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Mechanism of NCA Polymerization. VIII.* The Base-Initiated Polymerization of β-Amino Acid NCAs

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ABSTRACT

The polymerization of β-alanine NCA, D,L-cis-2-aminocyclobutane-1-carboxylic acid NCA, D,L-cis-2-amino-4-cyclohexane-1-carboxylic acid NCA, and D,L-cis-2-aminocyclohexane-1-carboxylic acid NCA was carried out in various solvents by use of triethylamine or pyridine as catalysts. The addition of these bases to a NCA solution leads to deprotonation of the NCAs and to the formation of large amounts of β-isocyanatocarboxylate ions which are detectable in the IR spectra. These isocyanates cause side reaction which prevent the formation of high molecular weight β-polyamides under all conditions studied. The role of electrophilic cocatalysts such as N-acylamino acid NCAs and chlorophenyl isocyanate was investigated. In contrast to the base-initiated polymerization of α-amino acid NCAs, the polymerization of β-amino acid NCAs is inhibited by the addition of electrophilic cocatalysts. Thus, the activated monomer mechanism is not operating in the case of β-amino acid NCAs. Various N-acyl β-amino acid NCAs were synthesized by addition of β-amino acid NCAs onto reactive isocyanates.

*For Part VII see H. R. Kricheldorf and R. Mülhaupt, Makromol. Chem., 180, 1419 (1979).

INTRODUCTION

The polymerization of α-amino acid NCAs initiated by tertiary amines and other aprotic bases has been the object of many investigations, speculations, and discussions during the past twenty years. Two reasons are primarily responsible for this evolution. First, the base-initiated polymerization of α-amino acid NCAs seems to provide in most cases the highest degrees of polymerization [1-3]. However, high molecular weight polypeptides are of interest as fibers [4] and as model compounds for proteins [5]. Secondly, experimental difficulties and controversal interpretations of experimental results have prevented a rapid elucidation of the polymerization mechanism. Three basically different mechanisms of the tertiary amine-initiated polymerization of α-amino acid NCAs have been proposed, namely the zwitterion-mechanism [6], the carbamate-mechanism [7] and on activated monomer mechanism [3, 8]. Since the α-amino acid NCAs can react in various ways, a better understanding of their polymerization mechanisms includes good knowledge of structure-reactivity relationships. In this connection it can be useful to investigate also the reactions of other monomers with a structure similar to that of α-amino acid NCAs. For this reason and because high molecular weight poly-β-amino acids are interesting materials for fiber production it seemed to us worthwhile to investigate the base-initiated polymerization of β-amino acid NCAs in more detail. A study on the polymerization of β-amino acid NCAs initiated by primary or secondary amines was presented in the preceding paper [9].

EXPERIMENTAL

Materials

Chlorosulfonylisocyanate was gift of Hoechst AG. and was used after distillation. The aryloxysulfonylisocyanates were prepared from chlorosulfonylisocyanate and phenols in boiling toluene [10]. Tosyl isocyanate was purchased from Aldrich and used without distillation. Dioxane, tetrahydrofuran, diethyl ether, and triethylamine were twice refluxed and distilled over sodium wire. Aromatic solvents, methylene chloride, and dimethylformamide were refluxed and distilled over P_4O_{10}. The β-amino acid NCAs were prepared from diacid anhydrides and trimethylsilylazide [11]. The trimethylsilylazide was synthesized as described previously [12].

Syntheses

N-Carbamoyl-β-Amino Acid NCAs (General Procedure). A 50 mmole portion of the β-amino acid NCA was

dissolved in 60-100 ml dry methylene chloride and 50 mmole of a sulfonylisocyanate was added. In most cases, the reaction was complete after 8 hr at 20°C, as indicated by the absence of the isocyanate band (ca 2300 cm^{-1}) in the IR spectra of the reaction mixture. On the next day, the reaction mixture was concentrated in vacuo to ca. 30 ml, and the product was crystallized by portionwise addition of ligroin under cooling with ice (yields given in Table 1). Recrystallization (if necessary) was carried out with tetrahydrofuran/ligroin.

N-(4-Chlorocarbanilyl)-cis-2-aminocyclohexane-NCA (IIIf). In method A, 8.5 g (50 mmole) cis-2-aminocyclohexane NCA and 7.2 g (50 mmole) 4-chlorophenylisocyanate were refluxed in 50 ml dry dioxane for 4 hr. After this time the IR spectrum did not exhibit an isocyanate signal. The reaction mixture was then concentrated in vacuo, and the product was crystallized by portionwise addition of ligroin and cooling; yield 10.1 g (63%).

In method B, the reactants (50 mmole each) were refluxed together with 0.2 ml triethylamine in 50 ml dry methylene chloride for 6 hr. Afterwards the reaction mixture was concentrated in vacuo, and the product was crystallized by addition of ligroin under cooling with ice; yield 10.4 g (65%).

In method C, 0.1 g 1,4-diazabicyclooctane was used instead of triethylamine. The yield was 10.8 g (67%); properties are given in Tables 1-3.

Alcoholysis of N-(4-Chlorocarbaniloyl)-Cis-2-aminocyclohexane NCA. A 3.2 g portion (10 mmole) of the N-carbamoyl NCA was refluxed in 50 ml dry ethanol until a clear solution was obtained. Then, the reaction mixture was concentrated in vacuo, and the product crystallized by portionwise addition of diethyl ether under cooling with ice; yield: 1.9 g (59%); mp 168-170°C.

ANAL.: Calcd for $C_{16}H_{21}ClN_2O_3$ (324.81): C, 59.17%; H, 6.52%; N, 8.63%. Found: C, 59.20%; H, 6.73%; N, 8.45.

^{1}H-NMR in DMSO-d_6 (internal TMS) showed δ (ppm): 8.69 (s 1H, broad); 7.40 (q, 4H, J = 12.0 Hz); 6.34 (d, 1H, J = 9.0 Hz); 4.13 (q, 3H, J = 7.0 Hz); 2.73 (m, 1H); 1.74 (m, 8H); 1.20 (t, 3H; J = 7.0 Hz).

The filtrate was extracted with 50 ml of a 10% (by weight) potassium carbonate solution. However, upon acidification of this extract with concentrated hydrochloric acid no β-ureidocarboxylic acid separated.

Deprotonation of 1,3-Oxazine-2.6-dione. A 5.7 g (50 mmole) portion of 1,3-oxazine-2,6-dione were dissolved in 150 ml dry tetrahydrofuran and 3.7 g (50 mmole) tert-butylamine was added dropwise, whereby a crystalline precipitate was formed. Ligroin (100 ml) was added to the reaction mixture and after cooling to -10°C the tert-butylammonium salt was isolated by filtration; yield, 8.3 g (89%); mp, 118-120°C (dec.).

ANAL. Calcd for $C_8H_{14}N_2O_3$ (186.2): C, 51.59%; H, 7.57%; N, 15.04%. Found: C, 51.63%; H, 7.65%; N, 14.89%.

The IR spectrum (KBr) exhibits signals attributable to carbonyl groups and the C–C double bond at 1776, 1720 and 1630 cm^{-1}. The

TABLE 1. Properties of N-Acyl β-Amino Acid NCAs Synthesized by Addition of β-Amino Acid NCAs onto Isocyanates

Formula no.	Yield (%)	Mp (°C)	Formula (Mol. Wt.)	Elemental analysis			
					C(%)	H(%)	N(%)
I[b]	68.0	97-98	$C_5H_5ClN_2O_6S$ (256.6)	Calcd	23.40	1.96	10.92
				Found	23.80	2.11	11.05
Ic	63	93-95	$C_{12}H_{12}N_2O_7S$ (328.0)	Calcd	43.90	3.68	8.53
				Found	44.06	3.85	8.48
IIIb	93	128-129	$C_9H_{11}ClN_2O_6S$ (310.7)	Calcd	34.79	3.57	9.02
				Found	35.01	3.68	9.07
IIIc	85	143-145	$C_{16}H_{18}N_2O_7S$ (382.3)	Calcd	50.26	4.75	7.33
				Found	50.36	4.80	7.23
IIId	75	154-156	$C_{15}H_{16}N_2O_7S$ (368.4)	Calcd	48.91	4.38	7.61
				Found	48.99	4.37	7.40
IIIe	78	124-126	$C_{16}H_{18}N_2O_6S$ (366.4)	Calcd	52.45	4.95	7.65
				Found	52.70	5.10	7.73
IIIf	68	183-185	$C_{15}H_{15}ClN_2O_4$ (322.7)	Calcd	55.82	4.68	8.68
				Found	55.94	4.83	8.51
IIb	65	123-124	$C_9H_9ClN_2O_6S$ (308.7)	Calcd	35.31	2.93	9.07
				Found	35.38	3.15	9.09
IIc	84	126-128	$C_{12}H_{16}N_2O_7S$ (380.3)	Calcd	50.52	4.24	7.36
				Found	50.79	4.46	7.40
IId	74	150-152	$C_{15}H_{14}N_2O_7S$ (366.3)	Calcd	49.18	3.85	7.65
				Found	49.46	3.92	7.34

TABLE 2. ^{13}C-NMR Chemical Shifts δ (downfield from external TMS) of some N-Carbamoyl-β-Amino Acid NCAs in Trifluoroacetic Acid[a]

Formula no.	δ (ppm)		
	Carbonyls	N-Acyl residue	β-Amino acid residue
Ib	164.38 150.98 149.14	147.67; 139.85 130.82; 121.07 19.42	38.15; 28.11
IIb	165.71 150.82 148.01	— — —	123.69; 122.07 49.41; 38.24 26.49; 23.73
IIc	165.91 150.75 148.86	147.72; 139.79 130.78; 121.66 19.26	123.72; 122.04 49.15; 38.15 26.55; 23.63
IIIc	166.34 150.87 149.03	147.82; 139.97 130.78; 120.86 19.32	52.93; 39.78; 28.70 24.33; 23.57; 20.18
IIIe	166.52 150.82 149.20	148.07; 133.34 130.16; 128.60	52.65; 39.92; 28.60 24.27; 23.52; 20.23
IIIf	167.42 152.37	133.46; 133.16 129.60; 124.52	52.60; 40.14; 28.97 24.39; 23.63; 20.29

[a]Other N-carbamoyl β-amino acid NCAs are not soluble in trifluoroacetic acid.

^{1}H-NMR spectrum in DMSO (TMS int.) shows δ (ppm) = 7.10 (s, 3 H); 7.06 (d, 1 H, J = 7.5 Hz); 5.10 ppm (d, 1 H, J = 7.5 Hz); 1.22 (s, 9 H) ppm.

Polymerization of β-NCAs in the Presence of N-Carbamoyl β-NCAs General Procedure). A 50 mmole portion of a β-NCA (Ia or IIIa) was dissolved in 80 ml dry solvent and a N-carbamoyl β-NCA (Ic or IIIc) was added in most experiments (Table 4). Then either triethylamine was added in form of a 1 M solution in dry dioxane, or potassium ethanolate in form of a 1 M solution in ethanol. After 6 or 24 hr, the reaction mixture was poured into 600 ml diethyl ether. The precipitated polymer was filtered off, washed with diethyl ether, and dried at 60°C/12 Torr. In the case of experiments 5 and 9 (Table 4), the polymers were reprecipitated from formic acid/acetone. The ^{1}H- and ^{13}C-NMR spectra of the reprecipitated polymers were measured in TFA. Signals attributable to ethyl ester endgroups were not detectable.

TABLE 3. Wavenumbers of the Carbonyl Bonds in the IR Spectra (KBr) of Compounds of Structure III

Formula no.	Residue R	Wavenumber (cm^{-1})	
		Carbonyl C_6	Carbonyl C_2
IIIa	H–	1812	1760
IIIe	CH_3–C_6H_4–SO_2–	1812	1760
IIId	C_6H_5O–SO_2–	1828	1767
IIIc	CH_3–C_6H_4O–SO_2–	1829	1768
IIIb	Cl–SO_2–	1832	1768

Triethylamine-Initiated Polymerization of β-Ala-NCA (general procedure). A 5.8 g (50 mmole) portion of β-Ala-NCA was dissolved in 100 ml dry dioxane at 20°C and 1 ml 1 M triethylamine solution in dry dioxane was added at once. The flask was closed with a freshly prepared calcium chloride drying tube, and after 1, 4, or 12 hr the polymer was precipitated from 500 ml diethyl ether.

In two analogous series of experiments (Table 5) either 10 or 2.5 mmole of 4-chlorophenyl isocyanate or N-methoxycarbonylglycine NCA was added to the NCA solution before the addition of triethylamine. In the fourth series (Table 5), 10 or 2.5 mmole of tert-butylamine was mixed with 1 ml 1 M triethylamine solution (in dioxane) and added to the solution of β-Ala-NCA.

Polymerization of β-NCAs in the Presence of N-Methoxycarbonyl glycine NCA (General Procedure). A 50 mmole portion of a β-NCA and the cocatalyst (0.5-10 mmole) were dissolved in 100 ml dry dioxane or tetrahydrofuran, and triethylamine was added in form of a 1 M solution in dry dioxane. The polymers were precipitated from 600 ml dry diethyl ether and filtered under protection against moisture. IR- and ^{1}H-NMR spectra were measured immediately after drying (20°C, 10^{-2} Torr, 24 hr). The poly-β-alanine (Nos. 2-4, Table 6) was powdered, suspended in 60 ml dry dimethylformamide, and stirred with 7.3 g (0.1 mole) tert-butylamine for 24 hr at 20°C. Afterwards the poly-β-alanine was filtered, washed with diethyl ether, dissolved in 60 ml formic acid, and precipitated again from 600 ml dry diethyl ether.

Measurements

The IR spectra, (Figs. 1-3) were measured with a Phillips Unicam SP 1000; the kinetic results (Fig. 4) were obtained with a Perkin-Elmer Model 325 instrument equipped for protection against moisture.

TABLE 4. Influence of N-Carbamoyl β-Amino Acid NCAs (Ic, IIIc) on the Base-Initiated Polymerization of Cis-2-aminocyclohexane-1-carboxylic Acid NCA (IIIa) and β-Alanine NCA (Ia)

No.	Monomer	Catalyst and cocatalyst	NCA[a] Catalyst	NCA[a] Cocatalyst	Solvent	Temp. (°C)	Time (hr)	Yield (%)[b]
1	Cyclohexane-NCA IIIa	Triethylamine	50:1	—	Dioxane	60-62	24	61.5
2	" "	Triethylamine KOS-hexane-NCA IIIc	50:1	30:1	"	60-62	24	0
3	" "	Triethylamine KOS-hexane-NCA IIIc	50:1	10:1	"	60-62	24	0
4	" "	Triethylamine KOS-β-Ala-NCA Ic	50:1	30:1	"	60-62	24	0
5	" "	K-Ethanolate	50:1	—	DMF	25-26	6	60.0
6	" "	K-Ethanolate KOS-hexane-NCA IIIc	50:1	20:1	"	25-26	6	0
7	" "	K-Ethanolate KOS-hexane-NCA IIIc	50:1	10:1	"	25-26	6	0
8	" "	K-Ethanolate KOS-β-Ala-NCA Ic	50:1	20:1	"	25-26	6	0
9	β-Ala-NCA Ia	K-Ethanolate	100:1	—	THF/ DMF (7:1)	25-26	6	83.0
10	" "	K-Ethanolate KOS-β-Ala-NCA Ic	100:1	40:1	" "	25-26	6	0

(continued)

TABLE 4 (continued)

No.	Monomer	Catalyst and cocatalyst	NCA[a] Catalyst	NCA[a] Cocatalyst	Solvent	Temp. (°C)	Time (hr)	Yield (%)[b]
11	β-Ala-NCA Ia	K-Ethanolate KOS-β-Ala-NCA Ic	100:1	20:1	THF/ DMF (7:1)	25-26	6	0
12	" "	K-Ethanolate KOS-β-Ala-NCA Ic	100:1	10:1	" "	25-26	6	0
13	" "	K-Ethanolate KOS-hexane-NCA IIIc	100:1	40:1	" "	25-26	6	0

[a]Mole ratio.
[b]Polymer precipitated from diethyl ether.

TABLE 5. Influence of Nucleophilic and Electrophilic Cocatalysts on the Triethylamine-Initiated Polymerization of β-Ala-NCA (NCA/Base = 50:1) in Dioxane at 20°C

Cocatalyst (Coc)	NCA/Coc mole ratio	Time (hr)	Yield (%)	η_{sp}/c (cm^3/g)	$\overline{DP}$ (by ^{1}H-NMR)
None	—	1	56.0	12.3	—
		4	82.0	14.7	—
		12	100	17.1	—
Tert-butylamine	5:1	1	98.0	14.4	—
		4	100	14.5	—
		12	100	14.5	—
	20:1	1	78.0	9.5	—
		4	95	15.5	—
		12	100	17.4	—
N-Methoxycarbonyl glycine NCA	5:1	1	48.0	9.4	—
		4	59.5	10.3	—
		12	85.0	11.3	—
	20:1	1	49.5	13.0	—
		4	66.0	13.1	—
		12	92.5	13.6	—
4-Chlorophenyl isocyanate	5:1	1	13.5	9.6	6-7
		4	52.0	9.7	4-5
		12	80.0	9.2	5-6
	20:1	1	30.0	11.0	14-16
		4	73.5	12.0	—
		12	89.5	13.0	14-17

The ^{1}H-NMR spectra were measured on a JEOL JNM-PMX-60 instrument at 60 MHz in 5 mm sample tubes; internal TMS served for shift referencing.

The ^{13}C NMR spectra were measured on a Bruker WH-90 FT-NMR spectrometer at 21 kGauss (2.1 Tesla) in 10 mm sample tubes. A

TABLE 6. Reaction Conditions and Results of the Triethylamine-Initiated Polymerization of β-Alanine-NCA (Ia), Cis-2-aminocyclohexene-1-carboxylic Acid NCA (IIa), and Cis-2-aminocyclohexane-1-carboxylic Acid NCA (IIIa) with N-Methoxycarbonylglycine NCA as Cocatalyst

No.	NCA	NCA[a] Cat.	NCA[a] Cocat.	Solvent	Temp. (°C)	Time (days)	Yield (%)	η_{sp}/c (cm^3/g)[b]	$\overline{DP}$ (^{1}H-NMR)	
									CH_3–O–[c]	$(CH_3)_3C$–NH–[d]
1	Ia	50:1	5:1	Dioxane	20	3	98	11.4	6-7	
2	IIa	50:1	10:1	"	20	3	99	12.6	10-11	40-45
3	IIa	50:1	20:1	"	20	3	99	13.4	20-22	55-65
4	IIa	50:1	40:1	"	20	3	99	14.6	36-40	75-85
5	IIa	25:1	5:1	"	20	3			5-7	
6	IIa	25:1	10:1	"	20	3			10-13	
7	IIIa	10:1	20:1	Tetrahydro-furan	20	2	68	10.4	13-16	
8	IIIa	10:1	40:1	"	20	2	70	11.7	25-30	
9	IIIa	10:1	60:1	"	20	2	75	12.4	45-50	
10	IIIa	10:1	80:1	"	20	2	79	12.7	—	
11	IIIa	10:1	100:1	"	20	2	81	12.6	—	

[a]Mole ratios.
[b]Measured in formic acid at 20°C.
[c]After precipitation from diethyl ether.
[d]After treatment of the precipitated polymer with tert-butylamine in DMF and reprecipitation from formic acid/diethylether.

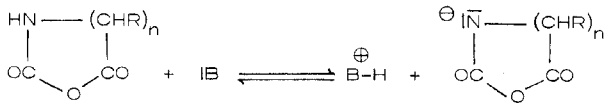
coaxial 4 mm capillary containing a 1:1 mixture (by volume) of dioxane-d_8 and TMS served for lock and shift referencing.

The viscosities were measured in a thermostated Ostwaldt viscometer at 20°C in dichloroacetic acid.

RESULTS AND DISCUSSION

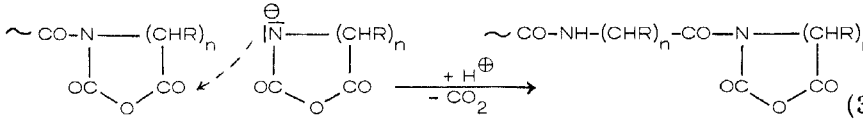
Deprotonation of β-Amino Acid NCAs

Two reaction mechanisms are primarily discussed in the case of the base-initiated polymerization of α-amino acid NCAs: the activated monomer mechanism [Eqs. (1)-(3)] and the carbamate mechanism [Eqs. (4)-(5)]. Most characteristic for the activated monomer mechanism are the NCA anions which are responsible for the initiation reaction (2) as well as for the propagation (3). However, if a strong base of low nucleophilicity, such as triethylamine or potassium tert-butylate is used as initiator and if nucleophilic impurities are absent, the carbamate mechanism also requires NCA anions for the initiation reaction. In other words Eqs. (2) and (4) become identical. Thus, it was the first step of this work to investigate whether β-NCA anions are formed upon addition of trialkylamines to a NCA solution in polar solvents. Since alcoholates are stronger bases than trialkylamines, there is no doubt that they can also deprotonate β-NCAs if the trialkylamines are basic enough. Experimental evidence for the formation of β-NCA anions was first obtained when β-NCAs were silylated with trimethylchlorosilane and triethylamine [11, 13]. While β-NCAs do not react with chlorosilanes in the absence of a tertiary amine, a fast and quantitative reaction takes place upon addition of triethylamine at 0°C. A similar result was obtained, when 2-nitrophenylsulfonyl chloride (NPS-Cl) was used instead of trimethylchlorosilane. NPS-β-NCAs were rapidly formed upon addition of triethylamine [14, 15]. In contrast to the crystalline NPS-β-NCAs, the reaction products of the silylation are not the N-trimethylsilyl-β-NCA, but the isomeric β-isocyanatocarboxylic acid trimethyl silyl ester. The nature of the endproducts is obviously the result of a thermodynamical control, because the Si–O bond is usually more stable than the Si–N bond, while a sulfenyl-N-bond is more stable than a sulfenyl–O bond. Furthermore, it should be mentioned here that triethylamine has a catalytic influence on the addition of β-NCAs onto aryl isocyanates (see below), an observation which also requires the intermediate formation of NCA anions for its explanation. Further evidence for the deprotonation of β-NCAs by triethylamine was obtained by measuring IR spectra of β-NCA/triethylamine mixtures (mole ratio 1:1) in tetrahydrofuran at -16 to -15°C. The IR spectra show in addition to the characteristic CO signals of the NCA ring the signal attributable to an isocyanato group at 2280 cm^{-1} (Fig. 1). This signal is more intense in the case of β-Ala-NCA than in the case of substituted



(1)

(2)



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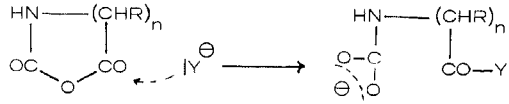
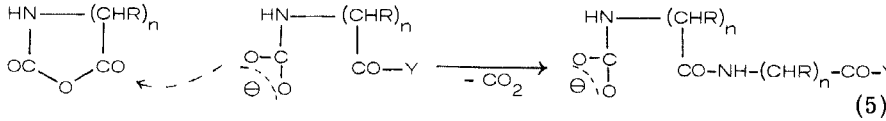


(4)



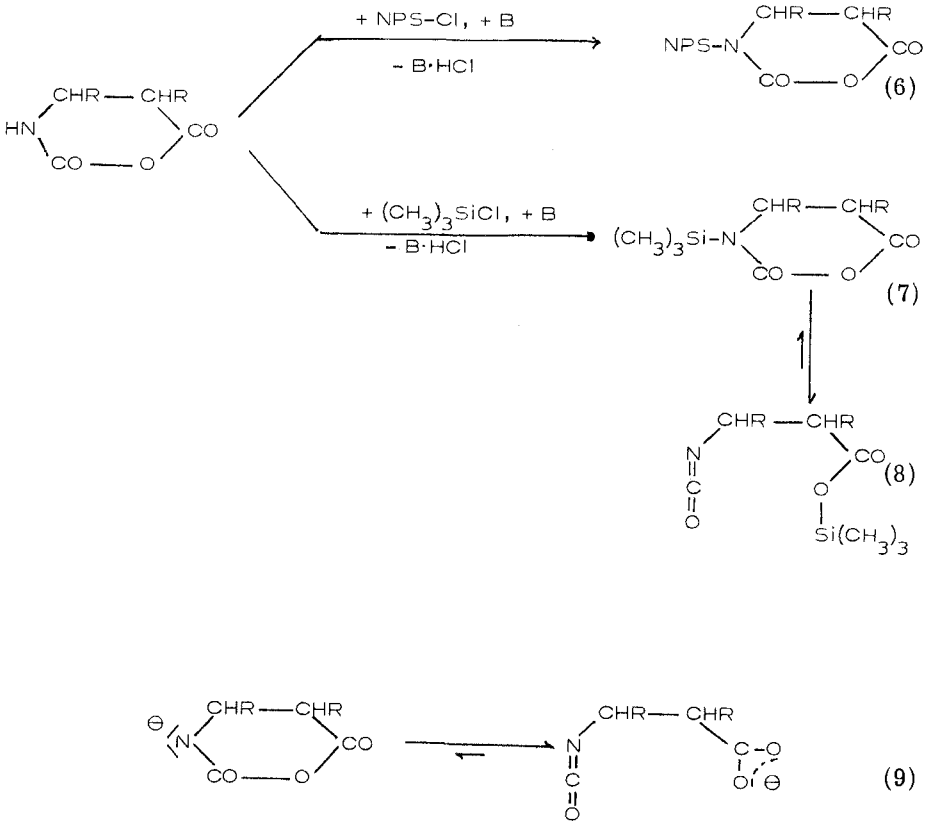
(5)

n = 1, α-amino acids

n = 2, β-amino acids

Y = any nucleophile which can attack the NCA ring

β-NCAs. Since β-NCAs do not exhibit isocyanate signals in the absence of bases, the IR results of Fig. 1 can only be explained by the two equilibria (1) and (9). Since the equilibrium (8) lies completely on the side of the isocyanate, we suppose that the equilibrium (9) behaves analogously. Two reasons account for the lower intensity of the isocyanate signal in the case of substituted β-NCAs compared with β-Ala-NCA. First, alkyl substituents enhance the electron density of the nitrogen, so that the anion is less stable; secondly, they favor the ring form (i. e., NCA anion) in the equilibrium (9) for reasons of



entropy. This interpretation also allows us to explain another observation. In the experiments of Fig. 1 it was observed that the isocyanates derived from substituted β-NCAs disappear so rapidly that the IR spectra must be measured immediately after the addition of triethylamine (Fig. 1B). In the case of β-Ala-NCA the isocyanate signal was observable for more than 2 hr. Obviously the NCA anions react with their isomers to form N-carbamoyl NCAs [10]. The rate of this reaction increases, of course, with increasing nucleophilicity of the NCA anions and with their concentration. The formation of carboxyl groups reduces the basicity of the medium, so that the deprotonation of β-NCAs is finally stopped. In this connection it is worth noting that β-amino acrylic acid NCA (1,3-oxazine-2,6-dione) is so N-H acidic and so little electrophilic that addition of primary and secondary amines leads the quantitative formation of ammonium salts [11]. By means of dimethyl sulfate, the 1,3-oxazine-2,6-diones can be alkylated in the presence of cold sodium carbonate [16, 17]. These results together with those presented in the preceding paper [9] clearly demonstrate that β-NCAs are easily deprotonated by

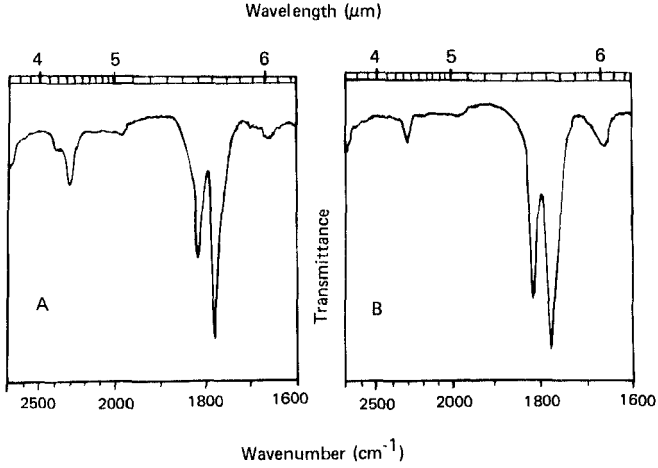
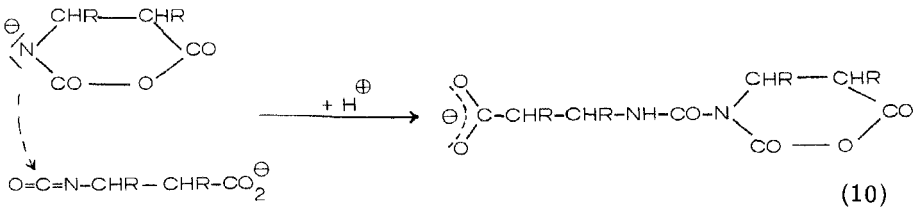
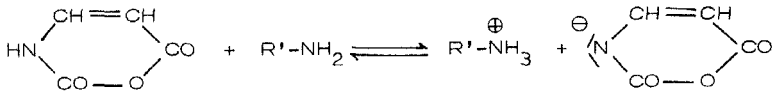


FIG. 1. IR spectra of tetrahydrofuran solutions of (A) β-alanine-NCA/triethylamine (mole ratio, 1:1) at -16°C after 40 min; (B) cis-2-aminocyclohexane-1-carboxylic acid NCA/triethylamine (mole ratio, 1:1) at -16°C after 1 min.

primary, secondary, or tertiary aliphatic amines; however, the extent of the deprotonation and the reactions of the NCA anions depend strongly on the structure of the β-NCAs.



(10)



(11)

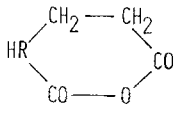
Synthesis and Properties of N-Acyl β-NCAs

Base-initiated polymerization of β-NCAs proceeding predominantly via the activated monomer mechanism (1)-(3) requires in addition to the formation of β-NCA anions that N-acyl β-NCAs are formed either by the reaction of a β-NCA anion with a β-NCA or by the addition of a β-NCA anion onto a β-isocyanato carboxylate, that the N-acyl β-NCAs react with nucleophiles, e. g., β-NCA anions exclusively at the carbonyl group C-6, and that the N-acyl-β-NCAs are more electrophilic than the β-NCAs themselves.

Since N-acyl-β-NCAs were not previously known, it was the second step in our investigation to study synthesis and properties of N-acyl β-NCAs.

In a previous paper we described various methods for the synthesis of N-acyl-α-NCAs; however, none of these methods allowed a general application onto a variety of α-NCAs [18]. Thus, it was initially not clear which of the methods used for α-NCAs would be successful in the case of β-NCAs. At first, we tried to achieve a direct acylation of the β-NCAs Ia, IIa, and IIIa by means of triethylamine and 3,5-dinitrobenzoyl chloride, which was successfully used in the case of α-NCAs. Although triethylamine hydrochloride was formed nearly quantitatively and although the IR spectra of the concentrated reaction mixture showed the characteristic carboxyl signals of the β-NCA ring, only impure, syrupy products were obtained. The phosgenation of N-acetyl-N-trimethylsilyl β-alanine trimethylsilylester was also unsuccessful, because the cyclization of the N-chloroformyl intermediate failed.

Thus, the only method which allowed us to isolate a variety of N-acyl β-NCAs was the addition of β-NCAs onto reactive isocyanates (Table 1). For this purpose mainly the sulfonyl isocyanates IVa-e were used, because the reaction of the β-NCAs with these highly reactive isocyanates proceeded at room temperature even in the absence of a catalyst. With respect to the β-NCAs the following order of reactivity was found by IR spectroscopic control of the reactions: IVa > IVb > IVC > IVd > IVe. This order is surprising, IVd was expected to be more electrophilic than IVb, since Br exerts a -I effect while the CH_3 group exerts a +I effect (negative σ parameter in the scale of Hammett). The substituted β-NCAs IIa and IIIa proved to be more nucleophilic than β-Ala-NCA, which was more nucleophilic than most α-amino acid NCAs. Obviously the electron density of the nitrogen is the most important factor for the reactivity of the β-NCAs. The higher nucleophilicity of the β-NCA IIIa to Ia was best seen when 4-chlorophenyl isocyanate was used as the reaction partner. In boiling dioxane, IIIa added quantitatively onto this isocyanate within 4 hr, while Ia remained unchanged. The addition of IIIa onto 4-chlorophenyl isocyanate was catalyzed by both triethylamine and diazabicyclooctane. Obviously the anion of IIIa was formed



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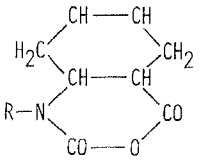
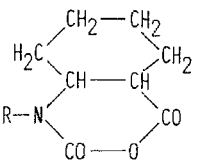


II



III

Ia: R = H–
Ib: R = $ClSO_2NHCO$–
Ic: R = $CH_3C_6H_4OSO_2NHCO$–

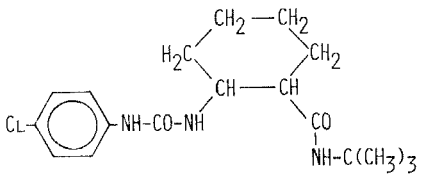
IIa: R = H–
IIb: R = $ClSO_2NHCO$–
IIc: R = $CH_3C_6H_4OSO_2NHCO$–
IId: R = $C_6H_5OSO_2NHCO$–

IIIa: R = H–
IIIb: R = $ClSO_2NHCO$–
IIIc: R = $CH_3C_6H_4OSO_2NHCO$–
IIId: R = $C_6H_5OSO_2NHCO$–
IIIe: R = $CH_3C_6H_4SO_2NHCO$–
IIIf: R = ClC_6H_4NHCO–

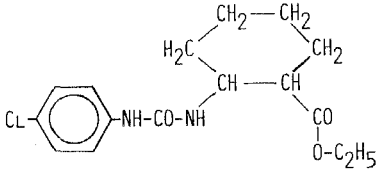
$X–SO_2–N=C=O$

IV

IVa: X = Cl
IVb: X = $CH_3C_6H_4O$–
IVc: X = C_6H_5O–
IVd: X = BrC_6H_4O–
IVe: X = $CH_3C_6H_4$–



V

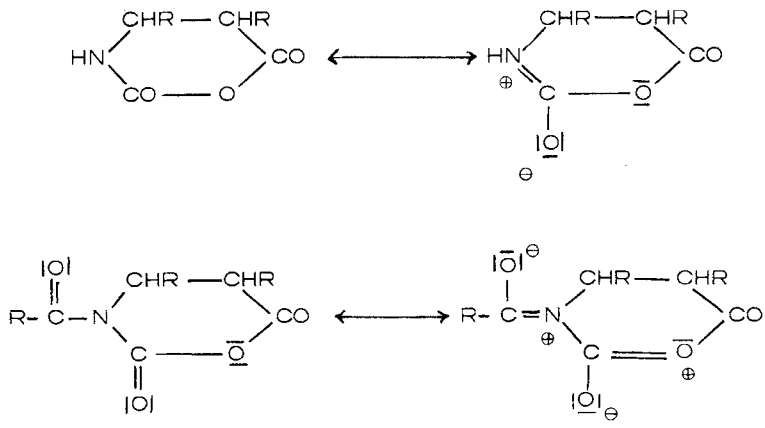


VI

as reactive intermediate. These observations support strongly the above mentioned conclusions concerning formation and reaction of β-NCA anions and β-isocyanatocarboxylates [Eqs. (1), (9), and (10) and Fig. 1].

The main difference in the properties of N-unsubstituted β-NCAs and their N-acyl derivatives is the lack of polymerizability of the

latter class of compounds. Thus, the storage of Ib, IIb-d, and IIIb-f presents no problems, because neither temperatures up to 50°C nor traces of moisture cause decomposition. However, upon heating above their melting points the N-carbamoyl β-NCAs decompose rapidly under evolution of carbon dioxide in analogy with the N-(2-nitrophenyl-)sulfenyl β-NCAs [15]. When heated in boiling dioxane in the presence of triethylamine, the N-carbamoyl β-NCAs were stable for several hours. With protic nucleophiles a stoichiometric reaction takes place which involves exclusively the carbonyl group at C_6. Thus, IIIf and tert-butylamine yielded the amide V, as described previously [9], and from IIIf and ethanol the ester VI was obtained. Unfortunately a direct kinetic comparison of the electrophilicity of the β-NCAs Ia, IIa, IIIa, and their N-carbamoyl derivatives is not possible, because the monomers Ia, IIa and IIIa undergo polymerization when reacted with protic nucleophiles [9]. Hence, only the IR spectra allow a comparison of the reactivity. It is in general accepted that, if compounds of similar structure are compared, the frequency of the C=O stretching vibration may be used as a measure for the reactivity of carbonyl groups. The data of Table 2 and Fig. 2 indicate the N-acyl residue has only a weak influence on the carbonyl groups of the β-NCA ring, so that the difference in reactivity between β-NCAs and N-carbamoyl β-NCAs is much smaller than between α-amino acid NCAs and their N-acyl derivatives [18]. This result is obvious with respect to the C_6 carbonyl group, since the N-acyl residue is several σ-bonds removed from this carbonyl group. However, the weak effect on the C_2 carbonyl group is surprising. A tentative explanation for the fact that the carbonyl group C_6 is apparently more influenced by the carbamoyl residue than the C_2 carbonyl is given by the mesomeric formula VII. With regard to the mechanism



VII

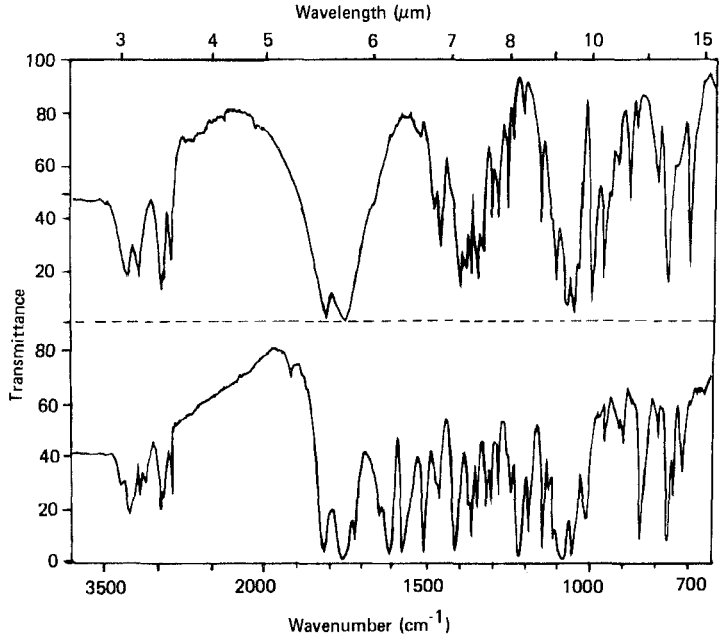


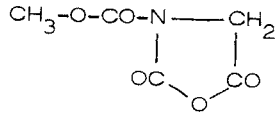
FIG. 2. IR spectra (in KBr) of (A) cis-2-aminocyclohexane-1-carboxylic acid NCA (IIIa); (B) N-(4-chlorocarbaniloyl-)-cis-2-aminocyclohexane-1-carbocyclic acid NCA (IIIf).

of the base-initiated polymerization of β-NCAs we reach the following conclusion. The N-acyl β-NCAs fulfill the conditions of the activated monomer mechanism that a nucleophilic attack must exclusively involve the C_6 carbonyl group. On the other hand, N-acyl β-NCAs are only slightly more electrophilic than the monomers themselves, so that a predominant polymerization of β-NCAs via the activated monomer mechanism is not favored.

The Role of Cocatalysts

The predominance of the activated monomer mechanism requires in addition to the formation of β-NCA anions [Eq. (1)] that the N-acyl chain-ends are substantially more reactive than the monomers, so that the propagation via these chain ends [Eq. (3)] is faster than the reaction of β-NCA anions with monomers [initiation reaction (2)] and faster than the reaction between carbamate groups and monomers [Eq. (5)]. This situation allows one to carry out a simple and decisive experimental test. N-acyl-β-NCAs added to a base-initiated

polymerization of β-NCAs should lead to an acceleration because the relatively slow initiation reaction (2) is replaced by a faster one, namely, by the reaction of β-NCA anions with the electrophilic cocatalyst [Eq. (12)]; in other words, N-acyl β-NCAs must behave as electrophilic cocatalysts of the base-initiated polymerization of β-NCAs. Table 4 summarizes the reaction conditions and results of experiments shaped to demonstrate the influence of the N-carbamoyl β-NCAs Ic and IIIc on the base-initiated polymerization of Ia and IIIa. The standard experiments 1, 5, and 9 (Table 4) were carried out without cocatalyst; while in the parallel experiments various amounts of N-carbamoyl β-NCAs were added. All experiments demonstrate that the N-acyl β-NCAs behave as inhibitors and not as cocatalysts. To test whether these results are limited to the N-carbamoyl β-NCA used for the experiment of Table 4, a second series of experiments was carried out with β-Ala-NCA as monomer (Table 5). In this case N-methoxycarbonyl glycine-NCA [18] and 4-chlorophenylisocyanate were used as electrophilic additives. Again an inhibitor effect was observed when the yields of $(\beta\text{-Ala})_n$ were compared with those obtained without electrophilic additives. Moreover, the addition of a nucleophilic cocatalyst (tert-butylamine) led to a remarkable acceleration. Both effects, the acceleration caused by tert-butylamine and the inhibition caused by the two electrophiles, increase with increasing concentration of these additives. Thus we must conclude that the base-initiated polymerization of β-NCAs proceeds mainly via nucleophilic chain ends, such as carbamate groups or amino groups which can result from the decarboxylation of protonated carbamate. The fact that highly electrophilic compounds behave as inhibitors, does not mean that a chain growth via N-acyl-β-NCA end groups [Eq. (3)] is impossible, It indicates only that the propagation via nucleophilic chain ends is usually much faster. Thus, we tried to find out whether a chain growth via N-acyl-β-NCA chain end is possible or not. For this purpose the three monomers Ia, IIa, and IIIa were polymerized in the presence of various amounts of N-methoxycarbonyl glycine NCA VIII, and the polymers were precipitated from dry diethyl ether after



VIII

a high conversion was reached. The endgroups of the isolated polymers were identified by IR and ^{1}H-NMR spectroscopy. The IR spectra show the bands characteristic of carbonyl of β-NCA groups at ca. 1820 and 1760 cm^{-1} (Fig. 3), in addition to the broad signal of the amide groups at ca. 1650 cm^{-1}. ^{1}H-NMR spectroscopy allows an

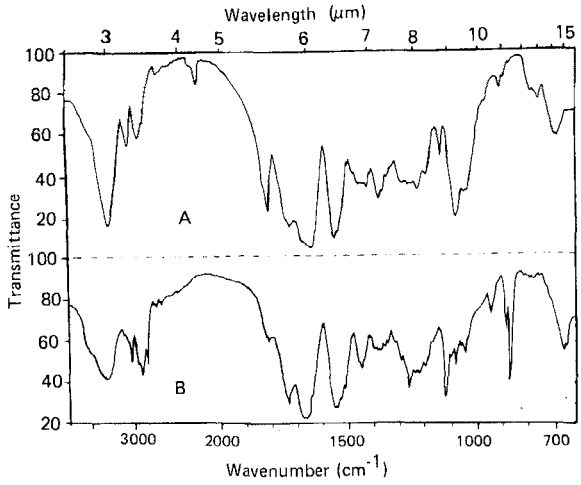


FIG. 3. IR spectra (in KBr) of (A) $(\beta\text{-Ala})_n$ obtained after 3 days from a triethylamine-initiated polymerization in dioxane at 20°C with N-methoxycarbonyl glycine NCA as cocatalyst (mole ratio NCA/cocat. 5:1), (No. 1, Table 6); (B) poly(cis-2-aminocyclohexene-1-carboxylic acid) obtained under the same reaction conditions (No. 5, Table 6).

identification of the methoxycarbonyl endgroup (δ = 3 ppm downfield of internal TMS in trifluoroacetic acid) and also a quantitative determination. It turned out that the concentration of this end-group agrees well with the NCA/cocatalyst ratio (Table 6). This finding let us conclude that the signals in question really result from endgroups and not precipitated, unreacted N-methoxycarbonyl glycine NCA. Additional evidence for this conclusion was obtained by treatment of the isolated poly-β-alanine with tert-butylamine in dimethylformamide. After reprecipitation from formic acid/diethyl ether the characteristic ^{1}H-NMR signal of tert-butylamide endgroups was found, while the IR bands of the N-acyl NCA endgroup were now absent (Nos. 2-4, Table 6). The lower concentration of tert-butylamide endgroups compared with N-methoxycarbonyl groups before the reprecipitation may be explained by fractionation resulting from reprecipitation. These observations clearly demonstrate that the relatively slow polymerization of β-NCAs in the presence of electrophilic additives proceeds via the activated monomer mechanism, so that oligomers and polymers with N-acyl β-NCA endgroups are formed.

Kinetic Investigation

The finding that the propagation of a base-initiated NCA polymerization can proceed via nucleophilic chain ends (5) and via electrophilic

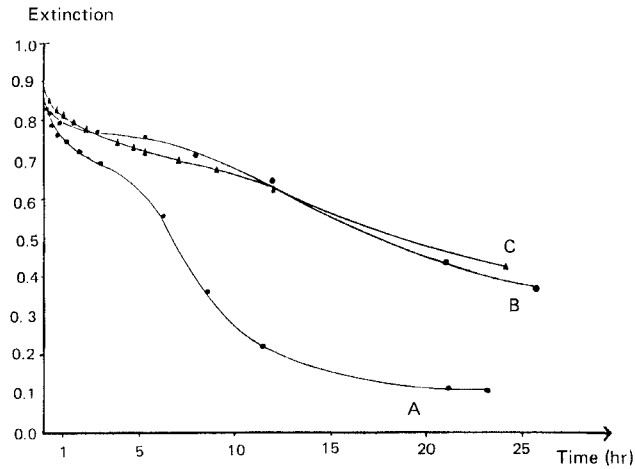


FIG. 4. Time (determined by IR spectroscopy) curves for the triethylamine-initiated polymerization of cis-2-aminocyclohexene-1-carboxylic acid NCA (IIa) in dioxane at 25°C (mole ratio NCA/triethylamine, 13:1): (A) without cocatalyst; (B) with N-methoxycarbonyl glycine NCA; (C) with 4-chlorophenyl isocyanate (NCA/cocatalyst 10:1).

ones (3) together with the fact that β-isocyanato carboxylate ions are present in the reaction mixture (Fig. 1) allowed us to conclude that the kinetic behavior of such a reaction mixture is rather complex. To obtain time-conversion curves the polymerization of cis-2-aminocyclohexene-1-carboxylic acid NCA (IIa) was investigated in dioxane at 25°C. This system was chosen because poly(cis-2-aminocyclohexene-1-carboxylic acid) is soluble in dioxane, so that the decrease of the monomer concentration can be followed by IR spectroscopy. For this purpose the intensities of the characteristic carbonyl bands of the monomer at 1810 and 1760 cm^{-1} were measured. The three curves, shown in Fig. 4, exhibit the expected inhibitor effect of N-methoxycarbonyl glycine NCA (curve B) and 4-chlorophenylisocyanate (curve C). However, the shapes of all three time/conversion curves are similar; four sections are distinguishable. The first one reflects an acceleration (first hour); the second section shows a slow-down of the polymerization, the third section represents again an acceleration, while the last section reflects the decrease of the polymerization rate caused by the consumption of monomer. Obviously such a time-conversion curve cannot be explained by a simple kinetic scheme based on one initiation reaction, one propagation reaction, and one termination step. Hence, we will present only a qualitative interpretation of the curves. The first short period of acceleration is caused by an increasing concentration of β-NCA anions and their reaction

products. The β-NCA anions are accompanied by the isomeric β-isocyanato carboxylic anions which in turn can react with the β-NCA anions according to Eq. (10). Hence, the concentration of carboxylic acid groups increases, so that the basicity of the medium decreases. Thus, the β-isocyanatocarboxylate ions behave, on the one hand, as inhibitors similar to other electrophilic additives; on the other hand, they behave as acids. The reduction of basicity prevents further formation of β-NCA anions and β-isocyanato carboxylate ions, so that finally no inhibitor is formed. This situation leads again to an acceleration of the propagation via nucleophilic endgroups until the most of the monomer is consumed. The second section of the time-conversion curves represents the situation with the highest concentration of electrophilic groups, e. g., N-carbamoyl-β-NCAgroups. During this period a slow propagation via the activated monomer mechanism is possible. It must be emphasized that the above scheme is only a tentative explanation of the kinetic behavior of monomer IIa; it is probably a simplification of the real situation.

Chain Growth by Condensation Reactions

At least in the case of β-Ala-NCA the mechanistic scheme of the base-initiated polymerization is further complicated by a third kind of propagation. When the polymerization of β-Ala-NCA was initiated by a high concentration of triethylamine (NCA/amine = 1:1-10:1), the ^{13}C-NMR spectra of the isolated reaction products displayed numerous signals in addition to the three characteristic signals of poly-β-alanine (Fig. 5B). These additional signals possess a relatively small line width which is characteristic of low molecular weight compounds or endgroups. The assignment of the signals was achieved by comparison with the model compounds IX-XII (see Table 7 and Fig. 5C). This assignment indicates that the main reaction products are oligomers and low molecular weight polymers with one carboxyl and one perhydrouracil endgroup XIII. The formation of these end products can be explained by condensation of the β-isocyanatopropionate ions [Eqs. (14) and (15)], followed by the cyclization of the β-isocyanato-acylamide groups [Eq. (16)].

Whether the polycondensation of the linear dimers is faster than the cyclization or whether the cyclic dimer is formed before chain growth can continue is a question we cannot answer. However, we can present additional experimental evidence for the individual steps of this reaction scheme. In a previous paper we described the synthesis of free β-isocyanatocarboxylic acids by cautious hydrolysis of their trimethylsilylesters [19]. The spontaneous polyaddition of these acids yields linear poly-N-carboxy anhydrides, which decarboxylate rapidly in the presence of tertiary amines to form polyamides. Furthermore we have described [20] the cyclization of β-isocyanato-acyl amides for the preparation of perhydrouracils starting with

TABLE 7. ^{13}C-NMR Chemical Shifts (Downfield from External TMS) of $(\beta\text{-Ala})_n$, Its Endgroups, and Model Compounds in TFA

Compound	Chemical shift (ppm)			
	CO	α-C	β-C	Further carbons
$(\beta\text{-Ala})_n$	177.3 ± 0.1	33.1 ± 0.1	37.1 ± 0.1	
Endgroup signals	178.69 157.38 174.59	32.48 30.21	37.50 34.49	48.18 (triethylamine) 7.93
NN'-carbonylbis-β-alanine (IX)	179.61 160.89	33.34	37.23	
Z-β-alanyl-β-alanine (X)	178.64 177.56 160.89	35.72 32.21	37.07 37.07	134.88; 129.11; 128.89; 128.30; 69.82
1-(2-Ethoxycarbonyl) ethylene-5,6-dihydro-uracil (XI)	176.44 174.56 157.29	30.21 33.23	34.90 37.22	63.60; 12.46
1-Phenyl-5,6-dihydro-uracil (XII)	174.50 158.05	30.48	35.17	133.18; 130.38; 130.11; 128.65

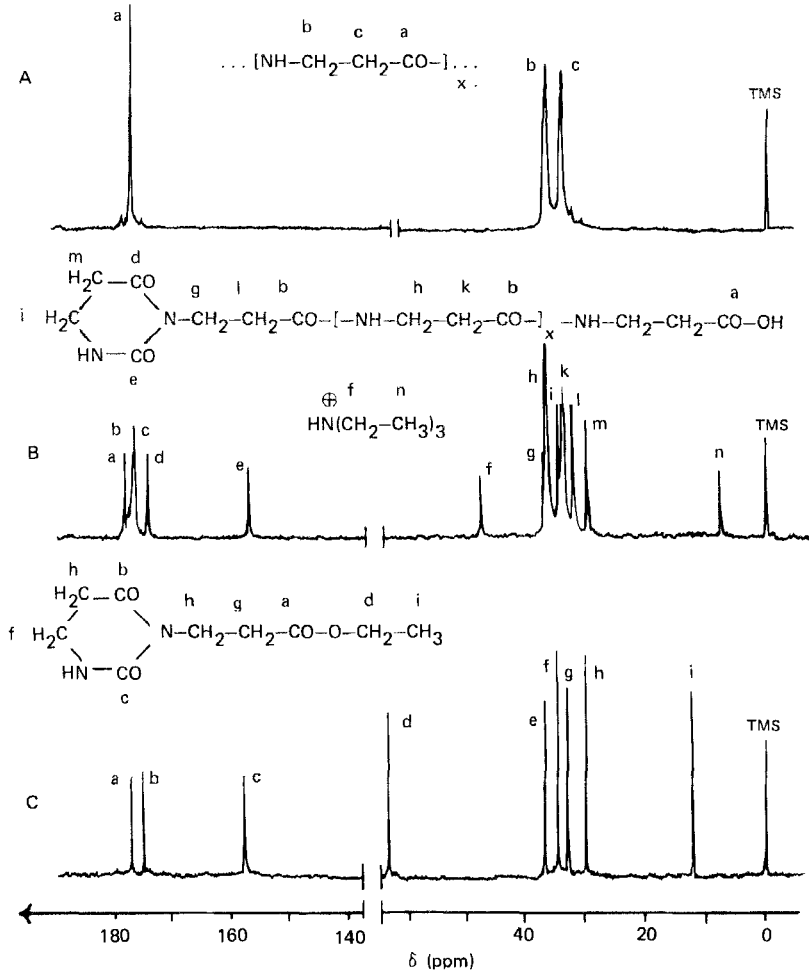
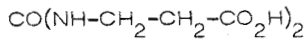
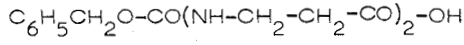


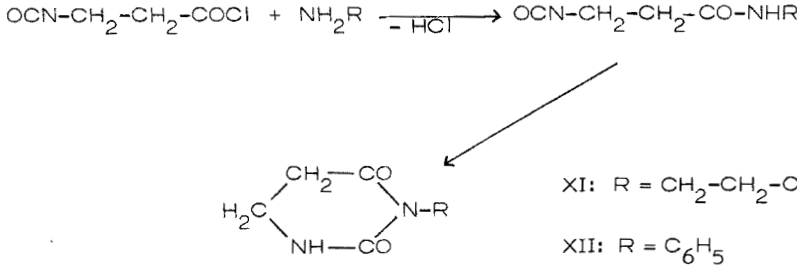
FIG. 5. ^{13}C-NMR spectra (22.63 MHz) measured in trifluoroacetic acid: (A) $(\beta\text{-Ala})_n$ obtained from β-Ala-NCA in pure pyridine (mole ratio 1:20) at 20°C; (B) $(\beta\text{-Ala})_n$ obtained from β-Ala NCA/triethylamine (mole ratio 1:1) in dioxane at 20°C; (C) 1-(2-ethoxycarbonyl ethylene-) 5,6-dihydrouracil.



IX

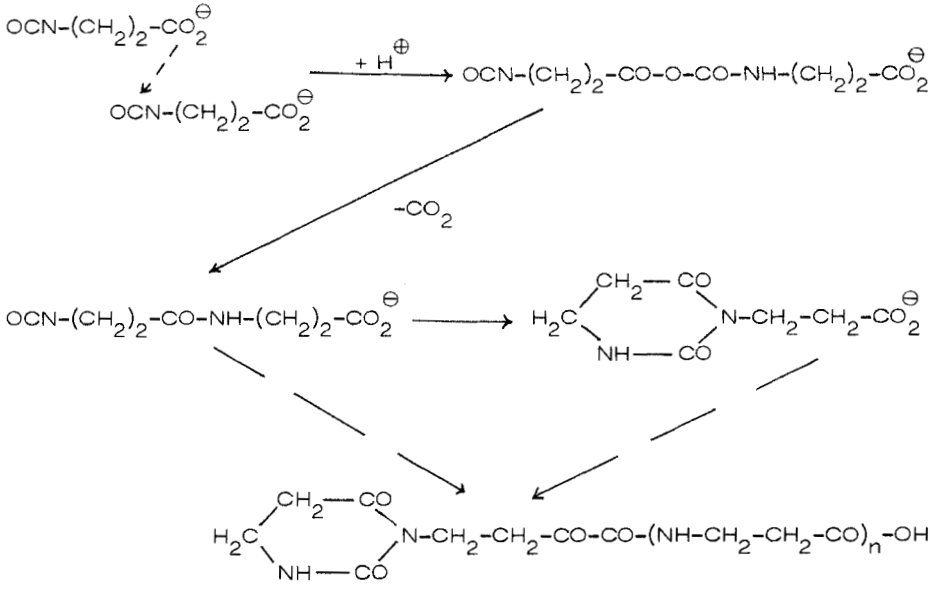


X



XI: R = $CH_2-CH_2-CO-OC_2H_5$

XII: R = C_6H_5



XIII

primary amines and β-isocyanatocarboxylic acid chlorides [Eqs. (12) and (13)]. This reaction is also catalyzed by tertiary amines and allowed us to synthesize the model compounds XI and XII. Finally we have observed that the intensity of the endgroup signals (Fig. 5B) increases with increasing concentration of the triethylamine used as initiator for the polymerization of β-Ala-NCA. Moreover, a weak base such as pyridine did not produce these endgroups (Fig. 5A). Since the concentration of β-isocyanatocarboxylate ions increases with increasing basicity of the reaction medium it is obvious that the additional ^{13}C-NMR signals in Fig. 5B stem from reaction products of the β-isocyanatocarboxylate ions. In this connection it is worth noting that the $(\beta\text{-Ala})_n$ obtained by the potassium ethanolate-initiated polymerization (No. 9, Table 4) did not exhibit any endgroup signal in its ^{13}C-NMR spectrum. The ^{13}C-NMR spectrum was identical with that of Fig. 5A, even though ethanolate ions are much more strongly basic than triethylamine. We see three reasons which can account for this alleged contradiction. First, the concentration of ethanolate was rather low. Secondly, the β-isocyanato carboxylate ions reacted with the ethanol, and the resulting N-ethoxycarbonyl-β-alanine neutralized a part of the ethanolate so that a further formation of β-isocyanatocarboxylate ions was never possible.

Finally we must explain why condensation products of β-isocyanato carboxylate ions are observed only in the case of β-alanine-NCA. The two main reasons have already been discussed. Substituted β-NCAs and their anions are more nucleophilic, so that the addition onto the isocyanate group [Eq. (10)] is faster. Furthermore, the concentration of β-NCA anions is increased at the expense of β-isocyanato carboxylate ions, because substituents favor the ring closure. In other words, the equilibrium (9) is shifted to the left more than in the case of β-Ala NCA. Figure 1A demonstrates that β-isocyanatocarboxylates and their reaction products are still observable after 40 min (even after 2 hr), while they have completely disappeared in the case of the substituted NCAs IIa and IIIa after 5 min. Thus, not only the reaction conditions but also the structure of the β-NCAs may have an influence of the polymerization mechanism. However, all polymerizations described in this work agree in that high molecular weights were not obtained. A comparison of the viscosity measurements with those reported in the preceding paper indicate that degrees of polymerization in excess of 100 were never achieved.

CONCLUSION

The silylation and sulfenylation of β-NCAs, the addition of β-NCAs onto isocyanates, and the IR spectroscopic study of deprotonation clearly demonstrate that trialkylamines, like primary and secondary amines, can deprotonate β-NCAs. The β-NCA anions and the isomeric β-isocyanatocarboxylate ions are compounds of an equilibrium [Eq. (9)]

strongly favoring the latter species. The β-NCA anions are mostly responsible for the initiation reaction (2), because they are the strongest nucleophiles in this system. This interpretation does not exclude the fact that nucleophilic impurities or additions contribute to the initiation reaction. The β-isocyanatocarboxylate ions are mainly responsible for the termination steps as discussed previously for the primary and secondary amine-initiated polymerization of β-NCAs. It is this role of the β-isocyanato carboxylate ions which presents the formation of high molecular weight poly-β-amino acids for β-NCAs not matter if nucleophiles or aprotic bases are used as initiators. However, it must be emphasized that weak bases such as 4-chloroaniline in the case of primary amines or pyridine in the case of tertiary amines cause less side reaction than strong bases, so that substantially higher molecular weights are accessible with weakly basic initiators. A comparison of Figs. 5A and 5B as well as the viscosity measurements reported in previous papers [9, 11] substantiate this hypothesis.

The experiments summarized in Tables 4-6 and Figs. 4 and 5 let us, furthermore, conclude that the base-initiated polymerization of β-NCAs involves three different mechanisms of propagation. The fastest and most important propagation results from the reaction of a nucleophilic chain end with the C_6 carbonyl group of a β-NCA. The active chain end may be a carbamate group or, after decarboxylation, an amino group. Nonpolar solvents, high temperatures, and high concentrations of acidic protons favor the formation of amino groups at the expense of carbamate groups. The chain growth via the activated monomer mechanism is slow, because the N-acyl-β-NCA chain ends are hardly more reactive than the monomers and because the concentration of β-NCA anions is low. Hence, a substantial contribution of this kind of propagation is only expected in the first stages of a base-initiated polymerization and only in the presence of an electrophilic cocatalyst. The third propagation mechanism, namely the condensation of β-isocyanatocarboxylate ions, is limited to the polymerization of β-Ala-NCA and requires a high concentration of strong base.

A comparison of the base-initiated polymerization of α- and β-amino acid NCAs reveals several analogies but also characteristic differences. Silylation, sulfonylation, and acylation of α-NCAs [15, 18, 21] demonstrate that these five-membered heterocycles are also deprotonated by strong bases. Furthermore, we see growing evidence for that also the base-initiated polymerization of α-NCA must be described by two or more propagation mechanisms [18, 22-27]. However, the activated monomer mechanism has a greater importance for α-NCAs, because it is the fastest reaction in this case. The relatively high electrophilicity of N-acyl α-NCAs and higher concentrations of α-NCA anions are responsible for this result. In the case of α-NCAs the equilibrium between NCA anions and isocyanatocarboxylate ions is shifted to the left far more than in the case of β-NCAs, because the formation of five-membered heterocycles is kinetically

and thermodynamically more favored than that of six-membered rings [11, 21]. (It must be kept in mind that the stability of heterocycles does not parallel that of cycloalkanes.)

The low concentration of α-isocyanatocarboxylate ions has two important consequences. First, polycondensation of this species does not occur, and, secondly, termination steps are less frequent, so that higher molecular weights are accessible by polymerization of α-NCAs. Yet, it must be emphasized that a low concentration of α-isocyanatocarboxylate ions is not the only reason that α-NCAs yield higher degrees of polymerization. The comparison of α- and β-amino acid NCAs is, in our opinion, useful for a better understanding of the properties of both classes of monomers.

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