Journal of Macromolecular Science, Part A

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

Copolymerization Kinetics of *N*-Carboxyanhydrides of ϵ-Benzyloxycarbonyl-L-Lysine and L-Valine

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To cite this Article Kumar, Ajay(1987) 'Copolymerization Kinetics of *N*-Carboxyanhydrides of ϵ-Benzyloxycarbonyl-L-Lysine and L-Valine', Journal of Macromolecular Science, Part A, 24: 6, 707 — 710

To link to this Article: DOI: 10.1080/00222338708058525

URL: http://dx.doi.org/10.1080/00222338708058525

J. MACROMOL. SCI.—CHEM., A24(6), pp. 707-710 (1987)

NOTE

COPOLYMERIZATION KINETICS OF *N*-CARBOXYANHYDRIDES OF ϵ-BENZYLOXYCARBONYL-L-LYSINE AND L-VALINE

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INTRODUCTION

Random copolypeptides have been considered as model compounds to understand, for instance, the conformational preference of individual monomers and the effect of comonomers on the folding of polypeptide chains [1, 2]. The kinetics of copolymerization of *N*-carboxyanhydrides (NCA) of α-amino acids were reviewed earlier [3]. Reactivity ratios have been used in a few cases to determine the sequence length distribution and interchain heterogeneity [4] to arrive at the most probable primary structure for the polypeptide backbone. In the present communication we report the kinetics of copolymerization of ϵ-benzyloxycarbonyl-L-lysine NCA and L-valine NCA in two solvents, dioxane and benzene/methylene chloride.

EXPERIMENTAL

L-Lysine and L-valine (E. Merck) were chromatographically homogeneous. The ϵ-amino group of L-lysine was protected with the benzyloxycarbonyl group. Triethylamine (E. Merck) was freshly distilled over sodium. The *N*-carboxyanhydrides were obtained by Goodman's method [5]; mp: valine NCA 70°C, benzyloxycarbonyl-L-lysine NCA 100°C.

COPOLYMERIZATION OF NCAs

The copolymerization of the NCAs was carried out at 25°C in either dioxane or benzene/methylene chloride (1/1 v/v) with 0.2 mol/L total monomer concentration. Triethylamine was used as initiator, monomer to initiator ratio 12.5. In dioxane the copolymers remained in solution during copolymerization, whereas in benzene/methylene chloride the copolymers precipitated even at $< 10\%$ conversion. In preliminary experiments a 50/50 mixture of ϵ-benzoyloxycarbonyl-L-lysine NCA and L-valine NCA was allowed to polymerize for various times, and the copolymer formed was precipitated with dry ethyl acetate and collected on preweighed G-3 sintered glass crucibles. The copolymer was washed with ethyl acetate and dried over phosphorus pentoxide under vacuum to constant weight. Conversion versus time plots were made, and the times for 10% conversion were determined to be 26 h in dioxane and 15 min in benzene/methylene chloride. Copolymerizations were carried out to low conversion with 40-80 mol% of the NCA of ϵ-benzyloxycarbonyl-L-lysine in the monomer feed.

MONOMER COMPOSITION IN COPOLYMERS

NMR spectra of the copolymers in trifluoroacetic acid (TFA) were recorded using a 90 MHz Perkin-Elmer R-32 unit with a sweep time of 300 s. The molar ratios of the two monomer residues in the copolymers were determined from the relative integrated area of peaks of the five phenyl protons of benzyloxycarbonyl group of lysine (at 7.20-7.45 δ) and of the six protons of the *gem*-dialkyl group of valine (at 1.0 δ).

RESULTS AND DISCUSSION

The intrinsic viscosity in dichloroacetic acid, and hence the MW, increased only slightly with conversion in dioxane (0.60-0.65 dL/g) or in the mixed solvent (2.00-240 dL/g). Hence, the present systems satisfy the conditions laid down by Wall [6] for analysis of data by the copolymerization kinetics theory.

The reactivity ratios in the two solvent systems were determined from the data in Table 1 by the Kelen-Tüdős [7] method (see Fig. 1). In dioxane, $r_V = 1.24$, $r_K = 1.06$; in benzene/methylene chloride, $r_V = 0.59$, $r_K = 0.87$.

In dioxane, r_K is somewhat less than r_V. In an earlier study [9] it was shown that the comonomer with a higher proclivity for forming an ordered

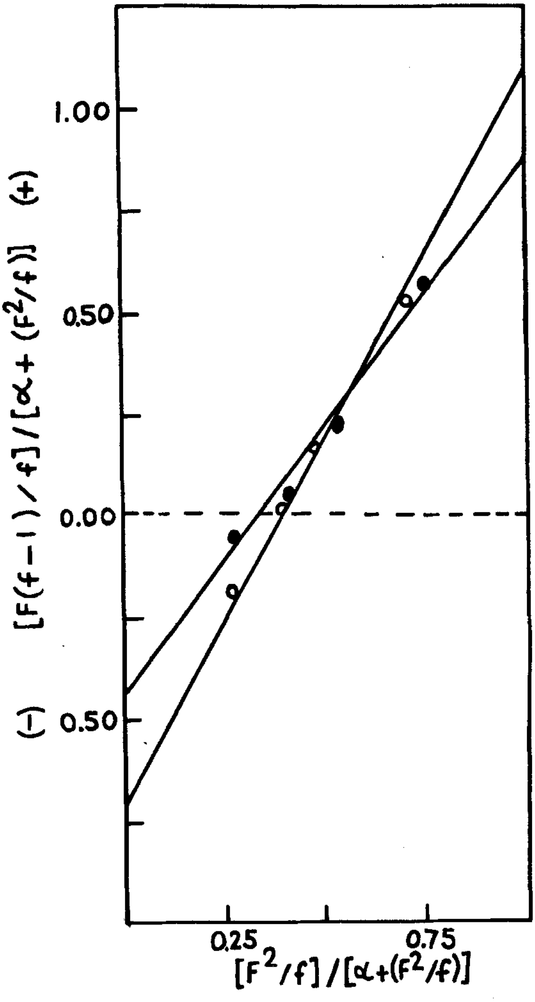

FIG. 1. Kelen-Tüdős plot (least square) for determination of reactivity ratios for the NCAs of ϵ-benzyloxycarbonyl-L-lysine and L-valine in dioxane (○) and in benzene/methylene chloride (1/1, v/v) (●).

TABLE 1. Composition of Feed and Products in the Copolymerization of the NCAs of ϵ-Benzyloxycarbonyl-L-lysine (*K*) and L-Valine (*v*) in Dioxane and in Benzene/Methylene Chloride (1/1, v/v) at 25°C[a]

Dioxane		Benzene/methylene chloride	
Feed, M_K	Copolymer, m_K	Feed, M_K	Copolymer, m_K
80.0	80.0	80.0	80.0
60.0	58.8	60.0	64.7
50.0	47.1	50.0	51.8
40.0	38.2	40.0	47.1

[a] All numbers given are mol% lysine. Conversion: 10%.

structure has a higher copolymerization reactivity ratio. According to Chou and Fasman [8], the proclivity parameter, P_α, for lysyl residues (1.07) is less than that for valyl residues (1.14). Thus, present data in dioxane are in accord with the above. Since r_K (0.87) was greater than r_v (0.59) in the mixed solvent, the nature of the solvent also plays a role in the copolymerization.

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Received January 18, 1986
Revision received June 2, 1986