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Carbamate Ions as Propagating Species in N-Carboxy Anhydride Polymerizations

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ABSTRACT

Polymerizations of N-carboxy anhydrides of L-phenylalanine, γ-benzyl-L-glutamate, O-carbobenzoxy-L-tyrosine, L-leucine, and sarcosine, as initiated by primary, secondary, and tertiary amines in N_2 or CO_2 atmospheres and in the presence or absence of NaH, indicate that they proceed via carbamate salt intermediates. This conclusion is supported by radiotracer studies as well as by NMR studies of the initial products of NCA-amine reaction mixtures.
The "activated monomer" mechanism of strong-base initiated polymerizations is discounted on the bases that polypeptides are not formed in aprotic tertiary amine-initiated systems (hydantoins and diketopiperazines are obtained instead) and that methoxyl end groups are detected in polypeptides initiated with ^{14}C-labeled $NaOCH_3$.

INTRODUCTION

There are many interesting aspects of the polymerization of N-carboxyl anhydrides [1-4], most of which are incompletely

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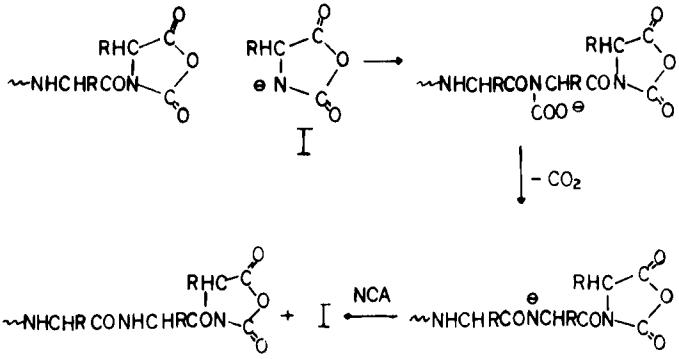
understood. These include the mechanisms of stereoselection and stereoelection [5-10], the influence of α-helical conformations [11] of growing chains on the reaction, the influence of monomer adsorption by polymer [12-15] and the mechanism of the reaction.

The polymerization of N-carboxy anhydrides (NCA's) is believed to proceed by either or two mechanisms, depending on whether the reaction is initiated by weak or strong bases. Polymerizations initiated by primary amines and some secondary amines are believed to proceed by the addition of NCA's to chains containing terminal amine units. Polymerizations initiated by strong bases, such as tertiary amines, secondary amines, and $NaOCH_3$, are thought to involve the addition of anions derived from NCA's to chain ends containing N-acyl-NCA moieties, viz.:



Evidence for the participation of species such as I in strong base-initiated polymerizations is provided by the relative activities of substituted pyridines as initiators [16], by the absence or low amounts of strong base initiator fragments bonded to polypeptides [17-19], by increases in molecular weight that occur when polymerization mixtures are concentrated [19-21], by the failure (in some cases) of tertiary amines to initiate the polymerization of N-substituted NCA's [16], and by the formation of 6-oxo-L-pipecolic acid when the N-carboxy anhydride of δ-benzyl L-α-aminoadipate is polymerized [22]. The "activated monomer" mechanism has been the basis of a method for preparing block copolymers [23] and silyl analogs of "activated monomers" have been described [24].

None of the evidence discussed above is unequivocal, unfortunately, and theoretical objections can be raised against certain

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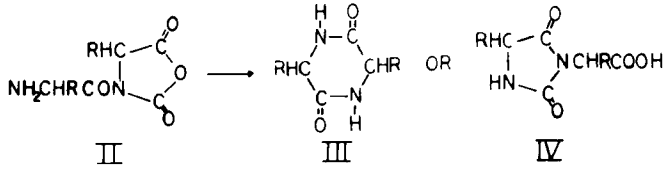
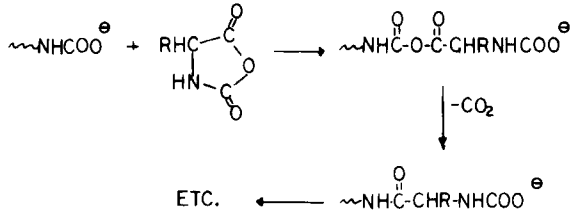
aspects of the "activated monomer" mechanism. The dimer II, which is generally proposed as the species first formed in such polymerizations, should be very prone to yield diketopiperazines (III) or hydantoin acetic acid (IV) derivatives. The behavior of



substituted pyridines reflects their reactivity toward proton donors; these need not necessarily be NCA's. It is conceivable that species such as I can be formed by strong bases and that they could initiate polymerization, but reaction of I with an NCA should yield a carbamate ion which should not be particularly prone to react with NCA to yield I. The participation of "activated monomers" in initiation and cyclization reactions does not prove that they are participants in propagation reactions. There are even suggestions that "activated monomers" and their analogs are capable of rearranging to isocyantes, which subsequently yield diketopiperazines and hydantoins [24, 25].

From time to time, carbamate ions have also been suggested as being the propagating species in NCA polymerizations [26-30], viz.:



Mechanisms involving propagating carbamate ions were abandoned when radiotracer studies failed to detect initiator fragments in polymers initiated by carbamate salts, metal alcoholates, and some hindered amines [17-19]. Zilkha and co-workers [31, 32] showed, however, that alkoxide ions do add to NCA's, and it

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would seem that the successful synthesis of depsipeptides [33] would also require this. NCA polymerizations initiated by recently developed catalysts are easily explained in terms of carbamate intermediates [9, 34-38], and related polymerizations also seem to involve such species [39]. The influence of CO_2 on NCA polymerizations also suggests that carbamate ions are important in such polymerizations.

The purpose of the present paper is to present results that lead us to believe that both weak and strong base-initiated polymerizations of N-carboxy anhydrides proceed by a common mechanism in which the propagating species are carbamate ions rather than free amines or N-acyl-NCA moieties.

EXPERIMENTAL

N-Carboxy Anhydrides

NCA's were prepared by adding liquid phosgene to amino acid suspensions in dioxane at 60°C until clear, homogeneous solutions were obtained. A slight excess of phosgene was added and the solution was then flushed to remove excess phosgene and HCl. The dioxane was then removed in vacuo at 60°C. The viscous residue was taken up in an equal volume of ethyl acetate, and this solvent was also removed in vacuo at 60°C. The solid residue was recrystallized repeatedly from ethyl acetate-hexane until the chloride content [40] of the product was below 0.01% (0.05% in one instance). The crystals were dried in vacuo at 40°C. The pure NCA's were stored in evacuated containers at -30°C. The following melting points were obtained for the NCA's prepared: O-carbobenzoxy-L-tyrosine, 104°C dec.; γ-benzyl-L-glutamate, 95°C; L-leucine 75°C dec.; L-phenylalanine, 90°C dec.; L-sarcosine, 99 to 100°C dec.

Solvents

Dioxane and benzene were stored over 4A Molecular Sieves for several weeks and then refluxed and distilled over NaH. Ethyl acetate and hexane were dried over Molecular Sieves.

Initiators

Amines were stored over BaO and were distilled prior to use. Solutions of amines in dioxane or benzene were stored under nitrogen

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and over 4A Molecular Sieves. The sodium salts of amines were prepared by treating purified amines with NaH, followed by removal of excess amine in vacuo and washing of the salt with dry benzene. Sodium methoxide solutions were prepared by adding freshly cut sodium to anhydrous methanol (1 g/50 ml), followed by dilution of the resulting solution with fresh methanol and dry benzene. The resulting solution was stored under dry nitrogen.

Polymerizations

Polymerization experiments were conducted in glassware that had been heated at 125°C for 24 hr and that was assembled while being purged in a stream of dry nitrogen. The nitrogen was passed through 4A Molecular Sieves prior to use. Solutions of monomers in dioxane (2.0 to 2.5 wt%) were prepared under nitrogen using a glove bag and were charged with initiator. Reactions were allowed to proceed at ambient temperature under nitrogen. The course of reaction was monitored by IR spectroscopy. Polymerization mixtures were poured into ether to isolate the polymers. These were reprecipitated several times from dioxane into ether. When ^{14}C measurements were to be made, the polymers were reprecipitated as many as 10 times. Intrinsic viscosities of the polymers in dichloroacetic acid were determined using a wide bore Ubbelhode-type viscometer.

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Radioactivity Measurements

Initiator and polymer activities were determined by scintillation counting using a Beckman β-Mate instrument and a dioxane-POP-POPOP cocktail. NSC Solubilizer was used when necessary to obtain homogeneous solutions. The ESR method was used to determine counting efficiency.

Nuclear Magnetic Resonance Studies

NMR studies of amine-NCA reaction mixtures in $CDCl_3$ were conducted with a Varian T-60 spectrometer. The general procedure was to add NCA to the amine solution and then record the spectrum of the mixture after 20 min. Polymer spectra were recorded using CF_3COOH as solvent. The ^{13}C-spectrum was obtained using a Varian CFT-20 spectrometer, courtesy of Dr. John Rieger, Varian Associates. This spectrum was recorded using CO_2-saturated $CDCl_3$ as a solvent and with an atmosphere of CO_2 above the

solution. (When air was allowed to enter the tube, a precipitate began to form. This was probably the diketopiperazine derivative.)

RESULTS AND DISCUSSION

Our preference for a mechanism proceeding by carbamate ion additions to NCA's is based on the following evidence.

1. PMR and CMR studies on the initial products of diethylamine-NCA reaction mixtures indicate that carbamate salts are formed and that they are reasonably stable in solution.
2. Tertiary amines fail to initiate NCA polymerizations in carefully purified systems, but polymerization occurs immediately upon the addition of small amounts of methanol or water. Similar results have been obtained by others [41, 42].
3. Polymerizations initiated by 1°, 2°, or 3° amines at NCA/amine ratios greater than 100 tend to terminate at low conversion when conducted in N_2-swept systems, and large amounts of diketopiperazines and hydantoin derivatives are formed. However, polypeptides are obtained in high yield in CO_2 saturated systems.
4. Addition of NaH to amine-initiated polymerization systems causes an immediate rate enhancement and the formation of high molecular weight polymers.
5. Radiotracer and spectroscopic studies indicate that methoxyl groups are present in polypeptides obtained from $NaOCH_3$-initiated polymerization reactions, in contrast to earlier reports [17, 18].

PMR and CMR Studies of Amine-NCA Reaction Mixtures

Figure 1 shows the 60 MHz PMR spectrum of L-phenylalanine NCA and the spectra of reaction products derived from this NCA and diethylamine. The spectra of the NCA-amine reaction products were obtained by first recording the spectrum of the product derived from a 3:1 amine/NCA mixture, followed by adding additional NCA to obtain various amine/NCA ratios, and then recording their spectra. The presence of two types of ethyl groups is clearly evident in the spectra of the 1:3, 2:3, and 1:1 reaction products; these are present in approximately equal amounts in the spectra of the 2:3 and 1:1 mixtures. Resonance is observed at 5.4 ppm in the spectra of all the mixtures, and its intensity is approximately the same as that

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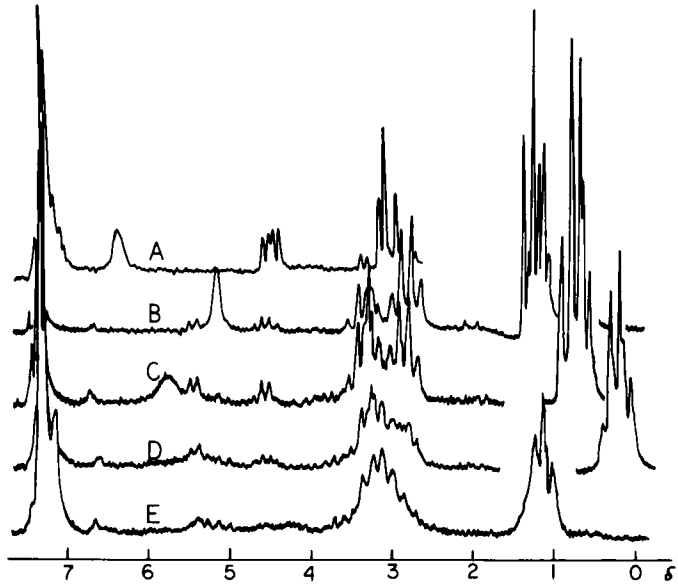
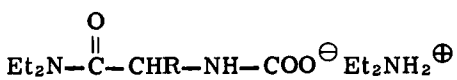


FIG. 1. 60 MHz PMR spectra of L-phenylalanine NCA–diethylamine reaction mixtures. Anhydride/amine ratios are: A, pure NCA; B, 1/3; C, 2/3; D, 1/1; and E, 2/1.

of methine proton resonance at ~4.5 ppm in the spectra of the 2:3 and 1:1 mixtures. We attribute this resonance to the NH proton of carbamate salt end groups.

Figure 2 shows that the same results are obtained when γ-benzyl-L-glutamate NCA-diethylamine reaction mixtures are studied. Two types of ethyl groups, present in equal amounts, are clearly indicated in the spectrum of the 2:1 reaction mixture. One of these is lost when the reaction mixture is worked up and the product is recrystallized. Also lost during workup is the structure responsible for the resonance observed at 5.6 ppm.

These results are most easily explained if carbamate salts result from the reactions of diethylamine with NCA's. Thus reaction of an NCA with two molecules of diethylamine should yield



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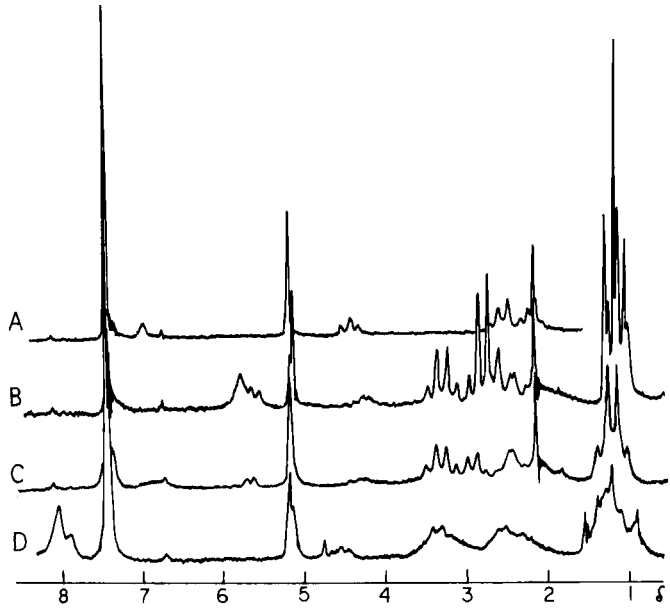

FIG. 2. 60 MHz PMR spectra of γ-benzyl-L-glutamate NCA—diethylamine reaction mixtures. Anhydride/amine ratios are: A, pure NCA; B, 1/1; C, 2/1; D, product isolated from C.

This structure contains two types of diethylamino moieties. Subsequent reaction of this structure with additional NCA should retain the integrity of these moieties:

$$Et_2N(COCHRNH)_n\,COCHRNHCOO^{\ominus}\,Et_2NH_2^{\oplus}$$

However, acidification of the carbamate salt during workup should result in a product that would not contain the diethylamino moiety responsible for resonance at ~2.9 and 1.2 ppm, but only the one responsible for resonance at ~3.4 and 1.3 ppm. In addition, the product would not resonate at ~5.6 ppm.

Additional support for the presence of carbamate salts in these reaction mixtures was obtained by treating a 1:1 phenylalanine/Et_2NH reaction mixture with benzyl chloride followed by isolation of the reaction product and examination of its PMR spectrum. The presence of the benzyl carbamate group is indicated by resonances at 4.8, 5.3, and 7.6 ppm. The relative area of the resonance due to phenyl protons of the phenylalanine unit is twice

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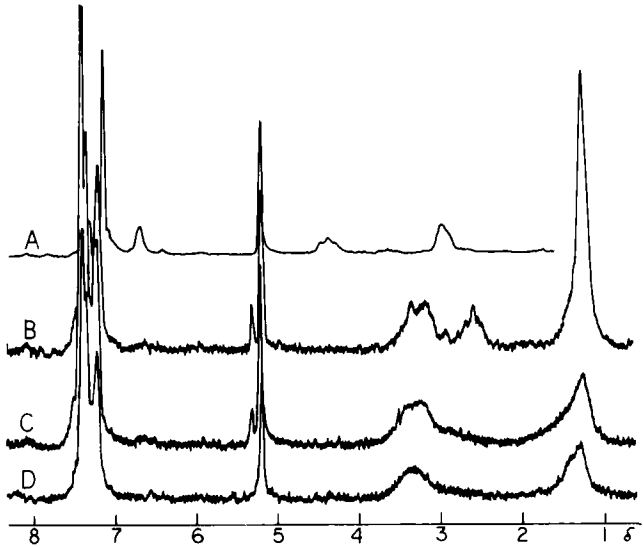

FIG. 3. 60 MHz PMR spectra of O-carbobenzoxy-L-tyrosine NCA and of reaction products in hexamethylenediamine. Anhydride/diamine ratios are: A, pure NCA; B, 1/1; C, 2/1; and D, 3/1.

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that due to phenyl protons of the benzyl group, as would be expected for product derived from a 1:1 NCA/amine reaction mixture.

Figure 3 shows the 60 MHz PMR spectra of reaction products obtained from O-carbobenzoxy-L-tyrosine NCA and hexamethylene diamine. The resonance observed at 5.3 ppm decreases in relative intensity as the anhydride-amine ratio increases. This resonance is also attributed to a carbamate salt.

Figure 4 shows the 20 MHz CMR spectrum of a 1:1 phenylalanine NCA/Et_2NH reaction mixture. Its most significant features are two intense methyl carbon resonances ($\delta c \sim 15$ ppm), eight methylene carbon resonances (38 to 45 δc), two of which are very intense (attributed to methylene carbons of Et_2N moieties), eight aromatic carbon resonances (125 to 135 δc), several C-1 aromatic proton resonances at ~ 141 δc in addition to a resonance that may be due to a carbonyl carbon, and two additional carbonyl carbon resonances at 158 and 180 δc. The spectrum is consistent with the following average structure:

$$(CH_3CH_2)_2NCOCH(CH_2\phi)-NH-CO-CH(CH_2\phi)-COO^{\ominus}\overset{\oplus}{N}H_2(CH_2CH_3)_2$$

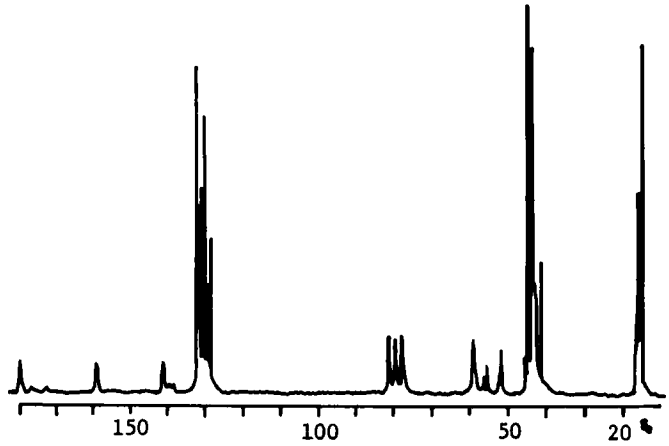

FIG. 4. 20 MHz CMR spectrum of a 1:1 L-phenylalanine–diethylamine reaction mixture ($CDCl_3$ saturated with CO_2).

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PMR studies on tertiary amine/NCA reaction mixtures were not very instructive, except in the negative sense that no evidence for the presence of "activated monomers" was obtained.

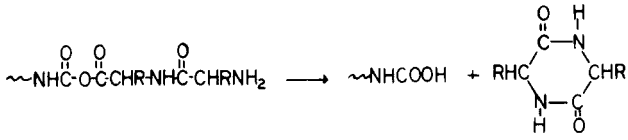
The Role of Carbon Dioxide

Other workers have noted that carbon dioxide enhances the rates of NCA polymerizations, and it has been suggested that this is due to the formation of acidic species that function as catalysts. If propagation is via carbamate ions, an alternative explanation is that CO_2 diminishes the tendency of carbamate salts to decompose. The following equilibria can be expected to occur in amine-initiated polymerizations:

$$\sim NHCOO^{\ominus}\ \overset{\oplus}{N}H_2R_2 \rightleftharpoons \sim NHCOOH + R_2NH \rightleftharpoons \sim NH_2 + R_2NH{+}CO_2$$

A high concentration of CO_2 should force the equilibrium to the left and thereby favor carbamate ion stability. This should lead to enhanced rates, higher molecular weight polymers, and lower yields of hydantoin and diketopiperazine byproducts. Such

by-products may result from reactions of terminal amine units with neighboring carbamoyl anhydride structures, viz.:



Our studies have shown that L-phenylalanine NCA shows a strong tendency to yield diketopiperazine and hydantoin derivatives in reactions initiated with Et_3N or Et_2NH in $CHCl_3$ or dioxane at room temperature when CO_2 is rapidly swept out of the reaction mixture, but that polypeptides are the principal products in CO_2 saturated systems.

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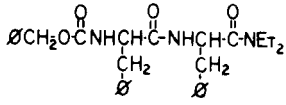
Formation of a Derivative of the Carbamate Salt

To obtain chemical evidence for the presence of carbamate ions in NCA-secondary amine reaction mixtures, L-phenylalanine NCA was slowly added to a solution of diethylamine in dioxane at room temperature until the NCA/amine ratio was unity. The reaction mixture was then treated with benzyl chloride and an exothermic reaction was noted. The product isolated from this reaction mixture was washed several times with methanol. Its PMR spectrum is shown in Fig. 5. The presence of a benzyl ester is indicated by resonances at 7.5 and 4.6 δ. The relative intensities of the aromatic proton resonances due to the benzyl (7.5 δ) and phenyl (7.2 δ) groups are roughly 1:2, in keeping with the following overall structure:



The Use of NaH in Initiator Systems

When we became convinced that NCA polymerizations proceed via carbamate salt intermediates, efforts were made to improve

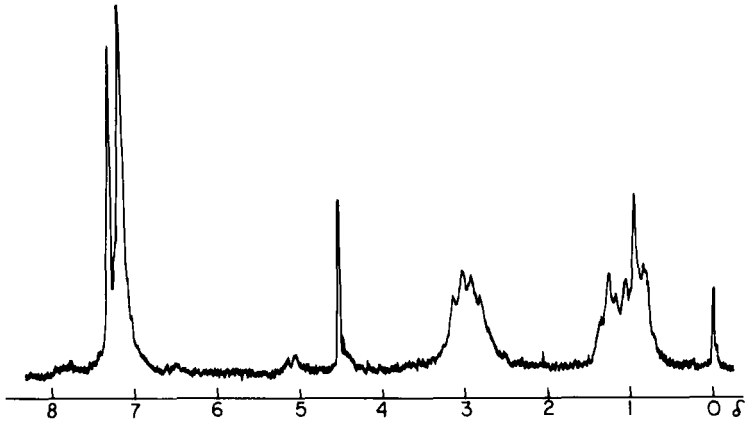


FIG. 5. 60 MHz PMR spectrum of the benzyl carbamate derived from the reaction product of L-phenylalanine NCA and diethylamine.

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the stability of such species in the polymerization systems. One approach to accomplish this was to provide an aprotic counterion for the carbamate ion. Sodium hydride was therefore added to various polymerization mixtures; the effects obtained were spectacular. For example, when the polymerization of O-cbzo-L-tyrosine NCA was initiated with hexamethylene diamine, a slow reaction yielding mostly the diketopiperazine and low molecular weight polymers ensued and terminated after 50% conversion. In contrast, a high molecular weight polymer (DP $\sim$ 200) was obtained under the same conditions when a product derived from the diamine and NaH was used for initiation.

This behavior is also noted in tertiary amine-initiated reactions. Figure 6 (Curve A) shows the rate of disappearance of O-carbobenzoxy-L-tyrosine NCA when initiated by Et_3N (anhydride/amine = 100) in dioxane at room temperature. The reaction occurs slowly, yields low molecular weight products, and terminates before conversion is complete. However, addition of sodium hydride (M/NaH = 2 to 5, although all NaH is probably not utilized) to the reaction mixture after the limiting conversion has been obtained causes a rapid reaction (Curve B) that yields high molecular weight polymers, $[\eta]$ = 1.9. Identical behavior is observed in γ-benzyl-L-glutamate NCA-triethylamine reactions (Fig. 7). It should be noted that NaH alone does not initiate the polymerizations of NCA's. We believe that products derived from NCA-tertiary amine reactions react with NaH to yield the initiating species.

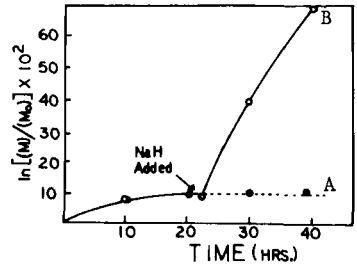

FIG. 6. Effect of adding NaH to a O-carbobenzoxy-L-tyrosine NCA-triethylamine reaction mixture.

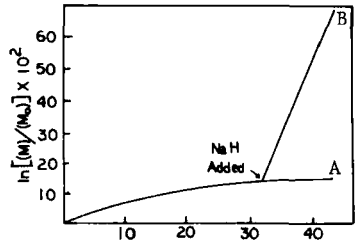

FIG. 7. Effect of adding NaH to a γ-benzyl-L-glutamate NCA—triethylamine reaction mixture. The abscissa is time in hours.

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Detection of Methoxyl Groups in Polymers Initiated with $NaOCH_3$

The results obtained in the radiotracer studies conducted by Goodman and Peggion [17-19] are inconsistent with an NCA polymerization mechanism that would involve propagating carbamate ions. It seemed important, therefore, to reinvestigate this aspect of the reaction. Polymerizations of γ-benzyl-L-glutamate NCA, sarcosine NCA, and L-leucine NCA in dioxane (first two) and DMSO (leucine) were initiated by ^{14}C-labeled sodium methoxide-methanol solutions [2.54×10^9 d/(min)(mole)]. The copolymerization of O-carbobenzoxy-L-tyrosine NCA with γ-benzyl-L-glutamate in dioxane was also initiated by the methoxide reagent. The polymers obtained were carefully purified and were counted. The NMR spectra of the polysarcosine (Figure 8) and polyleucine (Figure 9) were also recorded. These clearly indicate the presence of

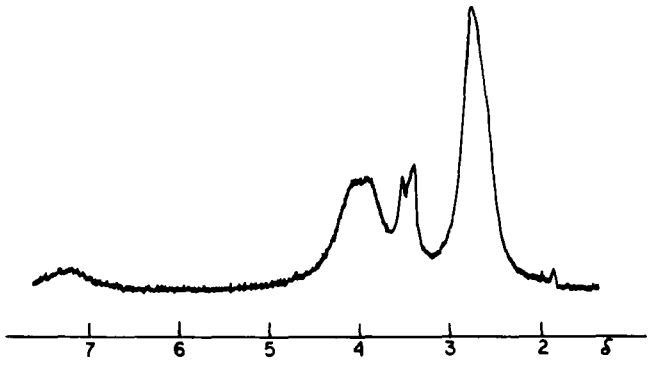

FIG. 8. 60 MHz PMR spectrum of poly(L-sarcosine) obtained from $NaO^{14}CH_3$-$HO^{14}CH_3$ initiated polymerization in dioxane. Solvent: CF_3COOH.

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methoxyl protons at ~3.5δ. All the polymers were found to contain appreciable quantities of methoxyl groups.

The polymers containing γ-benzyl-L-glutamate contained approximately one CH_3O group per molecule based on their radioactivity and their molecular weights as estimated by intrinsic viscosity measurements. [Homopolymer: $\overline{M}_v \sim 91{,}000$, activity = 1.98×10^4 d/(min)(g). Copolymer: $\overline{M}_v \sim 108{,}000$, activity = 1.24×10^4 d/(min)(g)]. However, a control experiment in which inactive poly(γ-benzyl-L-glutamate) was allowed to stand for 24 hr in the presence of $NaOCH_3$-CH_3OH reagent yielded a polymer having an activity of 0.63×10^4 d/(min)(g). It is apparent that transesterification of $NaOCH_3$ with benzyl ester units on the polymer occurs to a significant extent and that experiments of this type are best done with NCA's that are devoid of functional side groups. Low molecular weight (~600) polysarcosine was obtained. Its radioactivity [1.18×10^5 d/(min)(g)] was lower than expected for one CH_3O unit to be present per molecule, but the NMR spectrum of the polymer clearly indicated the presence of CH_3O-type protons.

The molecular weight of the polyleucine sample prepared has not been determined, but its specific activity was 2.1×10^4 d/(min)(g).

Additional work needs to be done in this area, but there seems to be little doubt that methoxide ion is capable of adding to NCA's to generate carbamate or carboxylate ions, which can be the sites of subsequent propagation.

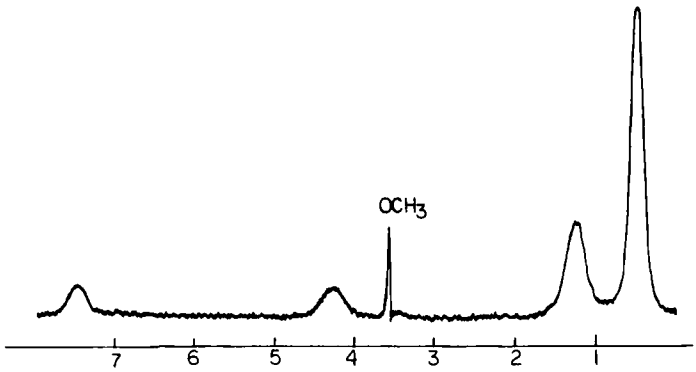

FIG. 9. 60 MHz PMR spectrum of poly(L-leucine) obtained from $NaO^{14}CH_3$-$HO^{14}CH_3$ initiated polymerization in DMSO. Solvent: CF_3COOH. The abscissa is in δ.

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SUMMARY

On the basis of results presented here and after a careful reconsideration of previously reported results concerning NCA polymerizations, we believe that such polymerizations proceed via propagating carbamate ions. We suggest that if "activated monomers" are present in such polymerization systems, they are responsible for the formation of hydantoin and diketopiperazine derivatives.

High molecular weight polymers are believed to be obtained from tertiary amine-initiated polymerizations of NCA's simply because small amounts of protonic cocatalysts are present in systems that yield polymers and because tertiary amine salts of carbamic acids are relatively stable. In this connection, it is interesting to note that Mori and Iwatsuki [43] have recently found that combinations of tertiary amines with primary and secondary amines, mercaptans, and alcohols are very effective initiation systems for NCA polymerizations. Low molecular weight polymers are believed to result from primary amine-initiated polymerizations because of the tendency of salts of carbamic acids with such amines to decompose, yielding CO_2 and primary amines. The latter are more likely to participate in termination reactions than carbamate ions. Of course, metal salts of carbamic acids are very stable, and polymerizations involving such species are likely to be very

successful. The considerable current activity along these lines indicates that others have also reached this conclusion.

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