Makromol. Chem. **180**, *1419–1433 (1979)*

Mechanism of the NCA Polymerization 7[a]

The Primary and Secondary Amine-Initiated Polymerization of β-Amino Acid NCAs[b]

*Hans R. Kricheldorf** and *Rolf Mülhaupt*

Institut für makromolekulare Chemie der Universität,
Stefan-Meier-Straße 31, D-7800 Freiburg

(Date of receipt: September 29, 1978)

SUMMARY:

The reaction of β-alanine *N*-carboxyanhydride (β-Ala NCA) **(1)** with various primary and secondary amines was investigated at room temperature. Three reaction products were found: poly(β-alanine), β-alaninamides, and *N'*-substituted β-ureidopropionic acids. The mole ratio of these reaction products depends on the reaction conditions, above all on the NCA/amine ratio, and on the nucleophilicity/basicity ratio of the amines. All amines with pK_a-values > 8,0, including the amino end-groups of the growing chains, cause the formation of β-isocyanatocarboxylate ions by deprotonation of the β-NCAs, and thus, the formation of β-ureidocarboxylic acids. If the chain ends are involved, this reaction sequence is a termination step, and it is this termination step which is responsible, for that high polymerization degrees (> 60) are not accessible by a primary or secondary amine-initiated polymerization of β-NCAs. The β-ureidocarboxylic acid end-groups are detectable in the ^{13}C NMR spectra of the poly(β-amide)s.

Introduction

α-Amino acid *N*-carboxyanhydrides (α-NCAs) are known to be useful monomers for the synthesis of polypeptides; however, their polymerization mechanisms are not yet unambiguously established, and the structure-reactivity relationships are not completely known. Best elucidated is the reaction of α-NCAs with primary and secondary amines. This reaction leads to polypeptides, when high NCA/amine ratios and nucleophilic amines are used. The polymerization occurs via the nucleophilic attack of the amino chain end onto the carbonyl group C-5 of a monomer and has a kinetic similar to that of the "living" anionic polymerization of vinyl monomers[1,2]. Experiments with NCA/amine mole ratios < 1 yield amino acid amides and (or) α-ureidocarboxylic acids (hydantoic acids) as reaction products, depending on the concentration of the amine and of its nucleophilicity/basicity-ratio[3–5].

In the case of β-amino acid NCAs (β-NCAs) three synthetic methods are known[6–8] and numerous polymerization experiments are described[7–10], yet detailed studies on the polymerization mechanisms are still lacking. A detailed investigation of the reaction mechanisms of β-NCAs should clarify, if high molecular weight poly(β-amino acid)s are accessible. This point is of interest, because high polymerization degrees (> 70) are hitherto not reported for poly(β-amide)s derived from β-NCAs. Furthermore, a better understanding of the reactions of β-NCAs should also shed more light on the properties of α-NCAs.

---

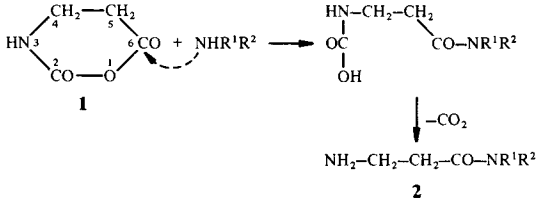
[a] Part 6, cf. H. R. Kricheldorf, J. Polym. Sci. Polym. Chem. Ed. **17**, 97 (1979)

[b] *N*-Carboxyanhydrides (perhydro-1,3-oxazine-2,6-diones).

Results and Discussion

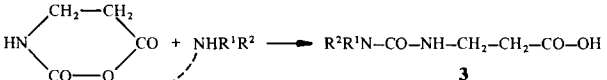
Stoichiometric reactions of β-alanine NCA

The conversion of primary or secondary amines with β-NCAs, e. g. β-alanine NCA (perhydro-1,3-oxazine-2,6-dione) (**1**), can in principle follow two reaction pathways. The amine can behave as a nucleophile and attack the carbonyl group in position 6 (Eq. (i)); less probable, but not "a priori" excluded is the attack at the less reactive carbonyl group in position 2 (Eq. (ii)). On the other hand, the amine can behave predominantly as a base and produce NCA anions (Eq. (iii)), which in turn rearrange to the isomeric β-isocyanatocarboxylate ions (Eq. (iv)). The addition of the amine group to the isocyanate group finally leads to *N'*-substituted β-ureidocarboxylic acids (e. g. **3**), which are also the end products of the nucleophilic attack (Eq. (ii)). In the case of excess NCA the amino acid amide (e. g. **2**) can also react with the NCA according to Eq. (i), so that finally a poly(β-



(i)

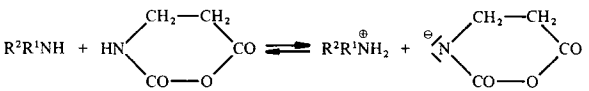
1 **2**



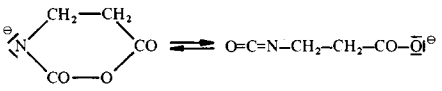
(ii)

3

	2a,3a	**b**	**c**	**d**	**e**	**f**	**g**
R^1	C_6H_5	$-CH_2CH_2$ (O)	$CH_2C_6H_5$	$(CH_2)_3CH_3$	$C(CH_3)_3$	C_2H_5	$CH(CH_3)_2$
R^2	H	$-CH_2CH_2$ (O)	H	H	H	C_2H_5	$CH(CH_3)_2$



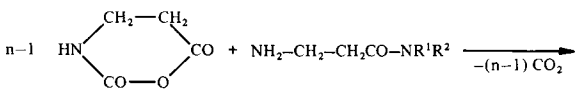
(iii)



(iv)

(v)

3



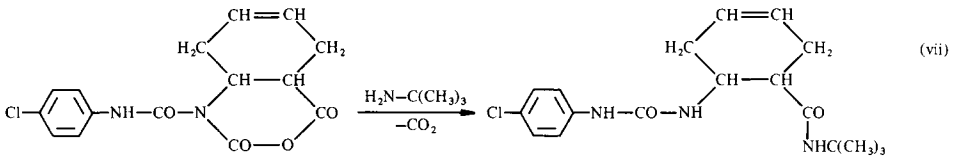
(vi)

4

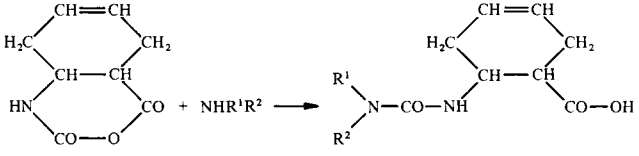
amide) (e.g. poly(β-alanine) **(4)**), is formed (Eq. (vi)). Thus, depending on the properties of the reactants and on the reaction conditions three kinds of reaction products can originate from the conversion of protic amines and β-NCAs: poly(β-amide)s **(4)**, β-ureidocarboxylic acids **(3)**, and β-amino acid amides **(2)**.

Since the polymerization of NCAs is often carried out at 20–25 °C, we studied the conversion of β-alanine NCA with various amines in the temperature range of 15–25 °C (s. Tab. 1). The structure of the amines was varied in such a way that the nucleophilicity/basicity ratio covered a as wide as possible range. If the bulkiness of the substituents of the amines is comparable, then the nucleophilicity parallels the basicity, if, however, the substituents become more bulky, while the basicity remains constant, then the nucleophilicity decreases strongly; hence, the nucleophilicity increases in the following series: A: aniline < benzylamine < butylamine; B: diisopropylamine < diethylamine < *tert*-butylamine < butylamine.

The results of Tab. 1 show that mainly the basicity of the amines is responsible for the composition of the reaction products. Increasing basicity and increasing concentration of the amines favor strongly the formation of *N'*-substituted β-ureidopropionic acids. This observation allows the conclusion that mainly the deprotonation of β-Ala NCA and the rearrangement of the NCA anion (Eq. (iv)) are responsible for the formation of the β-ureidopropionic acids **3a–g**, and not nucleophilic attack according to Eq. (ii). Additional evidence for the absence of that reaction was obtained from the conversion of the *N*-(*p*-chlorophenylcarbamoyl) NCA of 6-amino-3-cyclohexenecarboxylic acid **(5)***) with *tert*-butylamine. The electron-withdrawing substituent at the nitrogen prevents the formation of NCA-anions but favors the nucleophilic attack of an amine at the carbonyl group in position 2 (Eq. (ii)). Nevertheless, the only reaction product was *N*-*tert*-butyl-6-[*N'*-(4-chlorophenyl)ureido]-3-cyclohexenecarboxamide **(6)** (yield 94%). Thus, it is obvious



(vii)



(viii)

	8a	b	c
R^1	$-CH_2CH_2$	C_2H_5	$CH(CH_3)_2$
R^2	$-CH_2CH_2$ (O)	C_2H_5	$CH(CH_3)_2$

*) Systematic name: 1-(4-chlorophenylcarbamoyl)-1,2,4a,5,8,8a-tetrahydro-2,4-dioxo-4*H*-benzo[*d*]1,3-oxazine. The synthesis of *N*-acyl-β-NCAs is described elsewhere.

Tab. 1. Results of the reaction of β-alanine *N*-carboxyanhydride with various primary and secondary amines

Amine (pK_a)[b]	Yield of reaction products (PA, UA, AA)[a] in %, when starting with a mole ratio NCA/amine														
	20:1			5:1			1:1			1:2			1:20		
	PA	UA	AA	PA	UA	AA	PA	UA	AA	PA	UA	AA	PA	UA	AA
Aniline (4,60)	—	—	—	—	—	—	56	< 5	—[c]	56	< 5	—[c]	—	—	—
Morpholine (8,33)	—	—	—	—	—	—	—	—	—	0	53	4	—	—	—
Benzylamine (9,33)	—	—	—	—	—	—	0	22	28	0	26	19	—	—	—
Butylamine (10,66)	—	—	—	11	5(27)[d]	—[c]	0	35	15	0	46	14	—	—	—
tert-Butylamine (10,68)	68	4(85)[d]	—[c]	25	6(32)[d]	—[c]	0	49	0	0	92	< 2	0	92	< 2
Diethylamine (10,98)	73	4(92)[d]	—[c]	54	9(45)[d]	—[c]	0	60	9	0	56	4	0	55	13
Diisopropylamine (11,13)	76	5(95)[d]	—[c]	—	—	—	—	—	—	0	91	5	—	—	—

[a] PA = poly(β-alanine); AA = β-alanin amide; UA = β-ureido acid.
[b] Determined at 25 °C in water.
[c] Not determined.
[d] Yield in brackets are relative to amines, all other yields are relative to the NCA.

that the β-ureidopropionic acids **3a–g**, isolated from the experiments mentioned in Tab. 1, are formed exclusively via the reaction sequence of Eqs. (iii)–(v). Further experiments were carried out with the D,L-*cis*-6-amino-3-cyclohexenecarboxylic acid NCA*) **(7)**. Its conversion with morpholine, diethylamine, or diisopropylamine (mole ratios 1 : 1) led to the isolation of the β-ureidocarboxylic acids **8a** (yield 20%), **8b** (yield 66%), and **8c** (yield 83%). Thus, these experiments confirm that the results obtained with β-alanine NCA (Tab. 1) are not exceptions, but representative for most β-NCAs.

The raction of β-alanine NCA with aniline presented the difficulty that *N'*-phenyl β-ureidopropionic acid **(3a)** did not crystallize, probably because of an uncomplete separation from aniline and β-alaninanilide. In this case an unambiguous identification was obtained by spectroscopic comparison (IR and ^{1}H NMR) of the crude reaction product with a pure ureido acid prepared from phenyl isocyanate and silylated β-alanine hydrochloride **9**.

Furthermore, we were not able to isolate the β-alaninamides **2a–g** in a crystalline form. The crystallization of the corresponding hydrochlorides and picrates failed likewise. In order to proof that in addition to the β-ureidopropionic acids β-alaninamides were really formed, in the case of the experiments with benzylamine the following identification was carried out. Starting with Boc-β-alanine and pentachlorophenol the activated ester **10** was prepared by means of dicyclohexylcarbodiimide, and then reacted with benzylamine. The resulting benzylamide **11** was dissolved in trifluoroacetic acid, whereby the Boc group was split off. The resulting trifluoroacetate solution was compared with the solution of the crude β-alanine benzylamide (from Tab. 1) in trifluoroacetic acid by means of ^{1}H- and ^{13}C NMR spectra.

$$\overset{\oplus}{N}H_3—CH_2—CH_2—\overset{\ominus}{C}O_2^{\ominus} \xrightarrow{ClSi(CH_3)_3} \overset{\ominus}{Cl}[\overset{\oplus}{N}H_3—CH_2—CH_2—CO—OSi(CH_3)_3] \quad \text{(ix)}$$

9

$$\mathbf{9} + C_6H_5—N=C=O \xrightarrow[-R_3N\cdot HCl/-(CH_3)_3Si—OH]{1.\ R_3N/2.\ H_2O} \mathbf{3a} \quad \text{(x)}$$

$$Boc—NH—CH_2—CH_2—CO—OC_6Cl_5 \xrightarrow[-C_6Cl_5—OH]{NH_2CH_2C_6H_5}$$

10

$$Boc—NH—CH_2—CH_2—CONHCH_2C_6H_5 \quad \text{(xi)}$$

11

Polymerization of β-amino acid NCAs

When the polymerization of α-amino acid NCAs is initiated by primary amines, the reaction mechanism is analogous to that formulated for β-alanine NCA (Eqs. (i), (vi)). From the viewpoint of kinetics two extreme cases can be distinguished.

I) The initiator is more nucleophilic than the amino end group of the growing peptide chain. In this case rate of the start reaction (V_{St}) is higher than that of the propagation (V_{Pr}), and the polymerization degree (DP) depends on the monomer/initiator ratio in analogy with the "living", anionic polymerization of vinyl monomers: $k_{St} > k_{Pr}$; since the concentration of active chain ends equals that of the initiator:

$$V_{St} = k_{St}\,[\text{Amine}] \cdot [\text{NCA}] > V_{Pr} = k_{Pr}\,[\text{Amine}] \cdot [\text{NCA}]$$

$$\text{DP} = \frac{[\text{NCA}]}{[\text{Amine}]} \cdot \frac{\%\ \text{Conversion}}{100}$$

*) Systematic name: 1,2,4a,5,8,8a-Tetrahydro-2,4-dioxo-4*H*-benzo[*d*]1,3-oxazine.

This course of the polymerization is characteristic for an initiation with primary alkylamines, including *tert*-butylamine[11], since the amino end-groups of peptides are less nucleophilic (pK_a = 9,2–9,6) because of the electron withdrawing carbonyl group in α-position. Secondary amines with easily accessible nitrogen, e.g. morpholine or dimethylamine, behave similarly to primary alkylamines[5].

II) In the case of aromatic amines which are less nucleophilic than the amino groups of peptides, the start reaction is slower than the propagation, and, hence, the polymerization degree can be initially higher than the monomer/initiator ratio:

$$k_{St} < k_{Pr}: \quad DP > \frac{[NCA]}{[Amine]} \cdot \frac{\% \text{ Conversion}}{100}$$

The primary and secondary amine-initiated polymerization of β-amino acid NCAs should in principle proceed similarly to that of α-amino acid NCAs, however, the results of Tab. 1 let expect, that characteristic differences are detectable. Not only secondary amines, but also basic primary ones, such as *tert*-butylamine, cause the formation of β-ureidocarboxylic acids, even if NCA/amine mole ratios ≫ 1 are applied. Hence, polymerizations with characteristics analogous to case I of the α-NCA polymerization cannot exist in the case of the β-NCAs. This is demonstrated by the *tert*-butylamine initiated polymerizations of β-Ala NCA (Tab. 2) and D,L-*cis*-6-am-

Tab. 2. Conditions and results of the polymerization of β-alanine *N*-carboxyanhydride initiated by 4-chloroaniline and *tert*-butylamine in 1,4-dioxane at 20 °C

No.	Initiator	NCA[a] / Init.	Time in d	Yield in %	$\frac{\eta_{sp}}{c}$ / (cm³ g⁻¹)	DP_{NMR}[b]	DP_{Cl}[c]
1	4-Chloro-aniline	5/1	6	77	28,0	26–29	25–30
2		10/1		88	31,0	35–38	32–37
3		20/1		93	32,5	43–47	40–47
4		40/1		97	41,0	46–51	45–55
5		60/1		96	38,5	57–61	—
6		80/1		98	39,0	60–66	—
7		100/1		96	39,0	100–125	—
8	*tert*-Butyl-amine	10/1	17	96	21,0	25–28	—
9		20/1		96	24,5	43–46	—
10		40/1		95	27,5	79–84	—
11		60/1		95	28,0	110–115	—
12		80/1		95	28,0	145–160	—

[a] Mole ratios monomer (M)/initiator (I).
[b] Determined by 90 MHz ^{1}H NMR spectra in trifluoroacetic acid.
[c] Determined by elemental analysis.

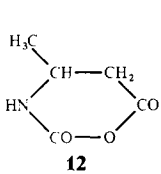
ino-3-cyclohexene-1-carboxylic acid NCA **5** (Tab. 3). In both series of experiments the alleged DP, calculated from the (^{1}H NMR) signal intensity of the *tert*-butylamide end-group, is higher than the monomer/initiator ratio, no matter how high this was chosen. Furthermore, the reaction products precipitated from diethyl ether, show two different kinds of *tert*-butyl groups in the 90 MHz ^{1}H NMR spectra. One signal represents the true *tert*-butylamide end-group, whereas the other one stems from the β-ureidopropionic acid **3e**. Reprecipitation from formic acid/tetrahydrofuran led to the removal of **3e**.

Tab. 3. Conditions and results of *tert*-butylamine initiated polymerization of *cis*-6-amino-3-cyclohexene-1-carboxylic acid *N*-carboxyanhydride **(5)**

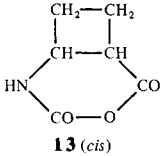
No.	Solvent	NCA[a] / Init.	Time in d	Temp. in °C	Yield in %	$\frac{\eta_{sp}}{c}$ / (cm³ g⁻¹)	DP_{NMR}[b]
1	1,4-Dio-	10/1	2	100	67,0	11,1	22–25
2		20/1			80,5	11,7	38–42
3		30/1			89,0	11,3	62–66
4		40/1			88,0	11,8	100–106
5	xane	60/1			99	11,7	140–150
6		90/1			82	11,8	185–200
7		120/1			95	11,8	230–250
8	Dimethyl-	30/1	17	20		20,3	65–70
9		60/1				21,5	130–140
10	formamide	90/1				21,6	170–190
11		120/1			95	22,2	350–400

[a] Mole ratios.
[b] Determined by 90 MHz ^{1}H NMR spectra in trifluoroacetic acid.

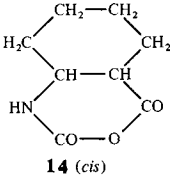
The formation of β-ureidocarboxylic acids by the initiator can only be avoided, if amines with pK_a-values < 9 are used as initiators. Then the polymerization of the β-NCAs corresponds to case II of the α-NCA polymerization. This is demonstrated by the 4-chloroaniline initiated polymerization of β-alanine NCA in Tab. 2 and by the 4-bromoaniline initiated polymerization of the β-NCAs **5** and **12–15** described previously[8]. The experiments No. 1–7 of Tab. 2 show that the alleged DP is $> \frac{[M]}{[I]}$ for NCA/amine ratios < 40, but approximately equal to $\frac{[M]}{[I]}$ for NCA/amine ratios ≥ 60. The viscosity measurements demonstrate, on the other hand, that the NCA/amine ratios > 50 do not lead to higher polymerization degrees. Only in experiments Nos. 1–4 of Tab. 2 the ^{1}H NMR spectroscopic end-group determination seems to provide true DP values. In all other experiments of Tabs. 2 and 3 the so called DP values give the concentration of the amide end-groups but not the true polymerization degrees. Thus, the viscosity measurements indicate,



12



13 (*cis*)



14 (*cis*)
15 (*trans*)

$$(CH_3)_3SiO{-}CO{-}CH_2{-}CH_2{-}NCO + NH_2{-}CH_2{-}CH_2{-}CO{-}OSi(CH_3)_3 \xrightarrow[(-2\,(CH_3)_3SiOH)]{(+2\,H_2O)}$$

16

$$HO{-}CO{-}CH_2{-}CH_2{-}NH{-}CO{-}NH{-}CH_2{-}CH_2{-}CO{-}OH \qquad \text{(xii)}$$

17

that a termination step occurs which is independent on the $\frac{[M]}{[I]}$ ratio, but dependent on the solvent and on the temperature.

On the basis of the results of Tab. 1 it was expected that this termination step involves the formation of a β-isocyanatocarboxylate ion and its reaction with the amino end-group of the growing chain. Since the pK_a-value of β-alanine is known to be 10,3 [12], the amino end-group of poly(β-alanine) is clearly basic enough to start the reaction sequence (Eqs. (iii)–(v)). The ^{13}C NMR spectra of isolated poly(β-alanine) from the experiments Nos. 1–7 of Tab. 2 exhibit indeed those signals expected for a β-ureidopropionic acid end-group (Fig. 1). The identification of these end-group

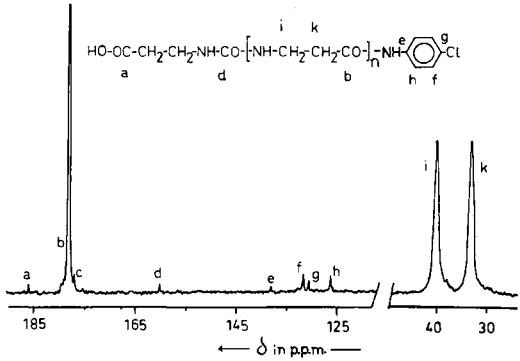


Fig. 1. 22,63 MHz ^{13}C NMR spectrum of poly(β-alanine) from experiment No. 4, Tab. 2, in H_2SO_4 (98 weight-%)

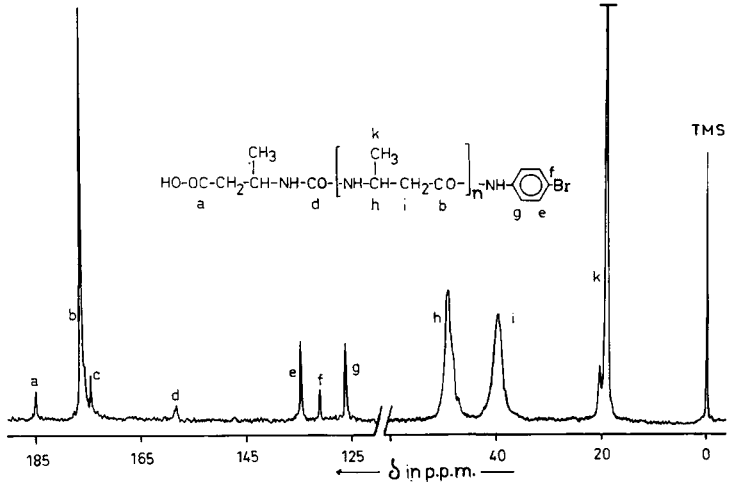


Fig. 2. 22,63 MHz ^{13}C NMR spectrum of poly(D,L-3-aminobutyric acid) in H_2SO_4 (98 weight-%). The polymerization of D,L-3-aminobutyric acid NCA was carried out in 1,4-dioxane at 70 °C with 4-bromoaniline as initiator ([M]/[I] = 10) [8]

signals is based, on the comparison with the ^{13}C NMR spectrum of 3,3'-ureylene dipropionic aid **(17)**, which was synthesized from silylated β-alanine and trimethylsilyl 3-isocyanatopropionate **(16)** (chemical shifts s. Exptl. Part). In addition to the polymerizations summarized in Tab. 2, three experiments with water as initiator were carried out in 1,4-dioxane at 20, 60, and 100 °C. The ^{13}C NMR spectra of the resulting poly(β-alanine)s exhibited also the end-group signals a, c*), d shown in Fig. 1 for a product initiated with 4-chloroaniline. The intensity of the end-group signals increased with increasing reaction temperature. Thus, it is clear that these end-group signals do not belong to side products formed by the basic initiators used for the experiments in Tabs. 2 and 3. Furthermore, these results demonstrate that the termination step caused by the 3-isocyanatocarboxylate ion is more frequent at higher temperature, because the equilibrium (Eq. (iii)) is shifted to the right with increasing temperature. The characteristic NMR signals of β-ureidopropionic acid end-groups were also found in the ^{13}C NMR spectra of poly(β-amide)s obtained from the β-NCAs **12–15**. As previously described[8] these β-NCAs were polymerized with 4-bromoaniline as initiator in 1,4-dioxane at 70 °C. According to the relatively high reaction temperature the end-group signals were rather intensive (s. Fig. 2). These observations indicate, together with the results of Tab. 3, that the behavior of β-alanine NCA with respect to termination steps is characteristic for most *N*-unsubstituted β-NCAs.

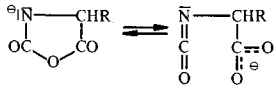
Conclusions

The above discussed results show that a polymerization of β-NCAs initiated by nucleophilic or basic catalysts cannot lead to high polymerization degrees (< 60), at least, if carried out at temperatures ≥ 20 °C. In contrast to the hypothesis of Komoto, Kawai et al.[10] chemical side reactions and not physical effects of the secondary structure of the poly(β-amide)s are responsible for the termination steps. These termination steps are clearly a consequence of structure and reactivity of the β-NCAs themselves and not a result of impurities or unsuitable initiators.

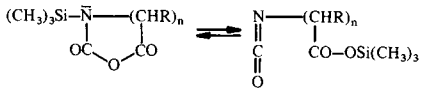
On the other hand, α-amino acid NCAs are known to yield easily polypeptides with DP > 100, when a primary amine initiated polymerization is carried out with pure reagents and with [M]/[I] ratios > 100. Moreover, we could not detect urea signals in the ^{13}C NMR spectra of polyglycine, polyalanine, and polyvaline prepared with benzylamine as initiator in 1,4-dioxane at 20 °C. Thus, the question arises, which property of the α-NCAs or of the polypeptides is responsible for their different behavior with respect to termination steps. Amino groups of α-amino acids are known to have a lower basicity ($pK_a = 9{,}0$–$9{,}9$) than those of β-amino acids ($pK_a = 10{,}3$–$10{,}5$). On the one hand, the active chain ends of polypeptides are, thus, less basic, but, on the other hand, the α-NCAs are more N—H acidic. Hence, the deprotonation of an α-NCA by an amino end-group of a peptide is just as probable as the deprotonation of a β-NCA by the amino group of a poly(β-amide). The different behavior of α-and β-NCAs with respect to termination steps must, therefore, be a consequence of the equilibria (Eqs. (iii) and (xiii)). It is clear that the gain of entropy resulting from ring opening is greater for a six-membered NCA than for a similarly substituted five-membered NCA. The question is, how different are the equilibria (Eqs. (iii) and (xiii)). Because of the fast polymerization under the conditions of deprotonation the equilibrium between NCA anions and isocyanatocarboxylate ions is difficult to measure. Fortunately, an acceptable model system does exist, namely the *N*-silylated NCAs **18**. The electropositive silicon replaces in this case the negative charge of the NCA anions with the same consequence, a rearrangement of

*) This signal could not be assigned.

the NCA ring (Eq. (iv)). The equilibrium concentrations between *N*-silylated α-NCAs and α-isocyanatocarboxylic acid silyl esters (**19**, n = 1) are near to 1 : 1 at room temperature[13], whereas the rearrangement of the *N*-silylated β-NCAs (**18**, n = 2) is so complete that they are spectroscopically



(xiii)



(xiv)

18 **19**

n = 1, 2

ly not detectable[8]. In our opinion, the equilibria of the NCA anions (Eqs. (iii) and (xiii)) behave analogously to Eq. (xiv), and this is the main reason for the fact that termination steps caused by isocyanatocarboxylates are much more frequent when β-NCAs are polymerized. This conclusion also agrees well with the results of Tab. 1 and those of Kopple[3,4]. Furthermore, we come to the conclusion that increasing ring size renders NCAs less suitable for polymerization, in agreement with experimental results obtained with the seven membered γ-amino acid NCAs[14].

Experimental Part

Diethyl ether, tetrahydrofuran (THF), and 1,4-dioxane were refluxed and distilled over sodium wire. The amines were distilled over freshly powdered calcium hydride.

Measurements: The 22,63 MHz ^{13}C NMR spectra were measured with a Bruker WH-90 in 10 mm diameter sample tubes with a coaxial 4 mm capillary containing a 1 : 1 mixture (by volume) of $[^2H]_8$-1,4-dioxane and TMS. The pulse width was 8 μs; 8 K data points on a spectral width of 5 000 Hz were used, and ca. 40 000 scans were accumulated. 400 mg of a polypeptide were dissolved in 2 ml of sulfuric acid (98 weight-%). The ^1H NMR spectra were measured on the same apparatus in deuterated trifluoroacetic acid with TMS as internal standard.

The viscosity measurements were carried out in an "Ostwald viscosimeter" thermostated at 20 °C.

The IR spectra were measured in KBr with a Perkin-Elmer-Model 137 "Infracord".

The melting points were measured on an electric heating plate and are not corrected.

β-Alanine NCA: 95 g (0,5 mol) of trimethylsilyl 3-isocyanatopropionate were dissolved in 400 ml of THF and shaken at 0 °C with 4,5 g of water until all water had dissolved (2–3 min). Then, 500 ml of diethyl ether were added portionwise with shaking, so that no water drops separated. The reaction mixture was stored at 0 °C; the next day the crystallized product was filtered off and washed with dry diethyl ether. The NCA was dried in a desiccator over P_4O_{10} at 10^{-2} mbar and consumed immediately after 30 min. A longer storage leads to polymerization even in a desiccator. The *cis*-D,L-6-amino-3-cyclohexene-1-carboxylic acid NCA (**7**) was prepared in a similar way[8].

Reactions of β-alanine NCA with primary and secondary amines. General procedure (see Tabs. 1, 4, and 5): 5,8 g (50 mmol) of β-alanine NCA were dissolved in 120 ml of dry tetrahydrofuran, and at 5–10 °C the amine (s. Tab. 1) was added at once. Cooling with cold water (10 °C) was continued for 30 min, then the reaction flask was stored at room temperature. The next day the reaction mixture was brought to dryness (i. vac.), and the residue was stirred with 50 ml of 2 M hydrochloric acid and 50 ml of a mixture of ethyl acetate and THF (volume ratio 3 : 2). The insoluble poly(β-alanine) was filtered off and dried at 80 °C/10^{-2} mbar (yield s. Tab. 1). The two layers of the filtrate were separated, and the acidic water phase was three times extracted portionwise with 50 ml of the above mentioned ethyl acetate/THF mixture. The combined organic extracts were dried over sodium sulfate and brought to dryness. The remaining crude *N'*-substituted β-ureidopropionic acids **3a–g** (yields s. Tab. 1) were recrystallized from tetrahydrofuran/ligroin after treatment with charcoal (properties s. Tabs. 4

Tab. 4. Properties of the *N'*-substituted 3-ureidopropionic acids isolated from the experiments of Tab. 1

β-Ureido acid	Mp. in °C	Empirical formula (molecular weight)		Elemental analysis		
				C	H	N
3-(*N'*-Phenylureido)propionic acid **(3a)**	170–172	$C_{10}H_{12}N_2O_3$	Calc.	57,68	5,82	13,45
		(202,2)	Found	57,39	6,09	13,43
3-(*N*-Morpholinocarbamoylamino)propionic acid **(3b)**	148–150	$C_8H_{14}N_2O_4$	Calc.	47,52	6,98	13,85
		(202,2)	Found	47,25	7,16	13,83
3-(*N'*-Benzylureido)propionic acid **(3c)**	128–130	$C_{11}H_{14}N_1O_3$	Calc.	56,45	6,35	11,61
		(222,3)	Found	56,80	6,51	11,73
3-(*N'*-Butylureido)propionic acid **(3d)**	114–116	$C_8H_{16}N_2O_3$	Calc.	51,05	8,57	14,88
		(188,2)	Found	50,68	8,58	15,02
3-(*N'-tert*-Butylureido)propionic acid **(3e)**	104–106	$C_8H_{16}N_2O_3$	Calc.	51,05	8,57	14,88
		(188,2)	Found	51,23	8,80	14,89
3-(*N',N'*-Diethylureido)propionic acid **(3f)**	124–126	$C_8H_{16}N_2O_3$	Calc.	51,05	8,57	14,88
		(188,2)	Found	51,41	8,67	14,68
3-(*N',N'*-Diisopropylureido)propionic acid **(3g)**		$C_{10}H_{11}N_2O_3$	Calc.	56,06	8,47	13,07
		(214,3)	Found	56,11	8,80	12,79

Tab. 5. IR and ^{1}H NMR spectroscopic characterization of the *N'*-substituted β-ureidopropionic acids

Compound	δ in ppm and *J* in $[^2H]_6$-DMSO	IR maxima in KBr in cm^{-1}
3a	2,90 (t; 2H, *J* = 5,0 Hz); 3,80 (*t*; 2H, *J* = 5,0 Hz); 7,43 (s; 5H)[a]	3370 (s), 3090 (m), 1720 (s), 1660 (s), 1605 (s), 1520 (m), 1459 (m), 1330 (m), 1229 (s), 704 (s)
3b	2,43 (2H, broad); 3,30 (6H, broad); 3,60 (4H, broad); 6,60 (1H, broad)	3420 (s), 3050 (s), 1750 (s), 1640 (s), 1555 (s), 1438 (m), 1380 (m), 1328 (m), 1280 (m), 1200 (m), 1158 (m), 1119 (m), 1002 (m), 870 (m)
3c	2,43 (t; 2, *J* = 7,0 Hz); 3,30 (q; H, *J* = 7,0 Hz); 4,13 (d; 2H, *J* = 6,0 Hz); 6,13 (t; 1H, *J* = 6,0 Hz); 6,57 (t; 1H, *J* = 6,0 Hz); 7,30 (s; 5H)	3380 (s), 3070 (m), 2980 (m), 1713 (s), 1640 (s), 1602 (s), 1455 (m), 1340 (m), 1238 (m), 935 (m)
3d	0,9–1,30 (7H, broad); 2,37 (t; 2H, *J* = 6,0 Hz); 3,13 (m, 4H)	3360 (s), 3120 (m), 1728 (s), 1655 (s), 1613 (s), 1590 (s), 1510 (s), 1458 (m), 1417 (m), 1342 (m), 1318 (m), 1239 (s), 1103 (s), 840 (s)
3e	1,21 (s; 9H); 2,33 (t; 2H, *J* = 6,0 Hz); 3,18 (t; 2H, *J* = 6,0 Hz)	3400 (s), 3010 (m), 1735 (s), 1658 (s), 1582 (s), 1485 (m), 1418 (m), 1380 (m), 1310 (s), 1245 (s), 960 (m)
3f	1,07 (t; 6H, *J* = 7,0 Hz); 2,45 (t; 2H, *J* = 7,0 Hz); 3,27 (m; 6H); 6,23 (t; 1H, broad)	3460 (s), 3520 (s), 1740 (s), 1610–1570 (s), 1440 (m), 1380 (m), 1305 (m), 1238 (s), 1086 (m), 1035 (m), 859 (m)
3g	1,17 (d; 12H, *J* = 7,0 Hz); 2,35 (t; 2H, *J* = 7,0 Hz); 3,20 (q; 2H, *J* = 6,0 Hz); 3,67 (q; 2H, *J* = 7,0 Hz); 5,80 (t; 1H, *J* = 6,0 Hz)	3465 (s), 3010 (s), 2580 (m), 1731 (s), 1600 (s), 1567 (s), 1462 (m), 1434 (m), 1357 (s), 1206 (s), 965 (m), 788 (m)

[a] In trifluoroacetic acid.

and 5). The acidic water solution was brought to pH 12–13 by addition of 4 M sodium hydroxide and extracted three times with 50 ml portions of a mixture of ethyl acetate and THF (volume ratio 3:2). The combined extracts were dried over sodium sulfate, and brought to dryness (finally 10^{-2} mbar for 8 h), whereby the crude β-alaninamides remained as syrupy residues. Because the morpholine derivative **3b** is soluble in acidic water, the above given procedure was modified as follows. The concentrated reaction mixture was shaken with 10 ml of 2 M hydrochloric acid to decompose carbamates. Then, the reaction mixture was mixed with 50 ml of 4 M sodium hydroxide and extracted twice with 50 ml portions of a mixture of ethyl acetate and THF (volume ratio 3:2). The alkaline phase was acidified with an ion exchange resin and brought to dryness. The residual crude **3b** was recrystallized from tetrahydrofuran/ligroin.

*Reactions of cis-*D,L*-6-amino-3-cyclohexene-1-carboxylic acid NCA* (**7**) *with secondary amines:* 8,3 g (50 mmol) of NCA **7** were dissolved in 100 ml of dry tetrahydrofuran, and 50 mmol of an amine were added at once at 10 °C. The reaction mixture was worked up as described for β-alanine NCA, and the following *N'*-substituted *cis*-D,L-6-ureido-3-cyclohexene-1-carboxylic acids were obtained:

6-Morpholinocarbonylamino-3-cyclohexene-1-carboxylic acid (**8a**): Yield: 2,6 g (20%); dec. p. 164–166 °C.

$C_{12}H_{18}N_2O_4$ (254,3)	Calc.	C 56,68	H 7,14	N 11,02
	Found	C 56,87	H 7,30	N 10,87

IR (KBr): 3460 (s), 2980 (s), 2915 (s), 1710 (s), 1625 (s), 1540 (s), 1446 (m), 1415 (m), 1275 (s), 1210 (s), 1123 (s), 1006 (m), 735 (m), and 675 cm^{-1} (m).

6-(N',N'-Diethylureido)-3-cyclohexene-1-carboxylic acid (**8b**): Yield: 8,0 g (66%); dec. p. 128–130 °C.

$C_{12}H_{20}N_2O_3$ (240,3)	Calc.	C 59,98	H 8,39	N 11,65
	Found	C 60,12	H 8,64	N 11,47

IR (KBr): 3450 (m), 3000 (s), 1720 (s), 1620 (s), 1535 (s), 1450 (m), 1390 (m), 1310 (m), 1275 (s), 1233 (s), 1200 (s), 1070 (m), 905 (m), and 673 cm^{-1} (m).

6-(N',N'-Diisopropylureido)-3-cyclohexene-1-carboxylic acid (**8c**): Yield: 11,0 g (83%), dec. p. 141–143 °C.

$C_{14}H_{22}N_2O_3$ (266,3)	Calc.	C 63,13	H 8,33	N 10,52
	Found	C 62,85	H 8,70	N 10,40

IR (KBr): 3480 (m), 3000 (s), 1718 (s), 1610 (s), 1540 (s), 1318 (m), 1276 (m), 1230 (s), 1210 (s), 1155 (m), and 670 cm^{-1} (m).

*cis-*D,L*-N-tert-Butyl-6-[N'-(4-chlorophenyl)ureido]-3-cyclohexene-1-carboxamid* (**6**): To the icecold solution of 6,4 g (20 mmol) of *cis*-D,L-6-[*N*-(4-chlorophenyl)carbamoylamino]-3-cyclohexene-1-carboxylic acid NCA (**5**) in 100 ml of dry tetrahydrofuran, 3,0 g (40 mmol) of *tert*-butylamine were added at once. After 24 h 200 ml of ethyl acetate were added and the organic phase was extracted three times with 50 ml portions of 2 M hydrochloric acid, two times with 50 ml portions of a $NaHCO_3$ solution (5 weight-%) and with 50 ml of water. The ethyl acetate solution was dried over sodium sulfate, concentrated to ca. 40 ml and diluted with ligroin. 6,6 g (94%) of the crude product crystallized after storage at − 10 °C. Recrystallization from tetrahydrofuran/ligroin yielded 5,1 g of a pure product; mp. 261–263 °C. No product could be isolated from the acidified $NaHCO_3$ extracts.

$C_{18}H_{26}ClN_3O_3$ (351,9)	Calc.	C 61,44	H 7,45	N 11,94
	Found	C 61,11	H 7,38	N 12,16

IR (KBr): 3440 (m), 3350 (s), 3223 (m), 2960 (s), 1708 (s), 1650 (s), 1615 (s), 1570 (s), 1520 (s), 1465 (m), 1412 (m), 1378 (m), 1328 (m), 1255 (s), 950 (m), 840 (m), and 698 cm^{-1} (m).

^1H NMR (trifluoroacetic acid/TMS int.): $\delta = 1{,}50$ (s; 9 H), 1,86 (s; broad 8 H), 2,91 (m; broad, 1 H), 4,50 (m; 1 H), 7,24 (s; 2 H), 7,44 (s; 2 H).

Boc-β-alanine pentachlorophenyl ester (**10**): 19,0 g (0,1 mol) of Boc-β-alanine and 27,0 g (0,1 mol) of pentachlorophenol were dissolved in 150 ml of dry THF and a cold solution of 22 g (0,105 mol) of dicyclohexylcarbodiimide in 100 ml of dry ethyl acetate were added. The reaction mixture was stored at 0 °C and filtered the next day. The filtrate was treated with dried (over P_4O_{10} i. vac.) charcoal and concentrated i. vac. Cooling with ice and portionwise addition of ligroin led to crystallization of the product, which was recrystallized twice from ethyl acetate/ligroin. Yield: 19,2 g (45%), mp. 124–126 °C.

$C_{14}H_{14}Cl_5NO_4$ (437,5)	Calc.	C 38,43	H 3,23	N 3,20
	Found	C 38,25	H 3,37	N 2,95

IR (KBr): 3400 (s), 3000 (m), 2940 (m), 1790 (s), 1700 (s), 1630 (s), 1398 (w), 1371 (s), 1279 (m), 1258 (m), 1178 (m), 1095 (s), 853 (m), 785 (m), and 721 cm^{-1} (m).

^1H NMR ($CDCl_3$/int. TMS) $\delta = 1{,}47$ (s; 9 H); 2,97 (t; 2 H, $J = 6{,}0$ Hz); 3,53 (q; 2 H, $J = 6{,}0$ Hz); 5,08 (t; 1 H, $J = 6{,}0$ Hz).

Boc-β-alanine benzylamide (**11**): 4,37 g (10 mmol) of Boc-β-alanine pentachlorophenyl ester and 1,08 g (10 mmol) of benzylamine were stirred in 50 ml of dry ethyl acetate at room temperature until the IR band at 1800 cm^{-1} had disappeared (ca. 3 d). Then, the reaction mixture was washed three times with 20 ml portions of 2 M sodium hydroxide saturated with soda and two times with a citric acid solution (5 weight-%), half saturated with ammonium chloride. The organic phase was finally dried over sodium sulfate and concentrated i. vac. Cooling with ice and dropwise addition of ligroin led to crystallization of the product. Yield: 0,9 g (33%); mp. 117–119 °C.

$C_{15}H_{22}N_2O_3$ (278,3)	Calc.	C 64,73	H 7,97	N 10,06
	Found	C 64,95	H 8,17	N 9,82

IR (KBr): 3350 (s), 3100 (w), 3018 (m), 2965 (m), 1710 (s), 1668 (s), 1570 (s), 1470 (s), 1380 (m), 1355 (m), 1300 (s), 1260 (m), 1182 (s), and 708 cm^{-1} (s).

^1H NMR ($CDCl_3$/int. TMS) $\delta = 1{,}42$ (s; 9 H), 2,42 (t; 2 H, $J = 7{,}0$ Hz), 3,28 (q; 2 H, $J = 7{,}0$ Hz), 4,33 (d; 2 H, $J = 6{,}0$ Hz), 6,16 (broad s; 1 H), 7,25 (s; 5 H), 8,14 (broad t; 1 H).

The solution of 100 mg of β-alanine benzylamide trifluoroacetate in 1 ml of trifluoroacetic acid showed the following ^1H NMR spectrum: $\delta = 294$ (broad 2 H); 3,58 (broad q; 2 H), 4,43 (broad d; 2 H); 7,24 (s; 5 H).

3,3'-Ureylenedipropionic acid (**17**): 26,7 g (0,3 mol) of β-alanine were refluxed under stirring in a mixture of 200 ml of dry chloroform, 50 ml of dry acetonitrile, and 40 ml of (0,3 mol) trimethylchlorosilane until the amino acid had completely dissolved (ca. 60 min). Then, 56,1 g (0,3 mol) of diethyl ether was added at once and then 30,5 g (0,3 mol) of triethylamine dropwise. The reaction mixture was refluxed for 50 min and concentrated to a final volume of ca. 150 ml. The residual mixture was diluted with 400 ml of dry toluene, cooled with ice and filtered under exclusion of moisture. The filtrate was concentrated i. vac. and extracted with 300 ml of 1 M sodium hydrogen carbonate solution. The water solution was acidified with ion exchange resin and brought to dryness (i. vac.). The residue was recrystallized three times from THF/diethyl ether. Yield: 13,5 g (22%); mp. 125–128 °C.

$C_7H_{12}N_2O_5$ (204,2)	Calc.	C 41,18	H 5,92	N 13,72
	Found	C 41,08	H 6,07	N 13,65

IR (KBr): 3390 (s), 3100 (m), 3000 (m), 2660 (w), 1725 (s), 1642 (s), 1608 (s), 1455 (m), 1344 (m), and 1240 cm^{-1} (m).

^1H NMR (D_2O/int. DSS*) $\delta = 2{,}56$ (t; 2 H, $J = 6{,}5$ Hz); 3,37 (t; 2 H, $J = 6{,}5$ Hz).

3-(N'-Phenylureido)propionic acid (**3a**): 8,9 g (0,1 mol) of β-alanine were refluxed in a mixture of 130 ml of dry chloroform, 20 ml of dry acetonitrile, and 13 ml (0,1 mol) of trimethylchlorosilane until a clear solution was obtained (ca. 30 min). Then, 11,9 g (0,1 mol) of phenyl isocyanate were added at once and 14 ml (0,1 mol) of triethylamine were added dropwise. The reaction mixture was refluxed for 4 h and after cooling it was stirred with 150 ml of 1 M hydrochloric acid. The water phase was extracted with 150 ml of a mixture of ethyl acetate and THF (volume ratio 1 : 1). This extract and the chloroform phase were combined, and after washing with 50 ml of 2 M hydrochloric acid it was dried over sodium sulfate. The dried solution was concentrated i. vac. to a final volume of ca. 50 ml, and the product was crystallized by cooling with ice and portionwise addition of ligroin. The product was recrystallized from THF/ligroin. Yield: 13,2 g (65%): mp. 170–172 °C (171–172 °C).

$C_{10}H_{12}N_2O_3$ (208,2)	Calc.	C 57,68	H 5,82	N 13,45
	Found	C 57,39	H 6,09	N 13,42

^1H NMR (trifluoroacetic acid/int. TMS) $\delta = 2{,}90$ (t; 2 H, $J = 5{,}0$ Hz); 3,80 (t; 2 H, $J = 5{,}0$ Hz); 7,43 (s; 5 H).

*) Sodium 4,4-dimethyl-4-silapentane-1-sulfonate.

Polymerizations

A) For the experiments of Tabs. 2 and 3 50 mmol of freshly prepared β-NCAs in 100 ml of dry solvent were used. All experiments of one series were carried out with the same batch of monomer. The reaction flasks were protected against moisture by freshly prepared calcium chloride drying tubes. The polymers were precipitated from 600 ml of diethyl ether and dried at 80 °C/10^{-2} mbar.

B) The experiments with water as initiator were carried out with 50 mmol of β-alanine NCA in 100 ml of dry 1,4-dioxane. After the solutions had reached the reaction temperature (60 and 100 °C) two drops of water were added, and the polymers were precipitated after 48 h from 500 ml of diethyl ether.

^{13}C NMR spectra in conc. H_2SO_4 (ext. TMS): $(\beta\text{-Ala})_n$, monomeric unit: $\delta = 178{,}3$, 38,8, and 32,8; end-groups: $\delta = 185{,}8$, 160,2, 37,6, and 34,1. Biscarboxyethylene urea (**17**): $\delta = 187{,}6$, 160,2, 37,6, and 34,1.

[1] M. Szwarc, Fortschr. Hochpolym.-Forsch. **4**, 1 (1965)
[2] C. Bamford, H. Block, High Polym. **26**, 687 (1971)
[3] K. D. Kopple, J. Am. Chem. Soc. **79**, 662 (1957)
[4] K. D. Kopple, J. Am. Chem. Soc. **79**, 6442 (1975)
[5] H. R. Kricheldorf, Makromol. Chem. **178**, 1959 (1977)
[6] L. Birkofer, R. Modic, Justus Liebigs Ann. Chem. **628**, 162 (1959)
[7] L. Birkofer, R. Modic, Justus Liebigs Ann. Chem. **604**, 56 (1957)
[8] H. R. Kricheldorf, Makromol. Chem. **173**, 13 (1973)
[9] H. R. Kricheldorf, Makromol. Chem. **175**, 3343 (1974)
[10] T. Komoto, K. Y. Kim, Y. Minoshima, M. Oya, T. Kawai, Makromol. Chem. **168**, 261 (1973)
[11] H. R. Kricheldorf, K. Bösinger, Makromol. Chem. **177**, 1243 (1976)
[12] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution" 1. Ed., Butterworth, London 1965
[13] H. R. Kricheldorf, G. Greber, Chem. Ber. **104**, 3131 (1971)
[14] H. R. Kricheldorf, Makromol. Chem. **176**, 57 (1975)