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Electrochemical Synthesis of Poly(amino acid)s, Poly(amino acid)-Urethane Copolymers, and Electroconductive Poly(amino acid)-Polypyrrole Complex Films

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When amino acid *N*-carboxy anhydrides (NCA's) were polymerized with various electrogenerated base (EGB) catalysts, the yield of poly(amino acid)s remarkably increased and the reaction time was extremely shortened compared with the conventional method using triethylamine catalyst. This novel polymerization method was successfully applied to the copolymerization of different kinds of NCA's and to the preparation of poly(amino acid)-urethane copolymers. NCA's were also polymerized with the EGB's in the matrix of polypyrrole simultaneously formed by the anodic polymerization of pyrrole to provide electroconductive poly(amino acid)-polypyrrole complex films which were stable in the air and flexible.

Poly(amino acid)s and their related polymers are widely used as synthetic leathers, medicines, medical materials, fibers, surfactants, and piezodevices. Poly(amino acid)s are commercially produced by the *N*-carboxy anhydride(NCA) method,[1] in which NCA's are polymerized with base catalysts such as primary and tertiary amines. It is well-known that the yield and quality of poly(amino acid)s are greatly affected by impurities in NCA's and kind of the base catalysts.[2] Since NCA's are usually prepared from amino acids and phosgene or trichloromethyl chloroformate(phosgene dimer), enormous efforts must be made to remove chlorine-contaminants from the NCA's, especially in the case of amino acid such as L-valine which is polymerized with difficulty.[2]

Recently, cathodically-generated anionic species, so-called electrogenerated bases(EGB's), have been widely used as reducing reagents, nucleophiles, and bases.[3] In our previous work,[4] it was found that the EGB catalysts polymerized valine NCA's much more efficiently than conventional catalyst such as triethylamine, though both catalysts would induce the polymerization in similar of reaction mechanism in which an initiation step is the abstraction of amido hydrogen of NCA's.[2] In this work, this cathodic polymerization was successfully extended to the preparation of a variety of homopoly (amino acid)s, copoly(amino acid)s, poly(amino acid)-urethane copolymers, and electroconductive poly(amino acid)-polypyrrole complex films.

Results and Discussion

EGB's are generated by the one-electron reduction of acidic hydrogen compounds (PB's) such as amides, carboxylic acids, phenols, alcohols, and carbon acids in general as shown below.[3].

$$\mathrm{XH} \xrightarrow[\mathrm{M^+Y^-}]{\mathrm{e}} \mathrm{X^-M^+} + \frac{1}{2}\mathrm{H_2} + \mathrm{Y^-}$$

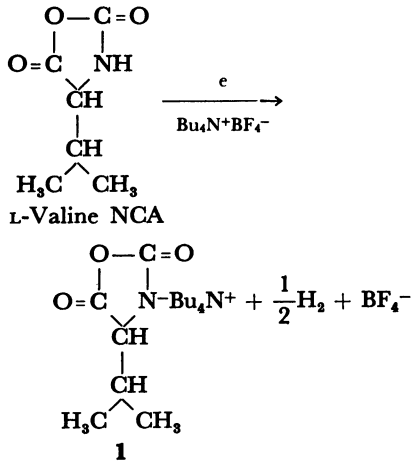
(PB) (Supporting electrolyte) (EGB)
(X: N, O, C)

The reactivity of the EGB's thus formed is affected by their counter cations (M^+) coming from supporting electrolytes (M^+Y^-) used.[5,6] In this work, two methods for the polymerization of amino acid NCA's with EGB's were employed. In the first method (Method A), amides such as α-pyrrolidone,[7] ε-caprolactam, acetanilide and *N*-methylacetamide and a phenol such as 2,6-di-*t*-butyl-*p*-cresol[10] were cathodically reduced in dry THF solutions and then EGB solutions thus prepared were added to THF solutions of NCA's. In Method B, NCA's, themselves were used as probases (PB's) without any other PB's, since they have molecular structures of amides. No contamination of poly(amino acid)s by the catalysts used was expected in this case where the self-catalyzed polymerization should proceed. The polymerization seemed to proceed not only on the surface of cathode but also in the whole cathodic solution (divided cell). In addition to these methods,a conventional one was examined by using triethylamine as the catalyst under the similar conditions (Method C). In all these methods, 0.05 mol/mol-NCA of the EGB and amine catalysts were used. Amounts of EGB's used were controlled by the amounts of charge passed.

Electrochemical and Chemical Syntheses of Homopoly(amino acid)s. As shown in Fig. 1, L-valine NCA was reduced in a potential range less negative than the background solution. Therefore, the EGB catalyst in Method B seemed to be anion (**1**) generated by the reduction of the NCA itself rather than the supporting electrolyte.

Results of the polymerization of L-valine NCA using EGB catalysts generated from various PB's in

Method A are shown in Table 1. Among the PB's used, α-pyrrolidone gave the best result in either reaction time or yield, optical rotating power($[\alpha]_D$) and molecular weight (kinematic viscosity) of poly(L-valine) obtained. The largest value of $[\alpha]_D^{20}$ is 155° (in CF_3COOH).[11] The molecular weight could not be directly measured because of insolubility of poly(L-valine) in solvents other than CF_3COOH. A standard sample of poly(L-valine) (MW, 7200) which was commercially supplied from Sigma Chemical Co. showed 0.616×10^{-6} m^2 s^{-1} of kinematic viscosity in 0.5 w/v% CF_3COOH solution at 25°C. However, estimation of the molecular weight from the viscosity could not be performed for lack of a standard sample with a different MW. The secondary structure of poly(L-valine) obtained was confirmed to be β-coil form from IR-spectrum (an amido carbonyl band observed at 1630 cm^{-1}).[12]



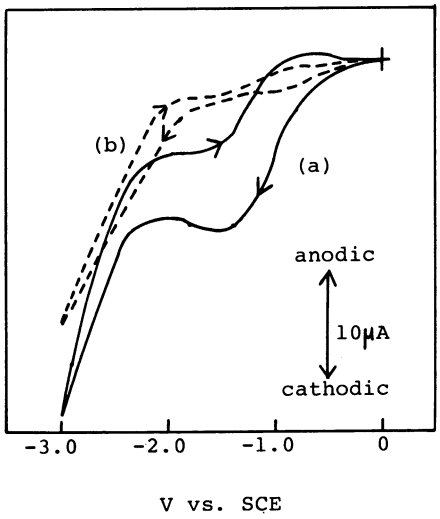


Fig. 1. Cyclic voltammogram of L-valine NCA at a platinum electrode (0.013 cm^2) in 0.1 mol dm^{-3} *n*-Bu_4NBF_4/THF. Scan rate, 0.1 V s^{-1}.
(a) 3.8 mmol dm^{-3} L-valine NCA. (b) Background.

As shown in Table 2, the EGB catalysts with Na^+ as their counter cations did not induced the polymerization of L-valine NCA. This fact is rationalized as due to low basicity of the EGB's with hard counter cations such as Na^+ of high Lewis acidity.[5] Inferior results obtained with the catalysts with *n*-Oct_4N^+ counter cation to those with *n*-Bu_4N^+ may be due to steric hindrance effect.

Results of the polymerization of various NCA's by the electrochemical (Methods A and B using α-pyrrolidone as PB and *n*-Bu_4N^+ as counter cation) and

Tabld 1. Polymerization of L-Valine NCA Using EGB Catalysts[a] Generated from Various PB's (Method A)

PB	Reaction time/h	Poly(L-valine)		
		Yield/%	$[\alpha]_D^{20}$/°	Kinematic viscocity /10^{-6} m^2 s^{-1}
α-Pyrrolidone[b]	0.02	98	−110	0.708
ε-Caprolactam	2	58	−95	0.676
N-Methylacetamide	2	26	−96	0.598
Acetanilide	2	16	−80	0.640
2,6-Di-*t*-butyl-*p*-cresol	2	19	−87	0.657

a) With Bu_4N^+ counter cation. b) Charge required to generate 0.02 mol/mol-NCA of EGB was passed.

Table 2. Influence of Counter Cations of EGB Catalysts on the Polymerization of L-Valine NCA by Methods A and B

Method	PB	Counter cation	Reaction time/h	Poly(L-valine)		
				Yield/%	$[\alpha]_D^{20}$/°	Kinematic viscosity /10^{-6} m^2 s^{-1}
A	α-Pyrrolidone	Na^+	2	7	−82	—[a]
A[b]	α-Pyrrolidone	*n*-Bu_4N^+	0.02	98	−110	0.708
A	α-Pyrrolidone	*n*-Oct_4N^+	2	50	−95	0.681
B	L-Valine NCA	Na^+	2	4	−101	—[a]
B	L-Valine NCA	*n*-Bu_4N^+	2	59	−120	0.670
B	L-Valine NCA	*n*-Oct_4N^+	2	55	−100	0.639

a) Not measured. b) Charge required to generate 0.02 mol/mol-NCA of EGB was passed.

chemical (Method C using triethylamine as base catalyst) methods are summarized in Table 3 for comparison. The Methods A and B were clearly superior to Method C in terms of reaction time and yield, while Method C gave poly(L-valine) and poly(L-leucine) with somewhat larger values of $[\alpha]_D^{20}$ than other methods. It is noticeable that *N*-methylglycine NCA without any acidic amido hydrogen atom could be polymerized by Method B. This NCA can not be polymerized with tertiary amine catalysts.[2] These facts may suggest possible cathodic formation of unknown effective catalyst other than *n*-Bu_3N which can be generated by electroreductive decomposition of *n*-Bu_4N^+. Therefore, polymerization mechanism in this case would be quite different from that in cases of other amino acid NCA's.

The molecular weight($\bar{M}n$) of poly(γ-benzyl L-glutamate) soluble in THF was estimated to be 1730

Table 3. Electrochemical and Chemical Polymerization of Amino Acid NCA's with EGB and Triethylamine Catalysts, Respectively

Amino acid	Method	Reaction time/h	Poly(amino acid)		
			Yield/%	$[\alpha]_D^{20}$/°	Kinematic viscosity /10^{-6} m^2 s^{-1}
L-Valine	A[a,b]	0.02	98	−110	0.708
L-Valine	B	2	59	−120	0.670
L-Valine	C	96	17	−145	0.654
D-Valine	A[a]	0.25	45	+94	0.699
D-Valine	B	2	93	+115	0.748
D-Valine	C	96	84	+100	0.711
DL-Valine	B	2	70	—	0.631
L-Leucine	A[a,c]	2	74	−109	0.711
L-Leucine	C	96	38	−124	—[d]
γ-Benzyl L-glutamate	B[b]	0.63	78	+22	—[d]
L-Tryptophan	B	2	36	—[e]	—[e]
L-Tryptophan	C	96	34	—[e]	—[e]
DL-Phenylalanine	A[f]	1.3	90	—	0.625
DL-Phenylalanine	B[f]	1.3	65	—	0.607
DL-Methionine	A	0.4	49	—	0.622
DL-Methionine	B	0.4	30	—	0.596
N-Methylglycine	B[g]	0.5	65	—	—[d]

a) α-Pyrrolidone was used as a PB. b) 0.01 mol/mol-NCA of catalyst was used. c) 0.02 mol/mol-NCA of catalyst was used. d) Not measured. e) Could not be measured because of insolubility. f) 0.1 mol dm^{-3} Et_4NOTs/DMF was used as an electrolytic solution. g) 0.08 mol/mol-NCA of catalyst was used.

Table 4. Electrochemical and Chemical Copolymerization of Amino Acid NCA's with EGB and Triethylamine Catalyst, Respectively

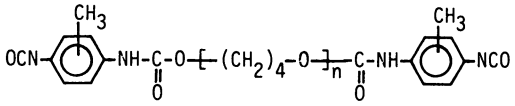
NCA		Method[a]	Copoly(amino acid)	
a+b	Mol. ratio a : b		Yield[b] /wt%	Mol. ratio[c] a : b
L-Leucine+γ-Benzyl L-glutamate	4 : 1	A	82	3 : 1
L-Leucine+γ-Benzyl L-glutamate	4 : 1	B	87	3 : 1
L-Leucine+γ-Benzyl L-glutamate	2 : 1	B	85	2 : 1
L-Leucine+γ-Benzyl L-glutamate	1 : 4	B	36	1 : 5
L-Leucine+γ-Benzyl L-glutamate	4 : 1	C	50	4 : 1
L-Valine+γ-Benzyl L-glutamate	1 : 1	A	57	1 : 2
L-Valine+γ-Benzyl L-glutamate	1 : 4	B	35	1 : 2
L-Valine+γ-Benzyl L-glutamate	1 : 1	C	38	1 : 2
DL-Valine+DL-Alanine	1 : 1	A	20	—[d]
DL-Valine+DL-Alanine	1 : 1	B	30	—[d]
DL-Valine+DL-Alanine	1 : 1	C	20	—[d]

a) Reaction time, 2 h. b) {[(a+b)(wt.) in copoly(amino acid)]/[(a+b)(wt.) in starting NCA's]}×100(%). c) Approximately estimated from ^{1}H-NMR. d) Not determined.

(polystyrene standard) by GPC. The secondary structures of poly(D-valine), poly(L-leucine) and poly(L-tryptophan) were confirmed to be β-, α helix- and α-forms, respectively, from IR spectra.[12]

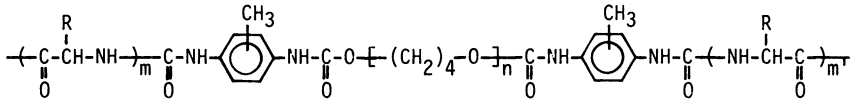
Electrochemical and Chemical Syntheses of Copoly (amino acid)s. The coplymerization of mixtures of amino acid NCA's was carried out in a manner similar to the homopolymerization in Table 3. As shown in Table 4, Methods A an B gave higher yields of copoly(amino acid)s than Method C. Properties of copoly(amino acid)s can be varied by changing either the combination or composition ratio, or both amino acid components. The composition ratio in copoly(amino acid)s formed was approximately equal to those of the starting mixtures of NCA's. It was confirmed that the copoly(amino acid)s with γ-benzyl L-glutamate could be cast from their benzene solutions to provide flexible transparent films, though their molecular weights and secondary structures were not determined. It has been also remained unknown whether the copoly(amino acid)s are homogeneous or block copolymers.

Electrochemical and Chemical Syntheses of Poly-(amino acid)–Urethane Block Copolymers. Improvement of properties of poly(amino acid)s can also be achieved by the block copolymerization of amino acid NCA's with urethane prepolymers (**2**).[2,13] The copolymerization was carried out in the presence of **2**(n, ca. 28) in a manner similar to the homopolymerization in Table 3 and the corresponding poly(amino acid)-urethane block copolymers(**3**) were obtained.



Urethane prepolymer (**2**)

As shown in Table 5, Methods A and/or B gave higher yields of the block copolymers than Method C. Molar ratios of amino acid components to the urethane prepolymer in the block copolymers thus obtained were almost equal to those in the starting mixtures in all the methods. The copolymers with γ-benzyl L-glutamate were able to cast from their THF solutions to provide flexible films. The molecular weight of a poly(γ-benzyl L-glutamate)–urethane copolymer with 17 of molar ratio of γ-benzyl L-glutamate to the urethane prepolymer was determined to be $\bar{M}$n 7900 and $\bar{M}$w 21100 (polystyrene standard) by GPC.



Poly(amino acid)-urethane block copolymer (**3**)

Table 5. Electrochemical and Chemical Block Copolymerization of Amino Acid NCA's with an Urethane Prepolymer (2; n, ca. 28) with EGB and Triethylamine Catalysts, Respectively

NCA		Method[a]	Poly(amino acid)–urethane block copolymer	
Amino acid	Mol. ratio to urethane prepolymer		Yield/%[b]	Mol. ratio of amino acid to urethane prepolymer[c]
L-Leucine	16	A	65	17
L-Leucine	8	A	67	9
L-Leucine	16	B	59	18
L-Leucine	8	B	74	7
L-Leucine	16	C	35	17
L-Valine	8	B	70	7
L-Valine	16	C	35	18
DL-Valine	16	A	53	18
DL-Valine	16	B	59	16
DL-Valine	8	B	74	8
γ-Benzyl L-glutamate	18	A	63	17
γ-Benzyl L-glutamate	9	A	61	8
γ-Benzyl L-glutamate	18	B	69	17
γ-Benzyl L-glutamate	9	B	70	8
γ-Benzyl L-glutamate	4	B	67	3
γ-Benzyl L-glutamate	9	C	40	10

a) Reaction time, 2 h. b) For amino acid component in block copolymer formed. c) Approximately estimated from ^{1}H NMR.

Table 6. Electrochemical Preparation of Flexiable Conductive Poly(amino acid)-Polypyrrole complex Films

Poly(amino acid) component	Thickness /mm	Polypyrrole content /wt%	Conductivity/Ω^{-1} cm^{-1}	
			Surface side	Back side
Poly(L-leucine)	0.4	48	15	35
Poly(γ-benzyl L-glutamate)	0.5	43	4	5
Poly(γ-benzyl L-glutamate)-urethane block copolymer	1.2	35	0.04	1

Electrochemical Preparation of Flexible Electroconductive Poly(amino acid)-Polypyrrole Complex Films. It is well-known that the anodic oxidative polymerization of pyrrole forms electroconductive polypyrrole coatings on anodes but they are not so flexible to be peeled off as films from the anodes.[14] It may be the way to get the electroconductive polypyrrole films to make blend polymers with other flexible polymers, but it is not so easy because of insolubility of polypyrrole in most solvents.

Efforts have been made to prepare flexible polypyrrole films. It has recently been reported that flexible polypyrrole films can be prepared by anodically polymerizing pyrrole using electrodes coated with a variety of nonconductive polymers such as poly(vinyl chloride), polystyrene, and poly(methyl methacrylate).[14-17] The films thus prepared show good thermal and mechanical properties.[14]

In this work, poly(amino acid)-polypyrrole complex films were prepared by anodically polymerizing pyrrole on platinum anode in the presence of amino acid NCA's in an undivided cell. It is noted that the polymerization of NCA's proceeds in the whole area of the cell, as described previously. Therefore, poly(amino acid)s formed in the vicinity of the anode during the electrolysis might be incorporated into polypyrrole films deposited on the anode surface. The films were easily peeled off from the anode. As shown in Table 6, there were not any great differences in conductivity between the surface and back sides. The films are also expected to have hydrophilic nature and affinity for biomaterials: This may suggest possibility of their in vivo use.

Experimental

Materials. Amino acid NCA's were prepared from amino acid and trichloromethyl chloroformate (phosgene dimer).[18] The urethane prepolymer(**2**) was kindly supplied by Mitsubishi Kasei Co. All the other chemicals were commercially available.

Syntheses of Homopoly(amino acid)s, Copoly(amino acid)s, and Poly(amino acid)-Polyurethane Copolymers. In Method A, PB's (0.7 mmol) were electrolyzed at a platinum cathode (12 cm^2) in 60 cm^3 of dry THF containing n-Bu_4NBF_4 (0.1 mol dm^{-3}). The electrolysis was carried out by passing 0.05 F/mol-NCA of charge under galvanostatic conditions (at 0.08 A dm^{-2} of current dencity) in a divided cell and then the resulting cathodic solution was added to an NCA solution. Electrolysis in Method B was also carried similarly in the absence of PB's.

After the electrolysis, precipitating poly(amino acid) was filtered and washed with THF. IR and ^{1}H NMR spectra were measured in KBr and CF_3COOH, respectively. Kinematic viscosity of poly(amino acid) (0.5 w/v% in CF_3COOH) was also measured using an Ubbelohde's viscometer at room temperature.

Preparation of Poly(amino acid)-Polypyrrole Complex Films. Amino acid NCA (1 g) was electrolyzed using platinum electrodes (12 cm^2) in 0.1 mol dm^{-3} n-Bu_4NBF_4/CH_3CN(200 cm^3) containing pyrrole (0.01 mol) for 1 h under galvanostatic conditions(20 mA) in an undivided cell. After the electrolysis, the film deposited on the anode surface was peeled off and its conductivity was measured under dry conditions by the two probe method. Poly(amino acid) content in the films was determined from UV-spectra of solutions which were prepared by extracting the films with CF_3COOH or benzene under ultrasonic irradiation.

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