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Copolymerization of N-Carboxyanhydrides of α - Amino Acids.

Ajay Kumar.
Apeejay Stya University, Palwal- Sohna Road, Sohna, Gurgaon, Haryana, India.

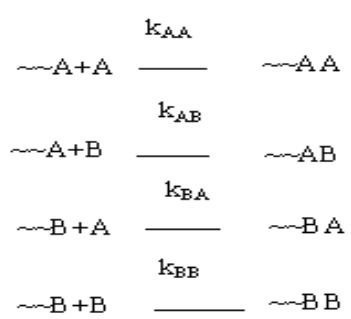
Abstract
A number of copolymers of natural and synthetic amino acids have been prepared by co-polymerization of their N- carboxyanhydrides (NCA). But, the co-polymerization process is incompletely understood in terms of reactivity ratios of the various co-monomers. The polymerization of NCA s initiated by amines or bases may proceed according to two different mechanisms, normal primary amine polymerization and strong base polymerization. The reactivity ratio "r" quantitat the relative reactivity of the two NCAs towards each other. Complete reactivity scale of NCAs monomer of amino acids would guide us to synthesis the copolymers of predefined sequence length distribution. The reactivity ratios of the various N-carboxyanhydrides of α - amino acids and co- monomers are reported.

Key Words
Copolymerization, Reactivity Ratio, N-Carboxyanhydrides of α - Amino Acids, Fineman and Ross, Kelen and Tudos.

Introduction
The copolypeptides from polymerization of α- amino acid N- carboxyanhydrides (NCA) have potential application in biomedical applications such as polypeptide adhesives for use as surgical sealant, antimicrobial polypeptides for the treatment of autoimmune disorders, polypeptide membranes for therapeutic delivery and polypeptide hydrogels for tissue engineering applications [39-42]. While these materials show great potential, much development is still required before they will be useful in some of these applications. However, the ability to prepare polypeptides with predictable structure and function will puts these applications within reach. Small peptide sequences, typically less than 100 residue in length are prepared most conveniently prepared using solid – phase synthesis. The chemical synthesis of high molecular weight copolypeptides is most directly accomplished by ring opening polymerization of α- amino acid N-carboxyanhydrides (NCA) monomers [1, 2] . However, in most cases, random sequence distributions have been assumed in co-polypeptides prepared via NCA copolymerization[3]. At present the co-polymerization process is incompletely understood in terms of reactivity ratio of the various monomers.

***Corresponding Author:**
ak.gupta59@rediffmail.com

Complete reactivity ratio scale of NCA monomer has not been determined and reported in the literature. Using the reactivity ratios values of the co monomers, it is possible to determine sequence length distribution of the co-monomers in the copolypeptides [28]. Thus by making use of the reactivity ratio data of N-carboxyanhydrides of α - amino acids it would be possible to synthesis co-polypeptides of nearly desired sequence and structure. Synthesis of well defined polypeptide-based materials via ring opening polymerization of α- amino acid N- carboxyanhydrides has been reviewed recently [42]. Here in I review data of the reactivity ratios of α- amino acid N-carboxyanhydrides available in the literature. The copolymerization reaction, for example between A and B can be represented by following step.



Where ~~ A denotes a growing chain with an A end residue and ~~ B a chain with B end residue. Under steady state conditions and at low conversion, the relationship between the composition in the lead

and the polymer, following Mayo and Lewis [4] and Alfrey and Goldfinger [5] could be formulated as,

$$\frac{m_A}{m_B} = \frac{M_A \quad r_A M + M_B}{M_B \quad r_B M + M_A} = \frac{f_A}{f_B}$$

where m_A and m_B represent the mole fraction of A and B in the co polypeptides, respectively M_A amd M_B are the corresponding terms in the monomer feeds and,

$$r_A = \frac{k_{AA}}{k_{AB}} \qquad r_B = \frac{k_{BB}}{k_{BA}}$$

The reactivity ratio r_T quantitat the relative reactivity of the two NCAs towards each other, where f_A and f_B are respectively the mole fractions of A and B in the copolymer. The monomer concentration in the polymerizing mixtures is given by M_A and M_B respectively. At low conversions, usually about 10% provided the respective monomer reactivities to different dM_A / dM_B. The simplest and most widely used method to calculate the reactivity ratios is the graphical presentation of Fineman and Ross [6]. In order to avoid errors of the Fineman and Ross method, Kelen -Tudos [7] method was adopted to obtain r_A and r_B. According to the literature the polymerization [8,9] of NCA compounds initiated by amines or bases may proceed according to two different mechanisms normal primary amine (Figure-1 a) polymerization and strong base polymerization (Figure-1b). The polymerization of N-carboxyanhydrides of amino acids by triethylamine proceeds via the formations of active monomer. An attack of the active monomer at the 5-carbonyl site of a neutral molecule of the monomer leads to a ring opening and formation of N – amino acyl derivative of NCA ring unit, this in turn reacts with another molecule of NCA (neutral) and propagation steps through the N- terminal end are as indicated below. In the presence of primary amine NCA[3, 8, 11-13] polymerization proceeds according to the so called normal mechanism [10-12]. The reaction is a multi step nucleophilic addition of the terminal amino group to carbonyl-5 of the NCA, followed by opening and evolution of carbon dioxide. There is wide evidence that in the normal primary amine initiate polymerization each initiator molecule originates one polymer chain so that the number average degree of polymerization is given by the molar ratio of monomer to initiator (A/I). But this is not so in case of tri-ethylamine initiated polymerization of NCA Apart from the mechanisms the problem in case of copolymerization is complicated for the preference toward one particular monomer during the chain elongation. Furthermore NCA [4] can polymerize by different mechanism depending upon the solvent and the initiator, thus the polymerization conditions are an additional factors influencing the resulting ratios and the ultimate sequence distribution along the chain. The reactivity ratios of the co-monomers so far determined by both the initiators have been tabulated in Table 1. Using the reactive ratios data the interchain compositional heterogeneity on the conformation in random copolymers such as γ - benzyl L- glutamate and L- valine and sequence length distribution of L-valine and ε - carbobenzoxy L- lysine have been determined [27,28]. Using reactivity ratios the following: random copolymers of *γ*-benzyl L-glutamate and L-methionine, [33] *γ*-benzyl L-glutamate and L-valine,[15, 34] glycine and alanine,[35], D,L-leucine and D,L-valine,[35,36] *N*-*ε*-carbobenzoxy L-lysine and β -benzyl L-aspartate,[24] *O*-acetyl L-tyrosine with L-valine and glycine, [21] L-alanine and L-valine,[37] L-alanine and sarcosine,[38] *N*-*ε*-carbobenzoxy L-lysine and L-valine, [22] and random terpolymers, such as of glycine, L-leucine, and L-valine[29] have been synthesized and studied .

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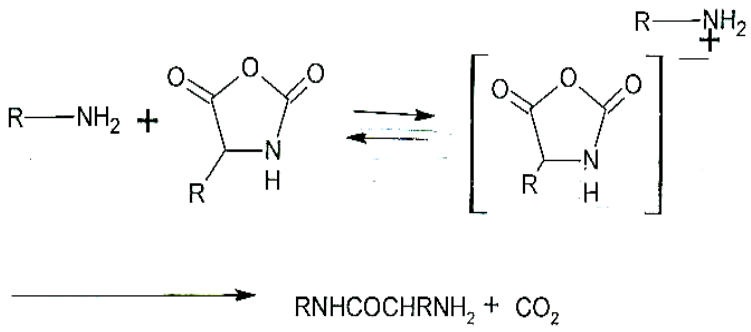

Fig. a

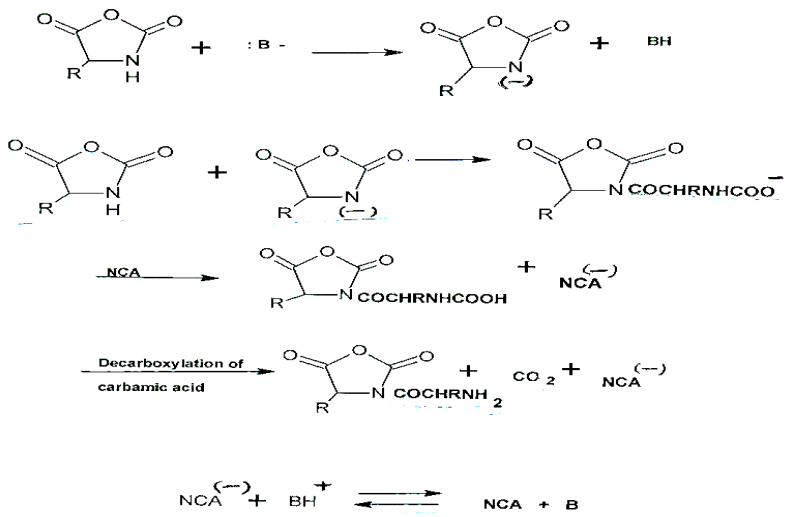

Fig. b

Table 1: Reactivity Ratios of NCAs of Amino Acids.

Co-monomers NCA		**Reactivity Ratios**		**Reference**
1	2	r_1	r_2	
L- Alanine	L-Valine	2.40-2.60	0.00-0.13	13
L-Alanine	L-Lencine	1.70	0.35	13
γ-Benzyl Glutamate	L-Lencine	1.57	0.61	14
γ-Benzyl Glutamate	L-Valine	2.70	0.30	15
γ-Benzyl Glutamate	L-Valine	2.10 2.96	0.60 0.17	16 19
γ-Benzyl Glutamate	ε-Carbobenzoxy L-Lysine	1.80 0.85	0.50 0.35	17 18
γ-Methyl-L-Glutamate	ε-Carbobenzoxy L-Lysine	2.0	0.50	18
Glycine	O-Acetyl l-Tyrosine	0.26	0.42	20
L- Valine	O-Acetyl l-Tyrosine	0.57	0.22	21
L-Alanine	O-Acetyl l-Tyrosine	2.68	0.12	21
ε-CBZ-L- Lysine	L-Valine	1.06	1.24	22
ε-CBZ-L- Lysine	L-Valine	0.6	0.22	22
γ-Benzyl-L-Glutamate	L-Valine	2.96	0.17	23
L-Alanine	Glycine	0.21	0.46-0.60	25
ε-CBZ L-lysine	β-Benzyl-L- Aspartate	1.2-0.9	1.3-0.9	24
DL- Alanine	L-Leucine	2.0	0.45	25
DL- Alanine	L-Leucine	1.14	0.65	25
DL- Ala	L-Leucine	2.30	0.30	26
γ-Methyl-L-Glutamate	γ-Benzyl –L-Glutamate	0.960	0.704	26
Trytophan	Glycine	0.3-1.0	5.5- 8.0	29
Trytophan	Alanine	0.2	10.5	30
Trytophan	L-*α*-amino-*n*-butyric acid(Abu)	0.2-0.6	10.16.5	29
Trytophan	Nor Valine	0.05-0.6	5.2-8.0	29
Trytophan	Nor Leucine	Less than 0.5	Less than 7	29
Trytophan	Leucine	Less than 0.9	Less than 10	29
Trytophan	O-Methyl Glutamate	0.8-1.6	5- 16	29
Trytophan	Methionine	Less than 0.8	Less than 12	29
γ-Methyl-L-Glutamate	L-Leucine	2.56 (0.2)	2.22 (0.09	31
ß-Benzyl-L-aspartate	L-Valine	2.78	0.43	32
ß -Benzyl-L-aspartate	L-Leucine	1.99	0.52	32
L-Valine	L-Leucine	1.40	0.59	32