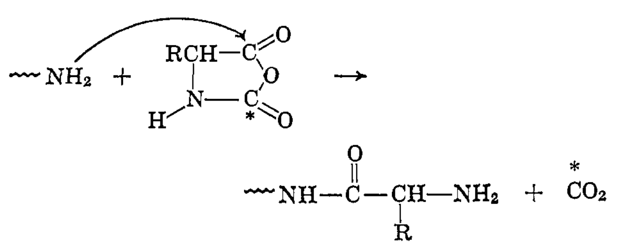
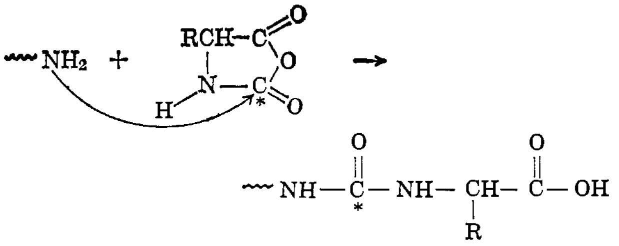


Attack at C^{-2} retains the C^{14} in the polymer.



remaining in the polymer is directly equal to the per cent of C-2 attack.

Polymerization of the C^{14}-labeled NCA was initiated in tetrahydrofuran by *n*-hexylamine. Results are presented in Table II. Radioactivity measurements were carried out on polymer and NCA in dimethylformamide solutions. Only about 0.15% of the C^{14} content in the NCA remained in the polymer. In other words, only one in every 670 carbonyl attacks was at C-2. Since the $\overline{DP}_w$ is 59, this means that fewer than one in ten chains was terminated by C-2 attack.

Table II. Polymerization of C^{14}-Labeled (at 2 Position) γ-Benzyl-L-glutamate NCA[a,b]

Initiator	A/I	$\overline{DP}_w$	kp, l./mole sec	Polymer radioactivity, (counts/sec mole of amino acid residue)
n-Hexylamine	50	59	0.0022	1.0×10^6
Sodium methoxide[c]	50	255	1.75	1.7×10^5

[a] Solvent tetrahydrofuran. [b] Radioactivity of NCA, 7.0×10^8 counts/sec mole. [c] Initiator added in methanol solution.

With aprotic initiated polymerization as with the amine mechanism, attack at the C-2 carbonyl of the NCA results in termination. A similar, but more complex, analysis of the Bamford–Szwarc mechanism shows that C-2 attack produces retention of C^{14} in the polymer.

The labeled NCA was polymerized in tetrahydrofuran with sodium methoxide as an initiator (Table II). Radioactivity measurements, performed as before, showed only 0.025% of the NCA radioactivity content to be in the polymer. This indicates that only one in every 4000 carbonyl attacks was at C-2 and fewer than one in fifteen chains was thus terminated by C-2 attack.

General Conclusions

Our investigations lead us to conclude that the polymerization of N-unsubstituted NCA compounds can be described by two mechanisms. For initiators which are weakly basic but good nucleophiles (in practice only primary amines) the "normal" amine mechanism applies very well. Strong base initiated polymerization proceeds by the Bamford–Szwarc activated-monomer mechanism. Tertiary amines although not strong bases are included in this category because they cannot act as nucleophiles. Secondary amines lie in a region of basicity and nucleophilicity where the two mechanisms are both operative. The structure of the secondary amine and the nature of the solvent determine which predominates.

Termination appears to be negligible. Reaction at C-2 is minor in both mechanisms. A future report from our laboratories will be concerned with the polymerization mechanism of N-substituted NCA compounds.

Acknowledgment. We thank the Diamond Alkali Co. and the National Institutes of Health, Grant No. AM 03868, for their liberal support.

Mechanism of N-Carboxyanhydride (NCA) Polymerization in Dioxane. Initiation by Carbon-14-Labeled Amines[1]

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Abstract: The polymerization of γ-benzyl-L-glutamate N-carboxyanhydride (NCA) was studied in dioxane using C^{14}-labeled isopropyl-, diisopropyl-, and methyldiisopropylamine as initiators. All the radioactivity was found in the polymers only with isopropylamine initiation. Diisopropylamine leads to polymers containing only a few per cent of the initial activity, and methyldiisopropylamine leads to inactive polymers. These results support the hypothesis that the NCA polymerization in dioxane mainly proceeds *via* simple "primary amine" mechanism with isopropylamine, and *via* "strong base" mechanism with methyldiisopropylamine. Both of these mechanisms appear to operate simultaneously in the case of diisopropylamine.

According to the literature[3] the polymerization of NCA compounds initiated by amines or bases may proceed according two different mechanisms, *i.e.*, (1) normal "primary amine" polymerization and

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(1) Independent work on the NCA's polymerization initiated by radioactive initiators was carried out by Goodman and Hutchison: *J. Am. Chem. Soc.*, **88**, 3627 (1966). Their results complement ours and their conclusions are in agreement with our findings.

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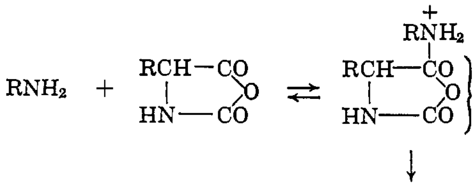
(3) M. Szwarc, *Advan. Polymer Sci.*, **4**, 1 (1965).

(2) "strong base" polymerization. Mechanism 1 is normally operative when primary amines are used as initiators. It consists of successive nucleophilic attacks of amino groups on 5-carbonyl groups of NCA molecules. According to this mechanism all the polymeric chains must contain at their ends a fragment of the initiator. Furthermore the number-average degree of polymerization ($\bar{P}_n$) must be equal to the ratio of the initial concentrations of monomer and initiator, *i.e.*, $\bar{P}_n = A/I$.

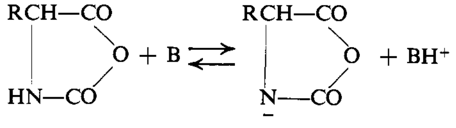


$$RNHCOCHRNH_2 + CO_2 \quad (1)$$

$$RNHCOCHRNH_2 + NCA \longrightarrow RNHCOCHRNHCOCHRNH_2 + CO_2 \text{ etc.} \quad (2)$$

Studies on polymerization kinetics and on molecular weight distributions of polymers[4,5] support the above mechanism.

Mechanism 2 is operative when tertiary amines, sodium methoxide, sodium hydroxide, or other strong bases are used as initiators. In this case polymers are obtained having $\bar{P}_n \gg A/I$, and high reaction rates are observed. Taking into account that N-substituted NCA compounds (like sarcosine) do not undergo polymerization by tertiary amine initiation, the following acid–base equilibrium was suggested by Bamford[6] as the initial step



(3)

where B is the initiating base. From the anion NCA⁻ propagation takes place, the detailed mechanism being still under investigation.

If initiation according to reaction 3 is operative, no fragments of the initiator should be found in the polymer chains.

It should be expected that primary and secondary amines might initiate the NCA polymerization by both the two above mechanisms, their relative importance being determined by the base strength and steric requirements of the initiating amine. On the other hand tertiary amines, owing to their proton deficiency, should initiate the polymerization only by mechanism 2. We have already shown that in dioxane isopropylamine behaves mainly as a primary amine type initiator,[4] while diisopropylamine behaves mainly as a strong base type initiator.[7–9]

This work deals with the use of C^{14}-labeled isopropyl-, diisopropyl-, and methyldiisopropylamine in the polymerization of γ-benzyl-L-glutamate NCA in dioxane, in order to determine the amount of initiator incorporated in polymeric chains.

Experimental Section

Monomer. γ-Benzyl-L-glutamate NCA was prepared from γ-benzyl-L-glutamate and phosgene according to the literature.[10]

Solvents. Dioxane was purified by Fieser's procedure,[11] dried over sodium, and distilled immediately before use. Dimethylformamide (reagent grade) was dried over P_2O_5 and then fractionally distilled under reduced pressure. Petroleum ether (bp 40–60°) and absolute methanol, both reagent grade, were used without further purification.

Labeled Initiators. Carbon-14 isopropyl-, diisopropyl-, and methyldiisopropylamine hydrochlorides were prepared as previously described.[12] The free C^{14} amines were obtained by exchange between the labeled hydrochlorides and the corresponding unlabeled pure amines. Radioactive standardization was carried out by distilling the labeled amines into aqueous solution of hydrochloric acid. The corresponding hydrochlorides were recovered, dried, and finally dissolved in known amounts of absolute ethanol. Known volumes of these solutions were mixed with the phosphor solution. The latter consisted of 5 g of 2,5-diphenyloxazole and 0.5 g of 1,4-bis[2(5-phenyloxazolyl)benzene] in 1 l. of toluene. Under the above conditions, the specific activities of the amines were the following: isopropylamine 65.3 μcuries/mmole; diisopropylamine 3.02 μcuries/mmole; and methyldiisopropylamine 8.74 μcuries/mmole.

Radioactivity Measurements. The radioactivity determinations were performed at −20° using a SELO scintillation counter with superscaler at 840 v and bias 5 v. Weighed samples of polymer were dissolved in a known volume of anhydrous dimethylformamide. These solutions were mixed with the phosphor solution and then the radioactivity was determined as described above.

Polymer Preparation. The polymers were prepared by NCA polymerization in dioxane at 25° with proper *A/I* ratios. The radioactive initiators were introduced by direct distillation into the reaction mixtures which were cooled to −190°. The exact amounts of the initiators were determined by counting the total radioactivity of the polymerization mixtures. The polymers were recovered by direct precipitation into petroleum ether under vigorous stirring. The polymers were redissolved in CH_2Cl_2, treated with an excess of unlabeled initiating amine, and then reprecipitated by pouring into petroleum ether. This procedure was repeated several times in order to avoid any physical absorption of the radioactive initiators on the polymers. The final polymers were washed with petroleum ether and dried under vacuum at 50° to constant weight.

Physical Adsorption Checks. In order to determine the physical adsorption of the labeled initiators on the polymers, preliminary checks were carried out before the polymerization experiments. Labeled amines were added to solutions of preformed polymers, in amounts corresponding to those of polymerization experiments. The polymers were then precipitated and redissolved several times according to the above procedure. The results show that the physical adsorption of the labeled amines on the polymers can be reduced to about 0.5% of the initial amounts.

Molecular Weight Determinations. The molecular weights of poly-γ-benzyl-L-glutamate samples were determined from intrinsic viscosity measurements in dichloroacetic acid using Doty's relation.[13] An Ubhelode viscometer was used.

Results and Discussion

The results of polymerization experiments of γ-benzyl-L-glutamate NCA in dioxane by C^{14}-labeled initiators are shown in Tables I and II. From these data it appears that the amines exhibit a different behavior.

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Table I. Polymerization of γ-Benzyl-L-glutamate NCA in Dioxane using C^{14}-Labeled Initiators

Experiment[a]	Initiator	A/I	$\bar{M}_w$	% radioactivity in polymer
P 2/c 14	Isopropylamine	16	53,000	100.0
S 1/c 14	Diisopropylamine	24	265,000	10.9
T 1/c 14	Diisopropylamine	15	152,000	11.4
U 1/c 14	Diisopropylamine	139	340,000	18.5
U 5/c 14	Diisopropylamine	330	190,000	16.0
V 1/c 14	Diisopropylamine	162	270,000	16.7
T 2/c 14	Methyldiisopropylamine	12	188,000	0.0
U 2/c 14	Methyldiisopropylamine	100	377,000	0.5

[a] In these experiments we used monomers deriving from various preparations. For this reason no correlation between A/I and $\bar{M}_w$ was found.

Table II. Extraction Experiments with Hot Methanol on Radioactive Polymers Prepared by Diisopropylamine Initiation

Experiment	A/I	$\bar{M}_w$	% radioactivity in polymer	% radioactivity after extraction by CH_3OH
T 1/c 14	15	152,000	10.9	2.1
U 1/c 14	139	340,000	18.5	9.5
U 5/c 14	330	190,000	16.0	0.0
V 1/c 14	162	270,000	16.7	7.5

(i) Initiation by C^{14}-Isopropylamine. With this initiator all the initial activity was found in the polymer. This fact agrees with previous literature[4,5] indicating that isopropylamine mainly behaves as a "primary amine type" initiator, according to mechanism 1. However it must be pointed out that the errors in counting methods are at least 4–5%. As a consequence it is impossible to exclude the presence of a few per cent of unlabeled high molecular weight polymer molecules, formed according to mechanism 2. A small numerical portion of such molecules may constitute a remarkably high weight percentage of the total polymeric mixture. It follows that from these results no evidence exists to exclude completely the operation of mechanism 2 in the NCA's polymerization initiated by isopropylamine in dioxane.

(ii) Initiation by C^{14}-Diisopropylamine. As may be seen from Table II, only a fraction of the radioactive initiator was found in the polymers. This result alone cannot rule out the simple primary amine polymerization mechanism. In fact a reaction scheme

$$\mathrm{RNHR + NCA \xrightarrow{k_i} RRNCOCHRNH_2 + CO_2}$$

$$\mathrm{RRNCOCHRNH_2 + NCA \xrightarrow{k_p} RRN(COCHRNH)_2H + CO_2\ etc.}$$

where k_p is much larger than k_i should lead to some incorporation of the initiator in the polymer chains; the higher k_p/k_i, the lower will be the quantity of the initiator consumed in the production of polymer. However the presence of mechanism 1 alone can be rejected on the basis of kinetic data. In fact, by diisopropylamine initiation in dioxane both k_p and molecular weight of the polymer are much higher than those observed using primary amines as initiators.[7] From these findings it can be concluded that amino groups are not the propagating species when diisopropylamine is used as the initiator in dioxane. As a consequence the results of Table I can be interpreted by supposing that, with this initiator, the two polymerization mechanisms are operative at the same time, the first one leading to radioactive, low molecular weight species, and the second one leading to nonradioactive, high molecular weight species. This interpretation seems to be supported by extraction experiments with hot methanol on the radioactive polymers. Hot methanol dissolves polymers with $\bar{P}_n \lesssim 30$.[4] As may be seen from Table II, almost all the radioactivity was extracted in some cases by this solvent. This indicates that low molecular weight species contain a fragment of the initiator at their ends, the residual high polymer being almost nonradioactive.

(iii) Initiation by C^{14}-Methyldiisopropylamine. With such an initiator, practically no radioactivity was found in the polymer. This means that the initiation step proceeds by mechanism 2. Such a result is to be expected since tertiary amines are aprotic bases, and a reaction which involves transfer of a proton from the base cannot occur.

Conclusions

The experiments with labeled initiators demonstrated that the γ-benzyl-L-glutamate NCA polymerization in dioxane with primary amine mainly proceeds by simple or "normal" amine initiation. In the case of diisopropylamine the results are difficult to be interpreted. Both kinetic considerations and extraction experiments seem to suggest that there is a competition between the two initiation mechanisms. With tertiary amine only mechanism 2 appears to be operative.

The above conclusions apply to the NCA polymerization in dioxane. From previous kinetic studies it appears that changing the solvent medium may change the relative importance of the two mechanisms when these are operating simultaneously.[14] Further results on this subject will be reported elsewhere.

Acknowledgment. The authors wish to thank Professor E. Scoffone for the continuous suggestions and stimulating discussions during this work.

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