to form secondary alkyl halides. In particular, none was detected in cleavage of propyl butyl ether carried to extensive conversions.

The reactivity in ether cleavage of propyl relative to ethyl, 1.00 (Table VI), is large. The value 0.65 (Table VI) is about the average for a group of halide exchange reactions.[13] In general, the value for propyl is distinctly less than 1.0.[12] Our value depends primarily upon the cleavage of ethyl butyl ether, the analyses for which were performed both by density and by vapor phase chromatography (Table II). The reactivity of propyl in a reaction which also involves a positively charged species, that of alcohols with hydrogen bromide in aqueous phenol,[9] is also large, 0.87. In fact, and not surprisingly, this reaction parallels the ether cleavage rather closely. It has been proposed that the relative reactivity of propyl in general should be about $^2/_3$ on the basis that rotation about the central carbon–carbon bond in propyl compounds would lead the terminal methyl group to obstruct the entering groups in $^1/_3$ of the possible configurations.[15] The effect would appear in the pre-exponential frequency factor.[15,16]

Relative Rates of Reaction of Ethers and Alcohols with Hydrogen Bromide.—Table I presents the first direct data on the relative rates of cleavage of the alkyl–oxygen bond in ethers and in alcohols. Ethers appear to be less basic than alcohols.[17] At concentrations of hydrogen bromide high enough to protonate both ether and alcohol completely, the relative reactivity would be that of the hydronium ions. With decreasing acidity, the ratios of hydronium ions would involve the relative basicities, and the alcohol would become relatively more reactive. The observed data fit this scheme. At a total mole fraction of hydrogen bromide of 0.63, butyl ether reacts 7.5 times as fast as propyl alcohol; at a mole fraction of 0.33, 1.4 times faster. At the higher mole fraction, butyl ether reacts about 12 times faster than isopropyl alcohol. To within the rather low precision of the data, the computed relative reactivities of propyl and isopropyl alcohols are the same as those of propyl and isopropyl groups in propyl isopropyl ether, 0.8 (Table VI). The ether–HBr medium is somewhat more favorable to nucleophilic displacement than hydrogen bromide in aqueous phenol in which isopropyl alcohol reacts 2.6 times faster than propyl alcohol (second series in Table VI).

Acknowledgment.—This research was supported by a grant from the National Science Foundation.

[15] N. Ivanoff and M. Magat, *J. chim. phys.*, **47**, 914 (1950).

[16] See also ref. 13, section (C) and (D).

[17] J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 80; J. Hine and M. Hine, THIS JOURNAL, **74**, 5266 (1952); E. F. Pratt and K. Matsuda, *ibid.*, **75**, 3739 (1953).

EVANSTON, ILLINOIS

COMMUNICATIONS TO THE EDITOR

THE POLYMERIZATION OF γ-BENZYL-L-GLUTAMATE N-CARBOXY ANHYDRIDE

Sir:

In a recent communication[1] Doty and Lundberg have claimed that during the primary-amine-initiated polymerization of γ-benzyl-L-glutamate N-carboxy anhydride in dioxane solution at 25° two successive stages may be recognized. Using *n*-hexylamine as initiator these authors concluded that the initial part of the polymerization (up to a degree of polymerization of approximately 8) is comparatively slow, with a rate constant of $5–7 \times 10^{-3}$ mole^{-1} l. sec.$^{-1}$. Following this stage in the growth of the polymer an acceleration was reported, the final rate constant being approximately 3×10^{-2} mole^{-1} l. sec.$^{-1}$. The acceleration was correlated with the adoption by the growing polymer chain of an α-helical configuration at a degree of polymerization of about 8. A similar effect, rather smaller in magnitude, was obtained with the DL-anhydride.

We have previously reported[2] that under certain conditions the polymerization of DL-leucine and DL-phenylalanine N-carboxy anhydrides show auto-acceleration. This is in no way connected with the size of the growing polymer, but results from the presence of impurities in the anhydrides. It can be eliminated in these cases by the use of dry-box techniques and purification of the anhydrides by sublimation. In view of these results it appeared desirable to repeat the experiments of Doty and Lundberg, particularly since γ-benzyl-L-glutamate N-carboxy anhydride cannot be purified by sublimation.

We have studied chloride and acid-free samples of the anhydride prepared by phosgenation of the amino acid (the technique apparently used[3] for the anhydrides of Doty and Lundberg) and also from the carbobenzoxy derivative of the amino acid by treatment with phosphorus pentachloride.[4] The materials were crystallized from chloroform in both cases and stored *in vacuo* until required. Dry-box techniques were used throughout, and the rates of reaction were measured in constant-volume and

[1] P. Doty and R. D. Lundberg, THIS JOURNAL, **78**, 4810 (1956).

[2] D. G. H. Ballard and C. H. Bamford, *Proc. Roy. Soc.* (*London*), **A223**, 495 (1954).

[3] E. R. Blunt and R. H. Karlson, THIS JOURNAL, **78**, 941 (1956).

[4] W. E. Hanby, S. G. Waley and J. Watson, *J. Chem. Soc.*, 3009 (1950).

constant-pressure systems of the type described in reference 2. Dioxane was purified as described by Fieser[5]; the final product showed no reaction with sodium in 24 hr. at room temperatures.

TABLE I

THE POLYMERIZATION OF γ-BENZYL-L-GLUTAMATE N-CARBOXY ANHYDRIDE IN DIOXANE AT 25°

Initiator type	$10^2[X]_0$,[a] mole l.$^{-1}$	$10^2[M]_0$[a] mole l.$^{-1}$	$[M]_0/[X]_0$[a]	10^2 initial propagation rate constant, mole^{-1} l. sec.$^{-1}$	Source of anhydride
n-Hexylamine	0.30	9.3	31	1.5	Phosgenation
	0.31	3.0	9.7	1.5	Phosgenation
	0.5	3.0	6.0	2.2	Phosgenation
	0.95	4.6	4.8	1.6	From carbobenzoxy derivative
	3.4	15.1	4.4	1.2	From carbobenzoxy derivative
	3.4	15.1	4.4	2.5	Phosgenation
4-mer	0.32	3.7	11.5	1.2	Phosgenation
5-mer	1.0	5.0	5.0	1.0	Phosgenation
	1.2	6.1	5.1	1.9	From carbobenzoxy derivative
	1.8	7.5	4.2	1.8	From carbobenzoxy derivative
	4.0	4.0	1.0	1.4	From carbobenzoxy derivative
	4.0	4.2	1.1	1.0	From carbobenzoxy derivative
15-mer	0.31	3.82	12.3	2.4	Phosgenation
	0.37	3.74	10.1	1.8	Phosgenation

[a] $[M]_0$, $[X]_0$ represent the initial anhydride and initiator concentrations, respectively.

When several recrystallizations were required to obtain chloride-free anhydride it was always found that the polymerization was auto-catalytic. However, the rate constant never increased to more than twice its initial value, and generally the change was much less than this. We have never observed the much larger increases noted by Doty and Lundberg. Our results are in fact those which would be anticipated for an unsublimed anhydride on the basis of our previous work.[2] Moreover, the acceleration was independent of the nature of the initiator, and similar results were obtained by initiation with *n*-hexylamine, and preformed polymers up to a degree of polymerization of 15. The observations are summarized in Table I.

Clearly polymeric initiators both larger and smaller than 8-mers give approximately the same rate constants. It should be noted that anhydrides which have been stored for several days in vacuum desiccators give appreciably higher rates than those in the table.

Recently, by modifying the conditions of preparation using the phosgene technique, we have been able to make an anhydride which required for its purification from chloride and acid only one rapid crystallization. The polymerization of this material showed no acceleration whatever. Figure 1 indicates the course of the reaction for initiation by *n*-hexylamine, using anhydride to initiator ratios of 5 and 15. In both cases, after the initial rapid reaction of the *n*-hexylamine (this kind of effect has been discussed elsewhere[2]), the reaction was first order over its whole course, with a velocity constant close to 9.5×10^{-3} mole^{-1} l. sec.$^{-1}$. We consider this represents the most reliable value so far obtained for the normal propagation coefficient for this anhydride. These results show definitely that this coefficient does not depend on the length of the

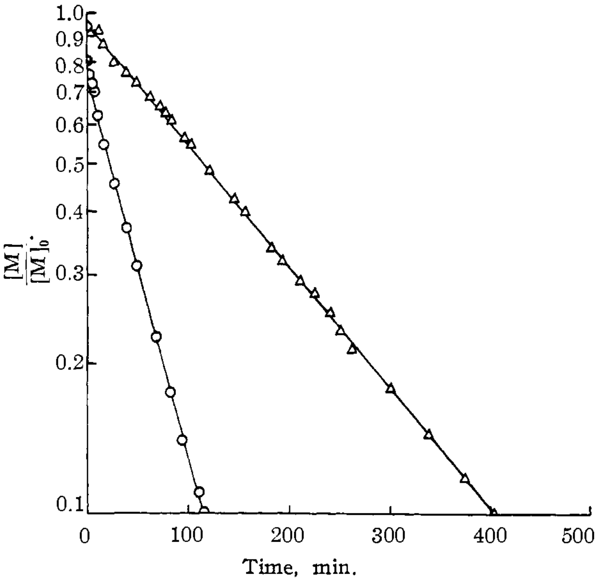

Fig. 1.—The polymerization of γ-benzyl-L-glutamate N-carbonic anhydride initiated by *n*-hexylamine, in dioxane at 25°. Initial anhydride concentration $[M]_0 = 0.151$ mole l.$^{-1}$. *n*-Hexylamine concentrations: ○, 3×10^{-2} mole l.$^{-1}$; △, 1×10^{-2} mole l.$^{-1}$.

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[5] L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., Boston, 1941, p. 369.

growing chain (after the first one or two units have been added to the initiator if the latter is not a preformed polymer) and suggest that the propagation reaction is essentially similar to that established for the polymerization of DL-phenylalanine and DL-leucine N-carboxy anhydrides. Similar observations have been made in nitrobenzene and N,N-dimethylformamide solutions.

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RECEIVED DECEMBER 17, 1956

POLYPEPTIDES. Xa. ADDITIONAL COMMENTS OF THE AMINE-INITIATED POLYMERIZATION

Sir:

The foregoing communication by Ballard and Bamford[1] disputes our finding of two successive propagation constants in the polymerization of γ-benzyl-L-glutamate N-carboxy-anhydride and thereby casts doubt on the identification we had made of the first, relatively slow propagation with the randomly coiled configuration and the second, faster propagation with the α-helical configuration which is attained by each growing chain when it passes a critical chain length.[2]

In each case the interpretations are consistent with the kinetic data reported: it is the data that differ so much in the two investigations. As a consequence the course of the polymerization must be quite different as well. It is our contention that our N-carboxy anhydride was in such a state of purity that the polymerization consists simply of a rapid initiation followed by chain growth characterized by two successive propagation constants, the second taking over from the first when the chain reaches a length of about eight.

Since there is no indication that Ballard and Bamford[1] have followed precisely the procedure of anhydride preparation and purification[3] we employed, their failure to reproduce our results is not surprising inasmuch as the kinetic effect we have isolated is easily suppressed. On the other hand, we have observed the behavior they report with relatively unpurified anhydride. Since upon sufficient recrystallization the behavior we have reported was always found we have naturally concentrated our attention on what appeared to be the purer and more reproducible anhydride. Although this work is reported in detail in forthcoming papers,[4,5] two particularly relevant points deserve mention here.

(1) If the N-carboxy anhydride is used after its first crystallization a linear first-order behavior similar to that of Ballard and Bamford[1] is observed throughout the polymerization (A in Fig. 1). However, after one recrystallization from methylene dichloride the two successive propagations are clearly evident (B in Fig. 1). Since the HCl content of the unrecrystallized anhydride was 1.0 mole % and since this could react with the initiator, n-hexylamine, to produce a possibly "active" impurity, we

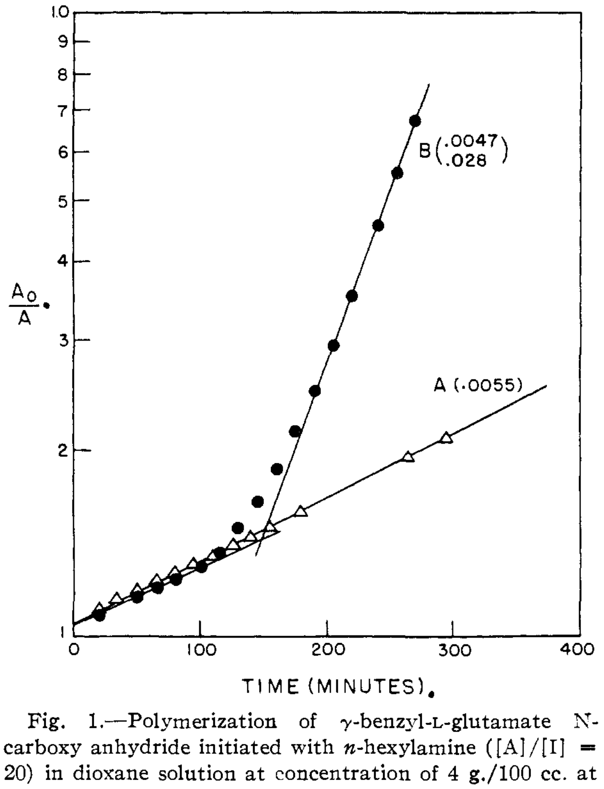

Fig. 1.—Polymerization of γ-benzyl-L-glutamate N-carboxy anhydride initiated with n-hexylamine ([A]/[I] = 20) in dioxane solution at concentration of 4 g./100 cc. at 25.0°. Case A corresponds to impure anhydride and case B to the same anhydride after one recrystallization.

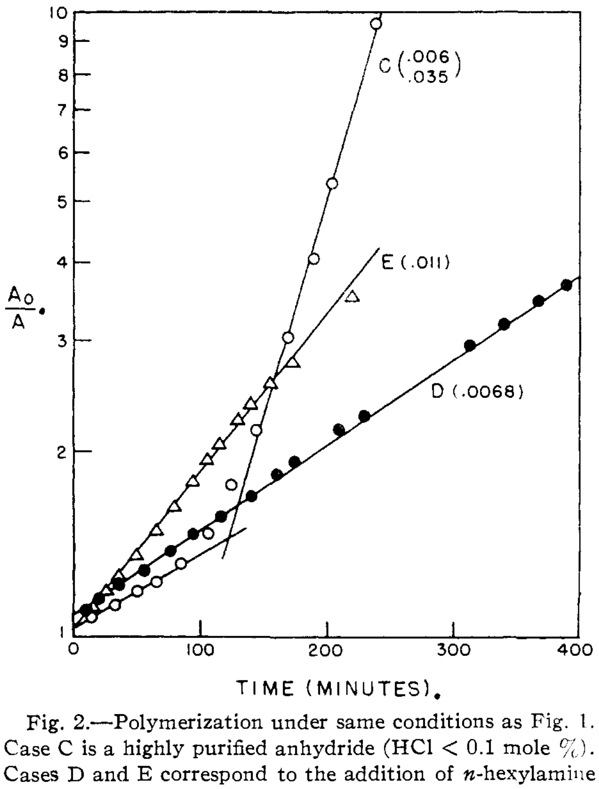

Fig. 2.—Polymerization under same conditions as Fig. 1. Case C is a highly purified anhydride (HCl < 0.1 mole %). Cases D and E correspond to the addition of n-hexylamine hydrochloride to the extent of 0.67 and 5.0 mole %, respectively.

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[1] D. G. H. Ballard and C. G. Bamford, THIS JOURNAL, **79**, 2336 (1957).

[2] P. Doty and R. D. Lundberg, *ibid.*, **78**, 4810 (1956).

[3] E. R. Blout and R. H. Karlson, *ibid.*, **78**, 941 (1956).

[4] R. D. Lundberg and P. Doty, *ibid.*, in press (1957).

[5] E. R. Blout and M. Idelson, *ibid.*, in press (1957).