NMR spectrum of poly(D,L-cis-2-amino-cyclohexane-1-carboxylic acid) (VI) from experiment 5, Table 2, in TFA.

The variation of the reaction conditions does not exert a strong influence on the extent of the stereospecificity of the β-NCA polymerization. Figures 2A and 2B represent the most different tacticities obtained for V in experiments 1-4 of Table 2, and Figs. 1A and 1B represent the most different tacticities found for polymer IV. Also in the case of polymer VI and VII the tacticities did not vary largely.

(3) A change of the solvent can alter the direction of the stereospecificity, even if the polymerization mechanism and other parameters of the reaction conditions remain constant. This is the case in experiments 2 and 3 of Table 2, because the two diad peaks of the C-1 and C-6 signals show inverse intensity ratios when Figs 2A and 2B are compared. In one of the corresponding experiments (Nos. 2 or 3) the formation of L-L (D-D) bonds was slightly favored, while in the other experiment L-D (D-L) bonds were preferentially formed.

These conclusions are in good agreement with our results concerning the stereospecificity of the polymerization of D,L-Ala-NCA [5], D,L-Val-NCA [5, 6], and D,L-Leu-NCA [6]. Also in the case of D,L-Leu-NCA and D,L-Val-NCA we have observed that the predominant formation of L-L (D-D) or L-D (D-L) bonds can depend on the nature of the solvent. A further example for a solvent-induced change of stereospecificity was found when Boc-D,L-Val-D,L-Val-OMe was synthesized from Boc-D,L-Val-OH and D,L-valine methyl ester [7]. Also in the case of poly-D,L-peptides the L-L/L-D ratio was mostly in the range 0.5-2.0 e. g., in all experiments where the

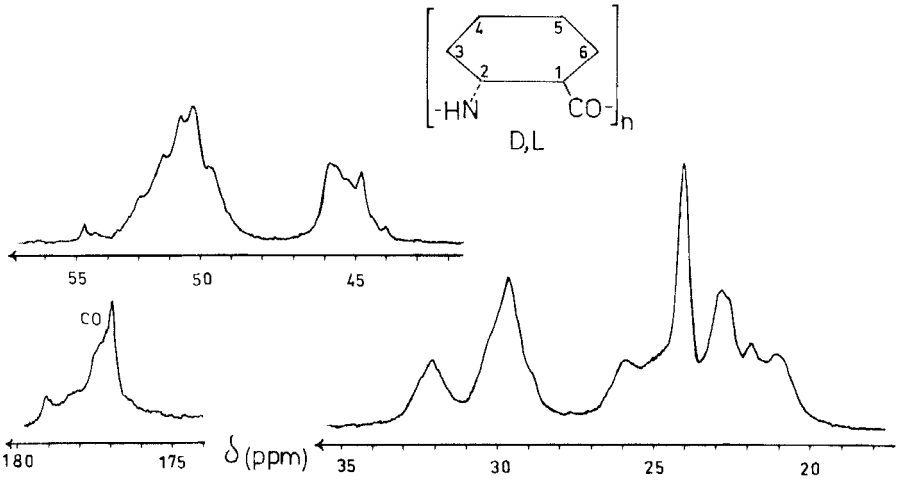

FIG. 4. 90.5 MHz ^{13}C-NMR spectrum of poly(D,L-trans-2-amino-cyclohexane-1-carboxylic acid) (VII) from experiment 7, Table 3 in TFA.

chain growth proceeds via nucleophilic chain ends [Eqs. (1) and (2)]. However, a characteristic difference between the stereospecificity of the α- and β-NCA polymerization must be emphasized. For the polymerization of D,L-α-NCAs a relatively high stereospecificity (L-L/L-D) $>$ 2) was found when the reaction conditions strongly favored the "activated monomer mechanism" [Eq. (3)]. This type of propagation involves the nucleophilic attack of an NCA anion onto an N-acyl NCA chain end, a reaction which is only predominant if basic catalysts, highly electrophilic cocatalysts, and polar solvents are used. In the case of β-amino acid NCAs we could demonstrate that the "activated monomer mechanism" is never prevailing, even under the most favorable conditions [8]. The low stereospecificity of the polymerization of D,L-β-NCAs with L-L/L-D ratios in the range of 0.5-2.0 is, thus, in good agreement with our mechanistic investigation.

CONCLUSION

The NMR spectra of this work show for the first time that it is possible to characterize the tacticity of β-polyamides (nylon 3) by ^{13}C-NMR spectra. However, both α- and β-carbons must have substituents to allow a resolution of diad and triad peaks. Even though we were not able to assign the observed splittings to individual diads and triads, we can conclude from the intensities of the diad peaks

that the polymerization of β-amino acid NCAs leads in all cases to nearly random sequences of D- and L- monomer units. These preliminary results also allow the conclusion that in the future the stereospecificity of all polymerizations can be investigated which lead to the formation of β-polyamides with α-β-disubstituted monomer units. This aspect is of particular interest for β-lactams since this class of monomers allows the synthesis of high molecular weight β-polyamides which are useful as fibers.

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