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Anionic Copolymerization of N-Carboxy Anhydrides of Tyrosine and Alanine

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ABSTRACT

The reactivity ratios for the anionic copolymerization of N-carboxy anhydrides of O-acetyl-L-tyrosine and L-alanine have been determined to be 0.115 and 2.65, using the Fineman-Ross and Kelen-Tüdös, methods.

Polyamino acids are widely used as protein models to study the part played by side chains of the constituent amino acids in determining the conformation of backbone polypeptide chains. Although sequential polypeptides would be the ideal models, random copolypeptides obtained by polymerization of N-carboxy anhydrides (NCA) of amino acids, suitably protected, have been extensively studied on account of the facile synthesis and polymerization of the NCAs. However, the study of copolymerization kinetics [1-6] in such systems has been rather restricted and is concerned mainly with polymerizations having NCA of γ -benzylglutamate as a comonomer. In what follows, results obtained on copolymerization kinetics of NCAs of O-acetyl-L-tyrosine and L-alanine, using n-butylamine as initiator in dioxane medium at low conversions, are presented.

MATERIALS AND METHODS

Reagent grade solvents were purified [7] and dried before use. L-Tyrosine (SD'S) and L-alanine (Sarabhai Merck) were used.

Preparation of N-Carboxy Anhydrides (NCA)

The phenolic hydroxyl of tyrosine was first protected by acetylation.

O-Acetyl-L-tyrosine (I) was prepared as follows. L-Tyrosine (25 g in 70 mL acetic anhydride) was treated with the acetylating mixture (18.2 mL of 60% HClO_4 and 14.6 mL acetic anhydride in 290 mL glacial acetic acid) at 5°C for 2 hr, after which 23 mL of n-butylamine and 6 mL of water were added. O-Acetyl-L-tyrosine (I) was precipitated with 500 mL ether, washed free of acetic acid and acetic anhydride, and crystallized from alcohol.

The NCAs were obtained following the method of Goodman [8]. Forty grams (0.18 mole) of (I) was suspended in 200 mL of dioxane and treated with phosgene (0.45 mole) solution in benzene. The solution was maintained at 50°C with constant stirring for 2 hr for (I) to dissolve completely. The NCA of O-acetyl-L-tyrosine (II) formed was precipitated with petrol and recrystallized from ethyl acetate-petrol. (Yield 95%, mp 103-105°C (decomp).) In the case of alanine NCA (III), a similar procedure was adopted. An alanine to phosgene ratio was maintained at 1:2.5 but the temperature for the reaction was 70°C and the time of reaction was 24 hr. (Yield 40%, mp 88-89°C.)

Copolymerization

In order to choose a suitable time of reaction for low conversion (~10%), preliminary experiments were run with 48:52 mixtures of L-alanine and O-acetyl-L-tyrosine using n-butylamine as initiator (anhydride:initiator, A/I = 100) in dioxane; polymerization was allowed to proceed to fixed intervals of time at 25°C and the yields were determined. From the results obtained (Table 1 and Fig. 1) a period of 100 min was chosen to study the copolymerization kinetics and determine the reactivity ratios at low conversions of about 10%.

NCAs (II) and (III) were mixed in different proportions as detailed in Table 2, and the copolymerization was carried out at 25°C under the same conditions as in the preliminary experiments, viz., 0.2 M concentration of NCAs in dioxane, and n-butylamine as initiator (A/I = 100). After allowing the polymerization to proceed for 100 min, the polymer was precipitated with ether and washed free of unreacted anhydrides. The mole fraction of tyrosine in the copolypeptides was determined as tyrosinate from optical density measurements

TABLE 1. Variation of Yield and Composition with Time in the Copolymerization of NCAs of O-Acetyl-L-tyrosine and L-Alanine (48:52)

No.	Time (hr)	% Conversion	Mole % of tyrosine
1	0.5	0.5	-
2	1.0	4.1	-
3	2.0	19.6	20.9
4	4.0	27.5	22.2
5	8.5	35.2	29.3
6	19.0	45.3	27.1
7	45.0	52.5	46.1

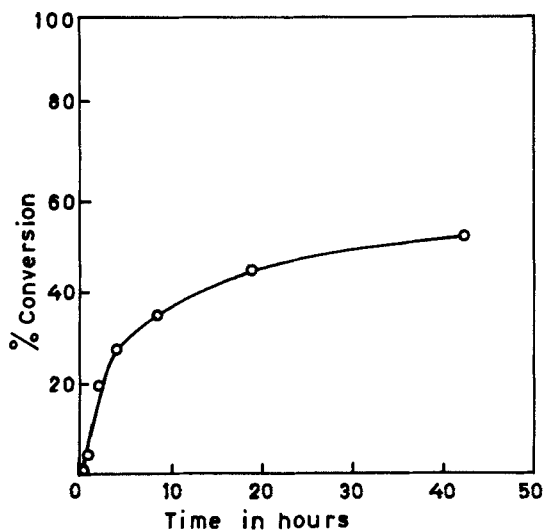


FIG. 1. Yield vs time curve for copolymerization of 48:52 mixtures of NCAs of L-alanine and O-acetyl-L-tyrosine at 25°C with n-butylamine as initiator (A/I = 100).

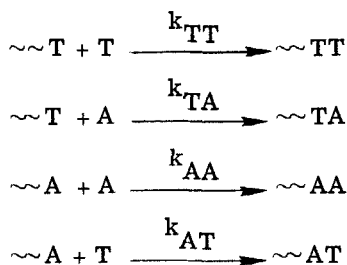
TABLE 2. Composition of Feeds and Copolypeptides

No.	Mole % tyrosine		F	f
	Feed M_T	Polymer m_T		
1	38.2	16.9	0.33	0.22
2	47.3	21.0	0.89	0.27
3	65.6	35.3	1.90	0.55
4	79.0	45.1	3.75	0.82

of deacetylated sample solutions at 290 nm; poly-L-tyrosine was taken as reference and an $\epsilon_{290} = 2220$ was used. The results obtained are incorporated in Table 2.

RESULTS AND DISCUSSION

The copolymerization theory developed by Wall [9, 10] has been extensively used in the study of free radical copolymerization. The applicability of the theory to ion-initiated copolymerization of N-carboxy anhydrides of amino acids has been justified [4]. Accordingly, ignoring "penultimate effects," the propagation steps in the copolymerization under study can be formulated as



where T denotes a growing chain with a tyrosine end residue, and A is a chain with an alanine end. Under steady-state conditions, at low conversions, the relationship between the composition in the feed and polymer could be formulated as

$$\frac{m_T}{m_A} = \frac{M_T}{M_A} \frac{r_T M_T + M_A}{r_A M_A + M_T}$$

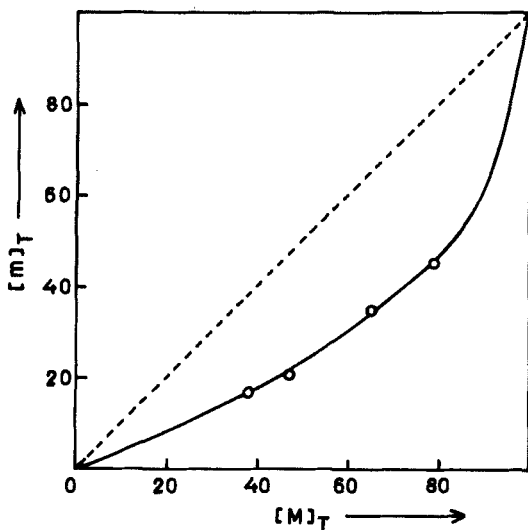


FIG. 2. Copolymer composition vs monomer feed in copolymerization of NCAs of O-acetyl-L-tyrosine and L-alanine.

where m_T and m_A represent the mole fractions of tyrosine and alanine in the copolypeptide, M_T and M_A in the monomer feed, and r_T ($= k_{TT}/k_{TA}$) and r_A ($= k_{AA}/k_{AT}$) the reactivity ratios which quantitate the relative reactivities of the two NCAs. The variation of concentration of tyrosine in the copolymers as against that in the feeds is shown in Fig. 2; the plot is smooth and does not have an inflection, indicating the absence of an azeotrope in the system under study.

The experimental data can be treated by different procedures to obtain the reactivity ratios. According to the Fineman-Ross method [11], applicable for low conversions,

$$\frac{F}{f} (f - 1) = r_1 \frac{F^2}{f} - r_2$$

where F is the ratio of the two monomers in the feed and f in the polymer, and r_1 and r_2 are the reactivity ratios. Figure 3 gives the least-square Fineman-Ross plot obtained from the data given in Table 2. The reactivity ratios were calculated to be $r_A = 0.11$ and $r_T = 2.6$.

In order to check whether data at extremes of feed ratios vitiated

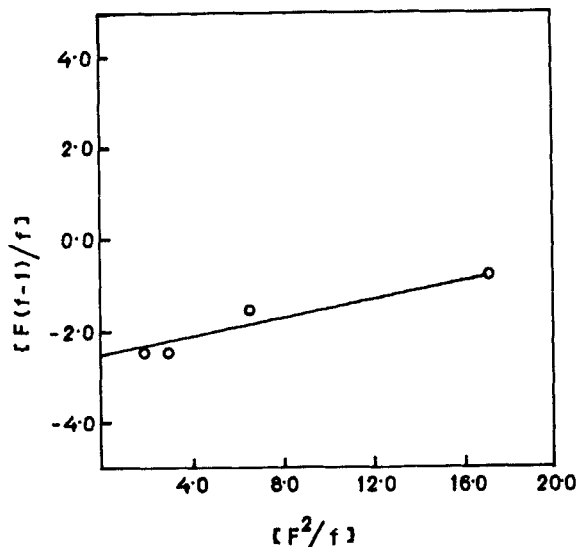


FIG. 3. Fineman-Ross plot for the copolymerization of NCAs O-acetyl-L-tyrosine and L-alanine.

the results obtained by the Fineman-Ross procedure, the reactivity ratios were evaluated by the Kelen and Tüdös [12] method. According to Kelen and Tüdös,

$$\eta = \xi(r_T + r_A/\alpha) - r_A/\alpha$$

where

$$\eta = F(f-1)/f(\alpha + F^2/f)$$

$$\xi = (F^2/f)/(\alpha + F^2/f)$$

and

$$\alpha = [(F^2/f)_{\max}(F^2/f)_{\min}]^{1/2}$$

where $(F^2/f)_{\max}$ and $(F^2/f)_{\min}$ are the lowest and highest (F^2/f) values from experimental data. A least-square plot of η vs ξ is shown in Fig. 4, from which the values of η are read off at $\xi = 1$ and

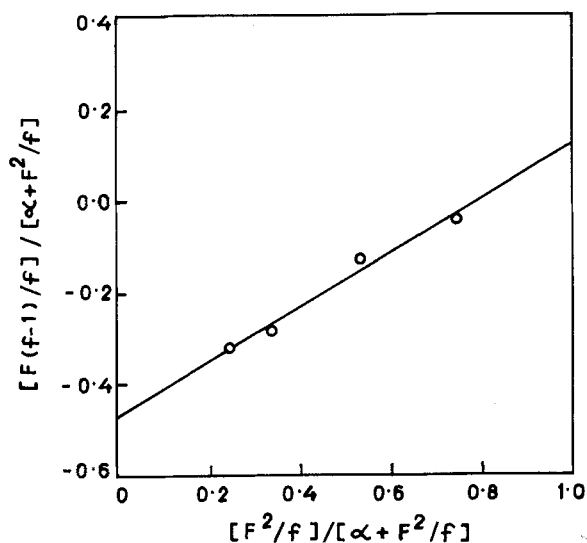


FIG. 4. Kelen-Tüdös plot for the copolymerization of NCAs of O-acetyl-L-tyrosine and L-alanine.

TABLE 3. Reactivity Ratios for Copolymerization of NCAs of O-Acetyl-L-tyrosine and L-Alanine

Method	r_T	r_A
Fineman-Ross	0.11	2.6
Kelen-Tüdös	0.12	2.7
Average	0.115	2.65

0, and r_A and r_T are determined, since at $\xi = 1$, $r_T = \eta$, and when $\xi = 0$, $r_A = -\alpha\eta$.

The values of r_T and r_A so obtained are given in Table 3. The two sets of values of reactivity ratios determined by the Fineman-Ross and Kelen and Tüdös methods are very close.

The numerical values of r_A and r_T indicate that in the initial stages of polymerization an alanine-rich polypeptide would be obtained. This is borne out in the experimental observation of the changes in the polypeptide composition with time of copolymerization; the tyrosine content of a copolymer (Table 1) was found to increase with the extent of conversion.

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