Makromol. Chem. **178**, *1959–1970 (1977)*

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Mechanism of the NCA-Polymerization, 5*)

Catalysis by Secondary Amines

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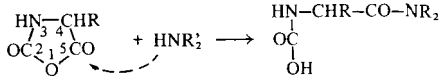
(Date of receipt: July 12, 1976**)

SUMMARY:

L-Phenylalanine NCA and glycine NCA react with excess diisopropylamine or dicyclohexylamine to give only polymeric products. In contrast, excess morpholine or diethylamine produces no polymerization but instead yield amino acid amides (**2**) and hydantoic acids (**6**), which indicate the intermediate formation of NCA anions **4**, which are in equilibrium with the isomeric α-isocyanatocarboxylates (**5**). Diisopropylamine and dicyclohexylamine in the presence of *N*-acetylglycine NCA (**13**) yield also quantitative polymerization of glycine NCA, from which oligomers **14** with acetyl and NCA end groups may be isolated. Under the same conditions morpholine and diethyl amine yield no polymerization, since these amines are acylated by excess *N*-acetylglycine NCA. These results show that secondary amines with small substituents react preferentially as nucleophiles so that the NCA-polymerization proceeds, as with initiation by primary amines, through propagation by nucleophilic end groups. Secondary amines with bulky substituents, in analogy with the tertiary amines, produce only NCA anions which polymerize according to the "activated monomer mechanism", i.e., through reaction with the electrophilic NCA chain end. Apparently contradictory experiments of *Seeney* and *Harwood* were reinvestigated and the results are discussed.

Introduction

The base initiated NCA-polymerization has for many years been the object of numerous investigations, and several polymerization mechanisms have been discussed[1-3]. Secondary amines as initiators are of particular interest, because they can react with NCAs **1** as nucleophiles and as aprotic bases. As nucleophiles they react exclusively with the NCA carbonyl group at C-5 of the oxazolidine ring (Eq. (i)), in analogy with primary amines, and the polymerization proceeds via the nucleophilic chain end which may be a carbamate (**3**), (Eqs. (iii)–(iv)), or a primary amino group (**2**) (Eqs. (i)–(ii)). As bases, secondary amines can deprotonate NCA **1**, in analogy with tertiary amines, and polymerization may follow via the "activated monomer mechanism" (a. m. mechanism) (Eqs. (v)–(vii)). In this case the propagation involves reaction of the NCA anion **4** with the electrophilic NCA chain end (Eq. (vii)).



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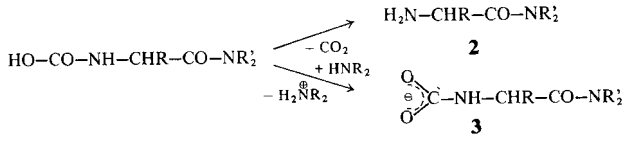
(i)



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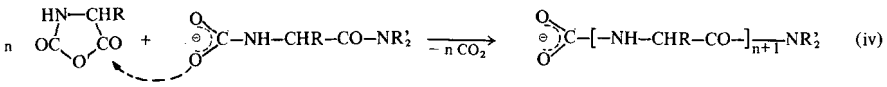
(ii)

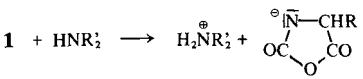
(iii)

*) Part 4: cf.[15].

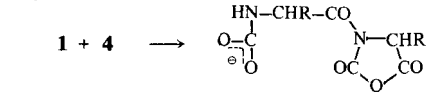
**) Revised manuscript of October 15, 1976.



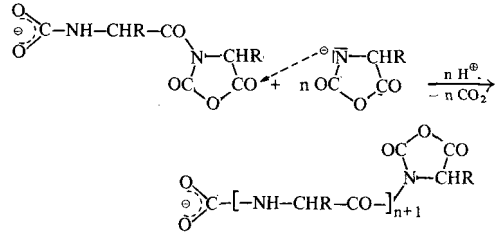
(iv)



(v)

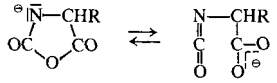


(vi)



(vii)

Goodman and *Hutchinson*[4] as well as *Peggion*, *Scoffone*, *Cosani* et al.[5-8] have shown that the NCA-polymerization initiated by ^{14}C-labeled diethylamine, dibutylamine, and diisopropylamine proceeds exclusively or predominantly according to the "a. m. mechanism". Radioactive dialkylaminocarbonyl end groups which should be formed by the nucleophilic attack (Eq. (i)) could not be detected. On the other hand, *Kopple* has been able to demonstrate[9] that a great excess of diethylamine or dialkylamine prevents the polymerization of NCAs **1**, and amino acid derivatives of low molecular weight are formed exclusively. The reaction products isolated by *Kopple* were hydantoic acids of type **6** and amino acid amides **2**, which result from the nucleophilic attack according to Eq. (i). The formation of hydantoic acids **6** was explained by deprotonation of NCAs **1** (Eq. (v)), subsequent ring opening of the resulting anions **4** (Eq. (viii)), and reaction of the isomeric α-isocyanatocarboxylates **5** with the secondary amines (Eq. (ix))[10].



(viii)

4 **5**

(ix)

6

On the contrary, *Seeney* and *Harwood* report in two recent papers[11,12] that diethylamine in excess reacts with NCAs only according to Eqs. (i) and (iii) to give the carbamates **3**. Many NMR spectra of reaction mixtures are given as proof. From these results the authors drew the conclusion, that the NCA-polymerization initiated by secondary amines would proceed exclusively by *Blout*'s "carbamate mechanism" according to Eqs. (i), (iii), (iv).

It was, accordingly, our purpose to reinvestigate the reaction of NCAs **1** with secondary amines and to elucidate the above mentioned contradictions.

Results

Kopple isolated 2-benzyl-5,5-diethyl hydantoic acid (**7**) with 80% yield from the conversion of D,L-phenylalanine NCA with a great excess of diethylamine[9]. *Seeney* and *Harwood* report, on the other hand, that the same conversion, with amine/NCA mole ratios of 3:1 to 1:1, results only in the formation of diethylammonium *N*-(1-diethylaminocarbonylphenethyl)carbamate (**8**) and diethylammonium *N*-[1-(1-diethylaminocarbonylphenethylaminocarbonyl)-phenethyl]carbamate (**9**)[12] according to Eqs. (i) and (iii).

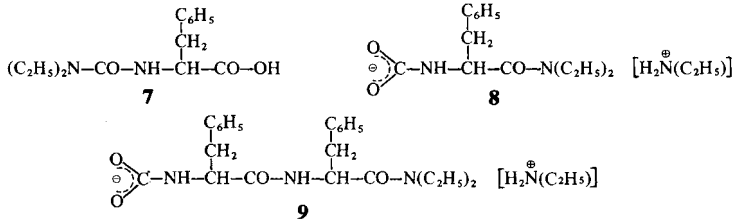
We reinvestigated the conversion of D,L-phenylalanine NCA with diethylamine according to the procedure of *Seeney* and *Harwood* and obtained ^{1}H NMR spectra of the reaction mixture (in chloroform) which are identical with the published spectra[12]. In contrast to *Seeney* and *Harwood*, however, we worked up the reaction mixtures obtained in dioxane and isolated the hydantoic acid **7** (Tab. 1, No. 1–3). In agreement with the results of *Kopple* the yield

Tab. 1. Conversion of α-amino acid NCAs with stoichiometric amounts of secondary amines in dioxane

No. of experiment	NCA of	Secondary amine	Mole ratio NCA/amine	Yield of polypeptide in %	Yield of subst. hydantoic acid in %	Reaction[a] temp. in °C
1	D,L-Phenylalanine	Diethylamine	1:1	0	32,0	25–40
2			1:3	0	75,0	25–40
3			1:6	0	86,0	25–40
4		Diisopropylamine	1:1	97,0	0	25–30
5		Dicyclohexylamine	1:1	98,0	0	25–30
6	Glycin	Morpholine	1:2	0	38,5[b]	25–45
7		Diethylamine	1:2	1,0	75,5[b]	25–45
8		Diisopropylamine	1:2	95,5	0	25–45
9		Dicyclohexylamine	1:2	97,0	0	25–45

[a] The temperature rises during the exothermic reaction.
[b] Products soluble in alkaline water.

of **7** increases with increasing excess of amine, since a higher basicity of the reaction medium favours the formation of the anion **4** and thereby of the isocyanate **5**. *Seeney* and *Harwood* have demonstrated the formation of the carbamate **8** by the doublet of the proton at the



nitrogen situated at $\delta = 5{,}4$ in the 60 MHz ^{1}H NMR spectrum*, but a spectroscopic comparison with an isolated carbamate has not been made. Furthermore, the appearance of signals from two different kinds of diethylamino residues has been taken as proof. As shown in Fig. 1, however, the diethylammonium salt of **7** has also a doublet at $\delta = 5{,}3$–$5{,}4$*, which is due to the proton at the nitrogen of the ureido group. The diethylammonium salt of **7**, furthermore, shows signals of two different diethylamino groups, in analogy with Fig. 1 in reference[12], so that we cannot accept the ^{1}H NMR spectra of *Seeney* and *Harwood* as evidence for the exclusive formation of the carbamate **8**. The published spectra do not exclude the presence of **7** in the reaction mixture.

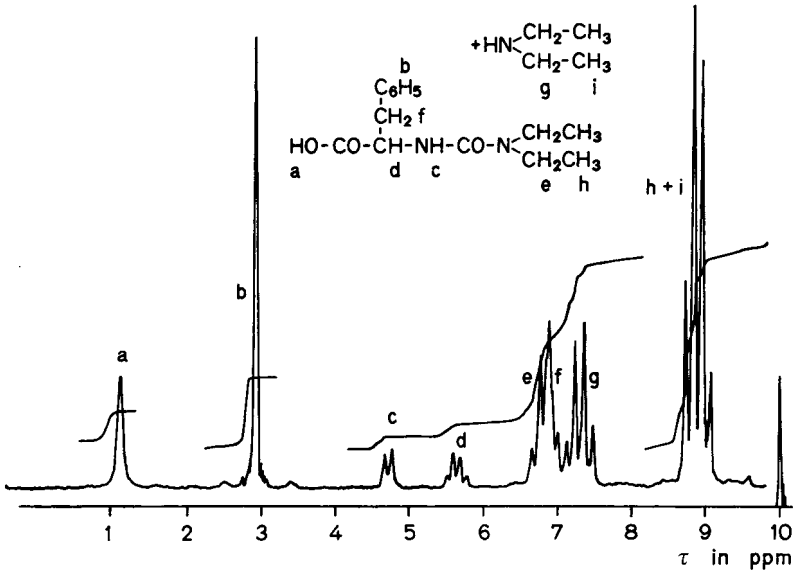


Fig. 1. ^{1}H NMR spectrum (60 MHz) of 2-benzyl-5,5-diethyl hydantoic acid diethylammonium salt in $CDCl_3$ at 20°C

According to *Seeney* and *Harwood* the reaction of phenylalanine NCA with diethylamine in a mole ratio of 1:1 leads to **9** as the main product[12]. The ^{13}C NMR spectrum of the reaction mixture and of benzyl *N*-[1-(1-diethylaminocarbonylphenethylaminocarbonyl)phenethyl]carbamate (**10**), which was isolated from the reaction mixture after the addition of benzyl chloride, should be indicative of this reaction. In the ^{13}C NMR spectrum *Seeney* and *Harwood* assigned the peaks at $\delta = 141$, 158 and 180*) to the three CO-groups of **9**[11,12]. We know, however, of no peptide amide or carbamate from the literature[13,14] nor from own experiments, which exhibits a CO-signal in the region of $\delta = 140$–145. Similar signals as reported in reference[12] are present in the ^{13}C NMR spectrum of the diethylammonium salt of **7** (Fig. 2); the peak at $\delta = 140$ must be assigned to the quarternary C-atom of the phenyl group. The ^{13}C NMR spectrum Fig. 4 in reference[12], therefore, cannot be taken as evidence for the formation of the carbamate **9** as the unique reaction product. A mixture of **9** with the diethylammonium salt of **7** would give a similar spectrum.

*) Chloroform served as solvent, TMS as internal standard.

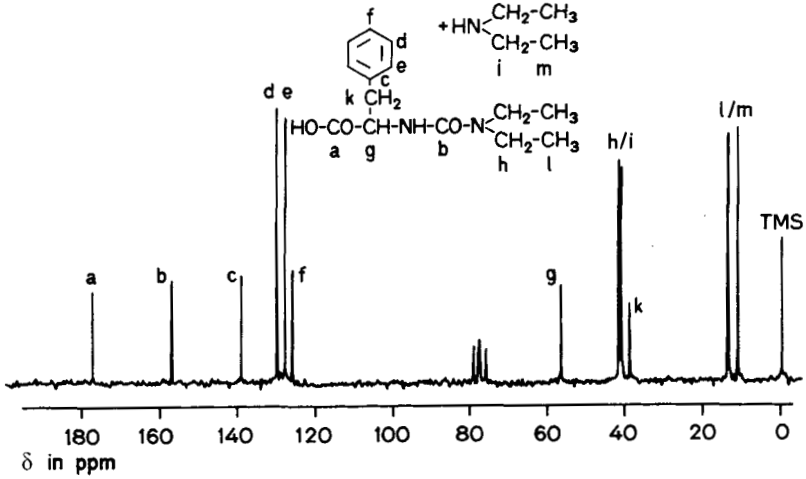


Fig. 2. ^{13}C NMR spectrum (20 MHz) of 2-benzyl-4,5-diethyl hydantoic acid diethylammonium salt in $CDCl_3$ at 30–40 °C

As evidence for the structure of the assumed benzylester **10** only a 60 MHz ^1H NMR spectrum is given in ref.[12], and the following chemical shifts were reported: $\delta = 4{,}6$ for the Z—CH_2-protons, $\delta = 7{,}5$ for the aromatic Z-protons and $\delta = 7{,}2$ for the aromatic phenylalanine protons. We found in the case of Z-Phe, Z-Phe-Ala, and Z-Phe-diethylamide (**11**), (prepared from Z-Phe and diethylamine) the following shifts: $\delta = 5{,}0$–$5{,}1$ for the Z—CH_2-protons, $\delta = 7{,}3$

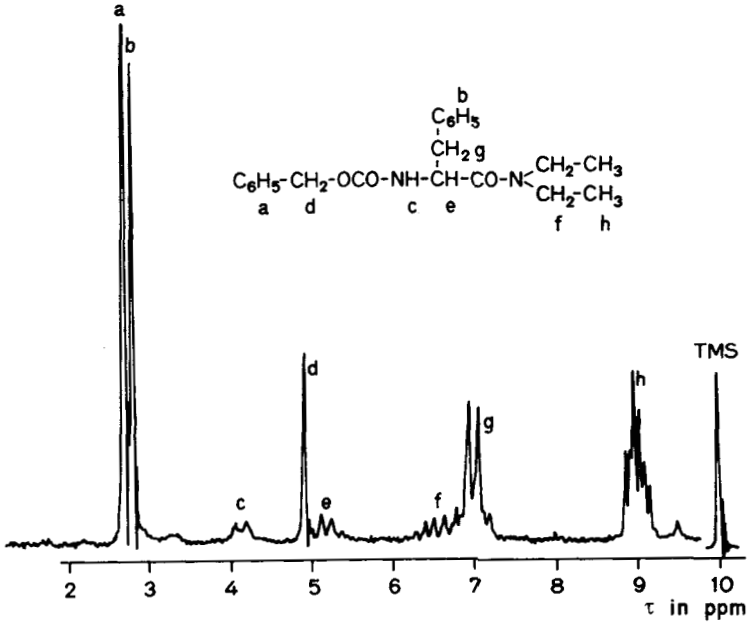


Fig. 3. ^1H NMR spectrum (60 MHz) of Z-phenylalanine diethylamide (**11**) in $CDCl_3$ at 20 °C

for the aromaic Z-protons, and $\delta = 7{,}1$–$7{,}2$ for the aromatic Phe-protons (Tab. 3). These deviations result perhaps from a different solvent or temperature, since *Seeney* and *Harwood* give no details with regard to these parameters in this case. The spectrum Fig. 5 in ref.[12] exhibits, however, two triplets at $\delta = 1{,}0$ and 1,3 with an intensity ratio of 2:1. These signals can only result from the methyl groups of two different diethylamino groups. Obviously, the two ethyl groups of a carboxylic acid diethylamide are not equivalent, since the amide bond possesses a rotational barrier. The maximal shift difference of the methyl groups due to this *cis/trans* isomerism, however, reaches 0,1 ppm as shown in the spectrum of **11** in Fig. 3, and both triplets must exhibit equal intensities. Finally, the ^{1}H NMR spectrum of benzyl 2-benzyl-5,5-diethylhydantoate (**12**) (Fig. 4), which can easily be prepared from the acid **7** and benzyl chloride, exhibits almost signals with shifts essentially similar to those of the isomer **11** (Fig. 3), except in the case of the less intense protons at the nitrogen. Therefore, we reach to the conclusion that the ^{1}H NMR spectrum Fig. 5 in ref.[12] does not prove the structure of the benzylester **10**, and that it cannot indicate the absence of **12** as contamination.

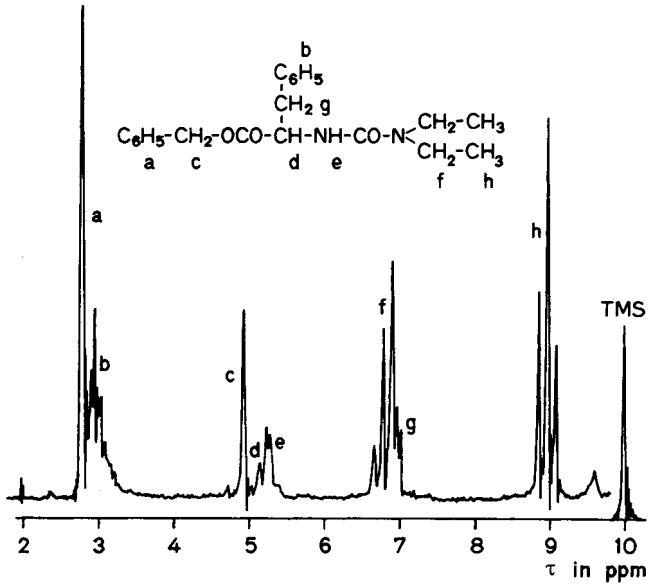
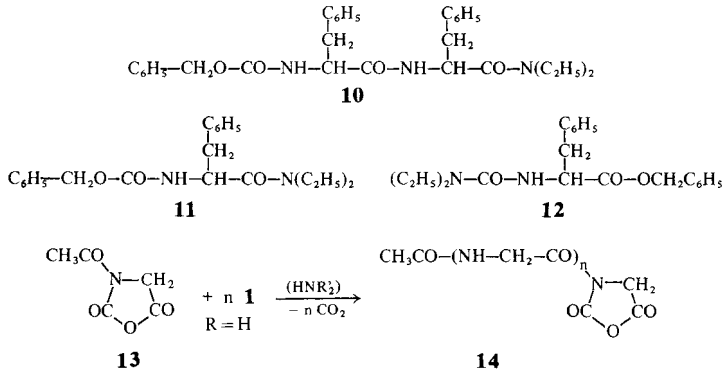


Fig. 4. ^{1}H NMR spectrum (60 MHz) of benzyl-2-benzyl-5,5-diethyl hydantoate (**12**) in $CDCl_3$ at 20°C

Even if the Z-peptide ester **10** had been isolated in pure form, it still would not have been possible to justify a new point of view concerning the reaction mechanism, unless the yield of the carbamate **8** or of its benzylester **10** had been essentially 100%*) or unless the complete absence of **7** had been demonstrated. There is no question that the reaction of NCAs **1** with diethylamine can yield small quantities of the carbamate **3** or of higher analoga; the results of *Kopple*[9] and the experiments from Tab. 1 indicate, however, that the nucleophilic

*) No yield is given in ref.[12].

attack according to Eq. (i) is not the unique reaction pathway. The deprotonation of NCAs and the subsequent formation of hydantoic acids **6** are concurrent reactions, and the polymerization of NCAs initiated by secondary amines can proceed, therefore, by two routs, namely, according to the "carbamate mechanism" (Eqs. (iii) and (iv)) or according to the "a. m. mechanism" (Eqs. (v)–(vii))[4]. The ratio in which the two mechanisms contribute to a polymerization depends on the structure of the secondary amine as well as on the reaction conditions. Thus, the conversion of Gly NCA with morpholine or diethylamine (Tab. 1) and the experiments of *Kopple* show that, under the same reaction conditions, the yield of the hydantoic acid derivative increases if the substituents of the amine become more bulky. Unusually bulky groups, as in the case of diisopropylamine or dicyclohexylamine, completely prevent stoichiometric reactions, i.e. acylation of the amine to **2** (Eq. (i)) and to **6** (Eq. (ix)). Such sterically hindered secondary amines react like tertiary amines exclusively as bases and produce a quantitative polymerization of the NCAs.



Tab. 2. Conditions and results of the polymerization of glycine NCA initiated by various secondary amines in the presence of *N*-acetylglycine NCA. Mole ratio glycine NCA/*N*-acetylglycine NCA = 4:1

Exp. No.	Catalyst	Mole ratio NCA/catalyst	Temp. in °C	Time in h	Yield[a] in %	Polyglycine $\bar{P}_n$[b]	*N*-Acyl NCA end groups by IR	*N*-Acyl NCA end groups by ^{1}H NMR
1	Dicyclohexylamine	250:1	30	1/12	65	8	+	+
2	Dicyclohexylamine	100:1	30	1/12	91	8	+	+
3	Diisopropylamine	250:1	30	1/12	70	8–9	+	+
4	Diisopropylamine	25:1	30	1/12	ca. 100	7	—	+
5	Diethylamine	250:1	25	12	0	—	—	—
6		25:1	25	12	0	—	—	—
7		4:1	25	12	<5	—	—	—
8	Morpholine	250:1	25	12	0	—	—	—
9		25:1	25	12	0	—	—	—
10		4:1	25	12	<5	—	—	—

[a] Related to CH_3—CO—(NH—CH_2—CO—)$_n$...

[b] The intensities of the acetyl signal ($\tau = 7{,}61$) and of the CH_2-signal ($\tau = 5{,}68$) in the ^{1}H NMR spectrum (CF_3COOH/TMS) were compared.

In order to prove that diisopropylamine and dicyclohexylamine really can initiate a NCA-polymerization by the "a. m. mechanism" the polymerization of glycine NCA was carried out in the presence of *N*-acetylglycine NCA (**13**) (Tab. 2). In analogy with similar experiments with triethylamine or pyridine[15], we could isolate the oligomers **14***), which exhibit in the IR and ^{1}H NMR spectra the signals of an acetyl and an NCA end group (Fig. 5). The

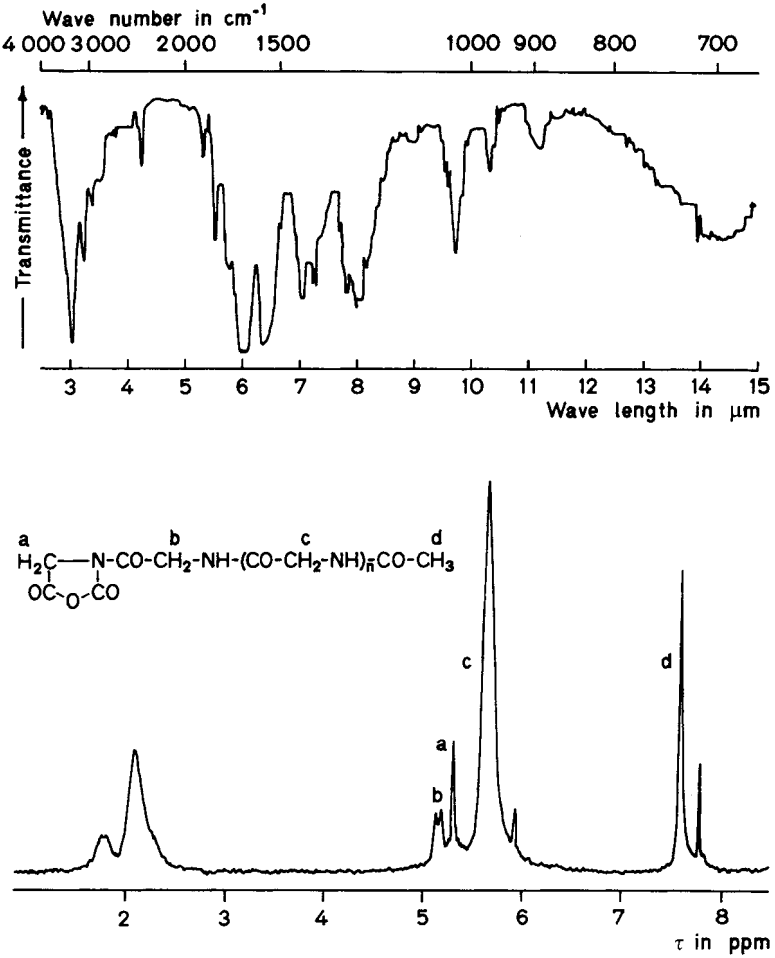


Fig. 5. IR spectrum (KBr) and ^{1}H NMR spectrum (100 MHz) of polyglycine with an acetyl and an NCA end group (**14**, R = H) from Exp. No. 3 in Tab. 2

signals of the reactive NCA end group are less intense in comparison with the stable acetyl end group due to side reactions which have already been discussed in a previous paper[15]. The rapid and quantitative polymerization of glycine NCA as well as the isolation of the oligomers **14** indicate that the initiation and the propagation follow the "a. m. mechanism".

*) Systematic name: α-acetyl-ω-2,5-dioxo-1,3-oxazolidin-3-yl oligo(iminomethylenecarbonyl).

In agreement with this mechanism and with the results of other investigators[4-10] is also the observation that the ^1H NMR spectra of the reprecipitated polyglycine from the experiments of Tabs. 1 and 2 did not exhibit signals of a diisopropylamide or a dicyclohexylamide end group. The unsuccessful polymerization experiments No. 5–8 in Tab. 2, demonstrate, on the other hand, that diethylamine and morpholine in low concentration behave predominantly as nucleophiles. A polymerization in the presence of excess acetyl NCA **13** cannot be initiated by a nucleophilic amine, because the amine itself or the immediately formed carbamate **3** are acylated by the strong electrophile **13**, which prevents the propagation via nucleophilic end groups. The experiments of Tabs. 1 and 2 as well as the results of *Kopple* indicate, therefore, that the nucleophilicity of the secondary amines is responsible above all for the first reaction step and for the polymerization mechanism.

Discussion of the polymerization mechanism

Seeney and *Harwood* as well as other autors define two classes of initiators for the base initiated NCA-polymerization, namely, strong and weak bases. In our opinion, however, this simple classification does not permit a reasonable interpretation of the hitherto published experimental results, since strong and weak bases exist in various classes of initiators, and the difference between protic and aprotic bases as well as between strong or weak nucleophiles cannot be described in terms of basicity. A comparison of various initiators should, therefore, take into consideration at least the following two questions:

1) Can the initiator undergo an irreversible linkage to the NCA (formation of stable end groups) or not?

2) How high is the ratio of nucleophilicity to basicity?

For example, secondary amines, like primary amines, can yield in contrast to tertiary amines stable end groups by nucleophilic attack at C-5 of the 1,3-oxazolidine ring, according to Eq. (i), independent of their basicity. Similarly, alcoholates can lead to ester end groups, although they are aprotic bases like tertiary amines. The identification of such end groups points to the initiation reaction (Eq. (i)), but is not an unambigous proof, since the "a. m. mechanism" produces polymers with an NCA end group, which can react with the initiator during the whole course of the polymerization. The absence of an amido (ester) end group indicates, on the other hand, an initiation reaction via NCA anions (Eqs. (v) and (vi)), but is not indicative of the "a. m. mechanism" (Eq. (vii)) (propagation via NCA anions) if no other criteria, e.g., the cocatalysis by *N*-acyl NCAs, are fulfilled too[15].

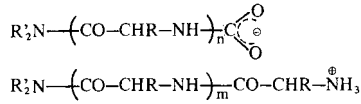
Which of the two possible initiation reactions, (i) or (v), is produced by a secondary amine, depends on its concentration and above all on the ratio of nucleophilicity to basicity. While the nucleophilicity of primary amines parallels their basicity, in the case of secondary and tertiary amines the steric requirements at the *N*-atom are also very important. Secondary amines like diisopropylamine, which are difficult to acylate, react with NCAs **1** in analogy with tertiary amines only as bases, whereas secondary amines with an easily accessible nitrogen (e.g. morpholine, dimethylamine) react predominantly as nucleophiles. The higher linear dialkylamines present an intermediate behavior, since in this case the reaction conditions, especially the concentration, is responsible for the course of the reaction. Our experiments demonstrate, therefore, in full agreement with the results of other authors[4-10], that the catalytic effect of secondary amines differs not only from that of other initiators, but also changes with the structure of the secondary amine.

Seeney and *Harwood* have not only proposed a single initiation reaction (Eqs. (i) and (iii)) for all secondary amines, but they conclude also from the observation of "stable carbamates", that the propagation proceeds exclusively via carbamate chain ends according to Eq. (iv). It has also been known for many years from the investigations of *Bailey*[16], that the reaction of NCAs with excess primary (but not tertiary) amines results in the formation of stable carbamates, so that a stepwise synthesis of peptides can be achieved by the conversion of NCAs with the double amount of an amino acid ester. All these experiments demonstrate, however, that conditions which furnish "stable carbamates", prevent the polymerization of the NCAs. The formation of amino acid amide or dipeptide carbamates (e.g. **8** and **9**) in the presence of excess amine does, therefore not proove an exclusive propagation via carbamate chain ends. Indeed, it has to be taken into account that the NCA-polymerization is generally carried out with low concentrations of primary or secondary amines, i.e., with high monomer/initiator ratios. But, when the initiator is consumed by the initiation reaction (Eq. (i)), the conditions for the stabilisation of the carbamate group (Eq. (iii)) are never achieved. In consequence, further chain growth must involve amino end groups, or otherwise polymeric ion pairs of type **15** have to be postulated. Proof of the existence of such ion pairs does however, not exist and moreover the ion pairs **15** would not be suitable to identify the "carbamate mechanism" for two reasons:

1) If a decarboxylation is excluded during the course of the polymerisation, only 50% of the chains could grow; all chains with an ammonium end group would remain in the oligomeric state.

2) If proton transfer and decarboxylation is accepted, so that all chains can grow statistically with an equal rate, then the propagation must involve amino chain ends to a large extend.

There is no question that in the beginning of an NCA-polymerization, initiated by the nucleophilic attack of a primary or secondary amine (Eq. (i)), some growing steps via carbamate ions can occur; nevertheless, exclusive propagation according to the "carbamate mechanism" has yet to be proven.



15

Experimental Part

Chloroform and dimethylformamide were heated at reflux and distilled over P_4O_{10}; dioxane and dialkylamines were heated at reflux and distilled twice over sodium wire.

The IR spectra were measured with a "Perkin-Elmer Infracord Md. 137" in KBr, the ^1H NMR spectra with a "Varian HR 220" (Fig. 5) or with a "Varian anaspect EM 360". $CDCl_3$ (trifluoro acetic acid in Fig. 5) served as solvent and TMS as internal standard (s. Tab. 3).

The ^{13}C NMR spectrum (Fig. 2) (10^4 scans) was measured with a "Varian CTF-20" in $CDCl_3$ (TMS as internal standard) and the following signals were found: $\delta = 11{,}3$, 13,9, 39,0, 41,2, 41,8, 56,8, 125,9, 127,8, 129,9, 139,2, 156,9, and 177,2.

Experiments of Tab. 1

2-Benzyl-5,5-diethyl hydantoic acid (**7**): The solution of 8,69 (50 mmol) of D,L-Phe NCA in 40 ml of dry dioxane was dropped within 5 min into a solution of 50, 150, or 300 mmol of diethylamine

Tab. 3. Chemical shifts and coupling constants in the ^1H NMR spectra of phenylalanine derivatives in $CDCl_3$

Z-Phenylalanine	6,94 (d, $J=5,0$ Hz); 5,36 (m); 5,00 (s); 4,75 (d, $J=8,0$ Hz); 2,85 (s); 2,76 (s); intensities 2:1:2:1:5:5
Z-Phenylalanine diethylamide (**11**)	8,97 (m); 7,00 (d, $J=7,0$ Hz); 6,38 (q, $J=7,0$ Hz); 6,56 (q, $J=7,0$ Hz); 5,24 (m); 4,94 (s); 4,15 (d, $J=9,0$ Hz); 2,80 (s); 2,67 (s); intensities 6:2:2:2:1:2:1:5:5
Z-Phe-Ala[a]	8,67 (d, $J=8,0$ Hz); 6,97 (m); 5,60 (m); 5,00 (s); 3,65 (d, $J=8,0$ Hz); 2,85 (s); 2,76 (s); intensities 3:2:2:2:1:5:5
Benzyl 2-benzyl--5,5-diethylhydantoate (**12**)	8,98 (t, $J=7,0$ Hz); 6,90 (m); 5,30 (m); 4,90 (s); 2,94 (m); 2,73 (s); intensities 6:6:2:2:5:5
2-Benzyl-5,5-diethyl hydantoic acid (**7**)	9,00 (t, $J=7,0$ Hz); 6,89 (m); 5,33 (m); 5,09 (d, $J=7,5$ Hz); 2,88 (s); intensities 6:6:1:1:5
2-Benzyl-5,5-diethyl hydantoic acid + diethyl-amine	8,90 (m); 7,30 (q, $J=7,0$ Hz); 6,87 (m); 5,63 (m); 4,73 (d, $J=6,0$ Hz); 2,92 (a); 1,07 (s); intensities 12:4:6:1:1:5:2

[a] Chloroform + 10% DMSO-d_6.

in 60 ml of dry dioxane. After 24 h the reaction mixture was stirred with 200 ml of ethyl acetate and 100 ml of 1 M NaOH, the separated water phase was extracted a second time with ethyl acetate and acidified. The product that separated as viscous oil was dissolved in 150 ml of ethyl acetate, dried over sodium sulfate, and treated with charcoal. After evaporation of the solvent the product was crystallized by cooling with ice and gradual addition of petroleum ether. mp 103–105 °C (Lit.[9]: 103,5–104,5 °C).

$C_{14}H_{20}N_2O_3$ (264,3)	Calc.	C 63,61	H 7,62	N 10,59
	Found	C 63,40	H 7,55	N 10,71

In the case of Gly NCA, the raw material which separated on acidification of the basic water phase, could not be crystallized[9].

Polymerization experiments Nos. 4, 5, and 8

After 24 h the precipitated polypeptide was filtered off, washed several times with diethyl ether, dried at 60 °C/12 mbar, and weighed. The dioxane filtrate was treated as described for **7**, but hydantoic acids were not found. For the ^1H NMR spectroscopic end group investigation the polypeptides were reprecipitated from dichloroacetic acid/dioxane and dried at 110 °C/10^{-2} mbar.

Benzyl-2-benzyl-5,5-diethyl hydantoate (**12**): 13,2 g (50 mmol) of 2-benzyl-5,5-diethyl hydantoic acid (**7**) and 6,5 g (>50 mmol) of benzyl chloride were stirred in 25 ml of dry dimethylformamide with 5,1 g (50 mmol) of triethylamine at 50 °C. After 24 h the reaction mixture was poured into 400 ml of ice-water, the oily product was extracted with chloroform, and the chloroform solution was dried over anhydrous calcium chloride. After removal of the solvent the residual product was crystallized by cooling and gradual addition of petroleum ether; mp 64–66 °C, yield 81%.

$C_{21}H_{26}N_2O_3$ (354,5)	Calc.	C 71,16	H 7,39	N 7,90
	Found	C 71,00	H 7,48	N 7,94

Z-Phenylalanine diethylamide (**11**): 15 g (50 mmol) of Z-L-Phe were mixed with 8,0 g (50 mmol) of diethoxy-(1,2,4-triazolin-1-yl)phosphine[17] in 30 ml of dry dimethylformamide and after 10 min 4,0 g (55 mmol) of diethylamine were added. The mixture was maintained at 40 °C for 4 h, then poured into 200 ml of 1 M HCl and the precipitated product was dissolved in 300 ml of ethyl acetate. The

separated ethyl acetate solution was washed with 50 ml of a 10% potassium carbonate solution, dried over sodium sulfate and concentrated to ca. 50 ml. The product was crystallized by cooling with ice and gradual addition of petroleum ether; mp 111–113 °C; yield 21%.

$C_{21}H_{26}N_2O_3$ (354,5)	Calc.	C 71,16	H 7,34	N 7,90
	Found	C 70,89	H 7,11	N 7,58

Experiments of Tab. 2

Exps. Nos. 1–4: 2,5 g (25 mmol) of glycine NCA and 0,9 g (8,2 mmol) of *N*-acetyl glycine NCA were dissolved in a mixture of 30 ml of dry dioxane and 10 ml of dry dimethylformamide. 0,5 ml (or 5 ml) of a 1 M dioxane solution of diisopropylamine or dicyclohexylamine were added and the reaction flask was stoppered with a freshly prepared P_4O_{10}-drying tube. After 5 min the reaction mixture was poured into a mixture of 2 ml of formic acid and 100 ml of dry diethyl ether. The precipitated polyglycine was filtered off, washed with dry diethyl ether and dried at 25 °C/10^{-2} mbar.

Exps. Nos. 5–10: These experiments were carried out as described above, but only in Nos. 7 and 10, a turbidity appeared after 12 h.

Synthesis of NCAs: D,L-Phe NCA was prepared by phosgenation of D,L-Phe in a mixture (1:1) of dry dioxane and methylene chloride at 50 °C. Gly NCA was obtained by conversion of Z-Gly-trimethylsilylester with an excess of freshly distilled thionyl chloride in dry chloroform[17]. Both NCAs were recrystallized twice in the presence of dry charcoal.

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