Kinetic Study on Free Radical Polymerization of 2-Acetamidoacrylic Acid and Formation of Hydrogel

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ABSTRACT: Radical polymerization of captodative (cd) substituted 2-acetamidoacrylic acid (**1**) was studied kinetically at 40°C. The rate constants of propagation (k_p) and termination (k_t) of **1** were estimated by a rotating sector and an inhibitor method using 1,3,5-triphenylverdazyl. Termination was depressed and k_p/k_t became high, which was responsible for the high radical polymerization reactivity of **1** in spite of the cd olefin. The hydrogel consisting of poly(acetyl dehydroalanine) network was synthesized by the copolymerization of **1** and bifunctional cross-linker with the structure analogous to **1**. The swelling ratio of the gel was dependent on the cross-linker concentration and reached a maximum of 1334 at 2% cross-linker concentration in the feed. The gel showed stimuli-response to pH and electric field, *i.e.*, the gel volume increased to twice as much when transferred from an acidic solution into an alkaline solution and the gel bent toward an anode side within a few minutes when the electric field was applied. Biodegradability of the polymers was examined using α -chymotrypsin.

KEY WORDS Radical Polymerization / Kinetic Study / Dehydroalanine / Captodative Substitution / Hydrogel /

Captodative (cd) olefins are olefins geminally substituted with an electron-withdrawing group (captive) and electron-donating group (dative), and often display special reactivity in free radical polymerizations due to the cd stabilization and polarization effects.¹ Dehydroalanines also belong to cd olefins, and the radical polymerizability of the dehydroalanines has been studied. *N*-acetyl dehydroalanine would homopolymerize very easily by radical initiators to give a high molecular weight or a monolayer polymer,^{2,3} but unsubstituted dehydroalanine and its methyl ester as well as the *N*-methyl derivatives of the butanamide analogue would not homopolymerize.^{4,5} That is, the polymerizability of dehydroalanine derivatives greatly depends on substituents. Correlation between the radical polymerizability and structure of the dehydroalanines, however, has little been studied up to now, and only a preliminary kinetic study is reported for *N*-acetyl dehydroalanine, *i.e.*, 2-acetamidoacrylic acid (**1**).⁶

Dehydroalanine polymers have two functional groups in the side chain, and act as polyelectrolytes and so on.⁷ Modification of these polar side groups is easy and optical active polynucleotide⁸ and comb-like polymer⁹ have been prepared. In particular, dehydroalanine polymers have potentially hydrophilic groups, and may be expected to form the hydrogel which shows a high swelling ratio and good mechanical properties due to a long polymer chain with low concentration of cross-linking. This

paper studies kinetically the radical polymerization of **1**, and the formation of the stimulus-response hydrogel by the cross-linking copolymerization of **1** and the bifunctional analogue (**2**).

EXPERIMENTAL

Materials

1 was synthesized by reaction of pyruvic acid and acetamide in benzene solution according to the literature.² Purification of **1** by recrystallization from ethanol gave white needles in a 50.4% yield; mp 198–199°C (lit.² 198–199°C). **2** was prepared by refluxing pyruvic acid 44.0 g (0.5 mol) and succinamide 11.6 g (0.1 mol) in 500 mL benzene for 7 h. White powder **2** produced was removed by filtration from the supernatant benzene and washed by hot water to remove unreacted starting materials to give 2.74 g of pure **2** in 11.4% yield; mp 229°C (decomp.).

¹H NMR (D₂O) of **2**: δ 2.53 (s, CH₂, 4H), 5.68 (s, =CH, 1H), and 5.92 ppm (s, =CH, 1H). *Anal.* Calcd for C₁₀H₁₂N₂O₆: C, 46.88; H, 4.69; N, 10.94%. Found: C, 46.59; H, 4.94; N, 11.13%.

Methyl 2-acetoxyacrylate (MAA) was synthesized by reaction of methyl pyruvate and acetic anhydride using *p*-toluenesulfonic acid as catalyst in a manner similar for ethyl 2-acetoxyacrylate.¹⁰ 2,2'-Azobisisobutyronitrile (AIBN) and 1,1'-azobis(cyclohexane-1-carbonitrile) (ACHN) commercially available from Wako Chemicals and 1,3,5-triphenylverdazyl (TPV) prepared by the method of Kuhn *et al.*¹¹ were all used after recrystallizations from ethanol. Commercial grade dimethyl sulfoxide (DMSO) used as solvent was purified by fractional distillation under reduced pressure.

Polymerizations

Polymerizations were carried out in a sealed ampoule with shaking at a given temperature. The ampoule con-

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taining the required amounts of reagents was degassed several times by a freeze-thaw method and then sealed under reduced pressure and placed in a constant temperature bath. The resulting polymer was isolated by pouring the contents of the ampoule into excess acetone. Kinetic study of the polymerization was carried out in DMSO in a quartz UV cell filled with N_2 gas containing required amounts of reagents at 40°C with monitoring the polymerization by UV spectrophotometry. The average life-time of propagating radicals (τ) was measured in a UV-quartz cell (1 mm thickness) by the rotating sector method using a sector with the ratio of dark to light periods = 2, 30 W chemical lamp as the light source, and ACHN as photosensitizer, in which the overall rate of polymerization was simultaneously estimated by following monomer concentration decay while monitoring UV-absorption at 289 nm due to the monomeric C=C bond of **1**. In the determination of initiation rate (R_i), the polymerization was carried out in a UV-quartz cell (10 mm thickness) using AIBN as initiator and TPV as radical trapping reagent, and R_i was estimated by following TPV concentration decay by UV spectrophotometry.

The copolymerization of **1** ($[1] = 1.0 \text{ mol L}^{-1}$) and **2** was carried out in DMSO using ammonium persulfate (5 mmol L^{-1}) as initiator at various molar ratios of **1** and **2** at 27°C for 30 h according to the method similar for the polymerization of **1**. The resulting copolymers, *i.e.*, organogels, were placed into a large amount of water, and washed with distilled water several times over 7 days to form the hydrogel samples. Some gel samples were again immersed in distilled water for 24 h at 50°C , and dried at 50°C for 6 h under vacuum and ground to a powder for the swelling experiments. The gel samples in the experiments of swelling ratio-variation with time and stimulus-response to pH and electric field were obtained by copolymerization at $[2]/[1] = 0.017$ molar ratio. In copolymerization at lower $[2]/[1]$ ratios, the copolymer produced was isolated by pouring the reaction mixture into excess acetone because they were soluble in water.

Hydrolyses and Biodegradation

Poly(2-aminoacrylic acid), *i.e.*, poly(dehydroalanine), was prepared by hydrolysis of the polymer of **1** in refluxing 70% H_2SO_4 aqueous solution for 4 h, followed by dialysis using seamless cellulose tube over 24 h. In the biodegradation of the polymer of **1**, the polymer sample (150 mg) was immersed in 50 mL buffer solution (58 mmol L^{-1} of Na_2HPO_4 and 9 mmol L^{-1} KH_2PO_4 , pH 7.6), followed by the addition of α -chymotrypsin and stirred at 30°C . The degradation of the polymer was estimated by pouring the reaction mixture into excess acetone and weighing the precipitated polymer.

Measurements

The swelling ratio (W/W_0) was defined as the weight of absorbed water (W) per weight of dried gel (W_0) at 27°C . Equilibrium swelling weights for the gel in water were measured using a bag made of nylon ($58 \mu\text{m}$, 260 mesh). Electric field response was examined by observing the gel shape when the electric field of 30 V was applied to the gel sample ($5 \times 70 \text{ mm}^2$) placed between the electrodes kept at 10 cm in aqueous solution. To study gel swelling at different pH-values, the weighed dry gel

sample was put in buffer solution of $\text{CH}_3\text{COOH}/\text{CH}_3\text{COONa}$ or $\text{NH}_4\text{Cl}/\text{NH}_3$, and remained in solution at 27°C for 2 h. The gel sample was weighed and pH of the exterior solution was measured.

^1H NMR spectrum was measured on a JEOL JNM-MY 60 spectrometer at 60 MHz in deuterated-DMF ($\text{DMF-}d_7$) using tetramethylsilane as internal standard or in $\text{D}_2\text{O}/\text{NaOD}$. UV absorption was recorded on Shimadzu UV-1600PC spectrophotometer in DMSO.

RESULTS AND DISCUSSION

Polymerization of **1**

Radical polymerization of **1** gives a high molecular weight polymer² and proceeds through the conventional radical polymerization kinetics,⁶ *i.e.*, the overall polymerization rate (R_p) depends on the square root of the initiator concentration and first order of the monomer concentration in DMSO. The polymerization kinetics using sector and inhibitor were thus studied on the basis of the rate equation familiar in ordinal radical polymerization. Figure 1 depicts the results obtained by the rotating sector experiment in the polymerization of **1** in DMSO using ACHN as initiator at 40°C , in which R_{ps} and R_{pL} represent the polymerization rates in intermittent irradiation of light using a sector and stationary irradiation of light, respectively. In this experiment, R_{pd}/R_{pL} was 0.09, where R_{pd} is the polymerization rate in the dark. From this Figure, average life-time of propagating radicals (τ) was estimated to be 2.15 s. TPV has been reported to be useful and convenient inhibitor for determining the initiation rate (R_i) because it absorbs light in the region (720 nm) where other reagents such as monomer and initiator have no absorption of light and hence, it is easy to estimate the induction period (t) by UV spectrophotometry according to the equation: $R_i = [\text{TPV}]/t$.¹² In the concentration of $[\text{TPV}] = 1.00 \times 10^{-5} \text{ mol L}^{-1}$ and $[\text{AIBN}] = 2.00 \times 10^{-2} \text{ mol L}^{-1}$, the induction period (t) was estimated to be 200 min, so that $R_i = 8.33 \times 10^{-9} \text{ mol L}^{-1} \text{ s}$.

Table I summarizes individual rate constants of the polymerization of **1**, in which the rate constants of the propagation (k_p) and termination (k_t) were calculated according to the following equations. In this Table, the rate

Figure 1. Determination of average life time of propagating radicals generated from **1**. ---: Calculated for $R_{pd}/R_{pL} = 0.09$ and $\tau = 1.00 \text{ s}$, and see the text for the abbreviations of R_{ps} , R_{pL} , and R_{pd} .

Table I. Rate constants of radical polymerizations of various olefins at 40°C

Monomer	$(k_p/k_t) \cdot 10^6$	$(k_p^2/k_t) \cdot 10^3$ L mol ⁻¹ s ⁻¹	$k_p \cdot 10^{-2}$ L mol ⁻¹ s ⁻¹	$k_t \cdot 10^{-6}$ L mol ⁻¹ s ⁻¹
1	144	189	13.1	9.10
MAA ^a	(16.5)	2.96	1.80	10.9
MMA ^b	8.92	—	—	—
MMA ^b	13.6	—	5.96	43.8
Styrene ^b	2.77	—	(1.02)	(36.8)

^a See ref 13 except k_t obtained in this study. The value in parenthesis was calculated from k_t and k_p . MAA: methyl 2-acetoxyacrylate. ^b See ref 14. The values in parentheses for styrene are cited from data of other authors in ref 14.

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$$k_p/k_t = R_p \tau/[1]$$

$$k_p^2/k_t = R_p^2/R_i[1]^2$$

monomers including *cd* substituted MAA,¹³ methyl methacrylate (MMA), and styrene are also listed for comparison,¹⁴ in which k_t of MAA was estimated from k_p already determined by ESR¹³ and k_p^2/k_t (2.96×10^{-3} L mol⁻¹ s) calculated from the initiation rate in this study using TPV in 1,1,2-trichloroethane in a similar manner for **1**. Obviously, k_p of **1** is higher, whereas k_t is lower than those of other monomers listed, and hence k_p/k_t becomes high. This is responsible for the high radical polymerization reactivity of **1** in spite of the *cd* olefin. Characteristic behavior, *i.e.*, electric interaction between the polymer chains^{2,3} and significant variation of R_p with the solvents used,⁶ has been pointed out for the polymer and polymerization of **1**. The restriction of mobility of radical chains as well as stabilization of the propagating radical ends should thus be taken into account to some extent in the polymerization of **1** owing to the association between monomers and polymers and captodative stabilization effect,¹⁵ and it may reflect the relatively large k_p/k_t of **1** as seen in the polymerization of MAA.¹³

Enzymatic degradation of the polymer of **1** was examined using α -chymotrypsin since polyamide has been reported to be degradable in the presence of α -chymotrypsin.¹⁶ About 30% weight loss of the polymer was observed after immersing in the buffer solution containing the enzyme for 2 days at 30°C. Detailed study on the biodegradation is now in progress.

Formation and Characteristics of Hydrogel

It is of interest that the homopolymer of **1** is readily soluble in water in contrast to the monomer **1** and hydrolyzed homopolymer of **1**.¹⁷ To prepare a hydrogel, **1** and **2** were copolymerized at 27°C for 30 h at molar ratios of [2]/[1] = 0.10, 0.050, 0.033, 0.020, 0.017, 0.013, and 0.010. The polymerizations proceeded smoothly to give a polymer in high yield, *i.e.*, 85.7–100% in such conditions. Large portions of the copolymers obtained at molar ratios of [2]/[1] = 0.013 and 0.010 were soluble in water and DMSO probably because of the formation of an insufficient network, but all other copolymers were insoluble in organic solvents and water and swelled in water due to crosslinking as shown in Scheme 2. To examine the network structure, the copolymerization reactivity of **1** and **2** was followed by monitoring decrease in UV absorption

Scheme 2. **Figure 2.** Dependence of cross-linker concentration in the copolymerization feed on the swelling ratio of the gel.

of the monomers at 295 nm during the copolymerization at several [2]/[1] ratios since both **1** and **2** show a small absorption at 295 nm due to the conjugated C=C double bonds of the monomers. Absorbance at 295 nm decreased gradually at nearly the same rate independent of [2]/[1] ratios at the initial stage of the copolymerization, suggesting similar reactivity of **1** with **2** in the copolymerization as expected from their structures. The resulting gels may thus be considered composed of networks of homogeneously cross-linked polymers although some irregular units may be incorporated into the copolymer at latter stages of copolymerization due to gel effects and so on.

Figure 2 shows the dependence of cross-linker concentrations in the copolymerization feed ([1] = 1.0 mol L⁻¹) on the swelling ratio of the copolymer. Apparently, the swelling ratio increases with decreasing cross-linker concentration as is generally known,¹⁸ and finally reaches maximum of 1334 at [2]/[1] = 0.02 molar ratio. The swelling ratio of 1334 obtained is comparable to that of acrylic gels used as water-absorbing materials.¹⁹ In 0.9% NaCl aqueous solution, the swelling ratio was reduced to *ca.* 100 for such hydrogel. Figure 3 shows the time-variation of the swelling ratio of the gel prepared by the copolymerization at [2]/[1] = 0.017 molar ratio. The gel absorbs almost half the potentially absorbing water within a few minutes and gradually reaches saturation. The swelling ratio varies little with temperature in the range from 20 to 70°C, but is dependent on pH of the medium and the swelling ratio increases with pH of

Figure 3. Swelling ratio of the gel as a function of immersion time in distilled water.

Figure 4. Dependence of the swelling ratio of the gel on the pH of aqueous solution surrounding the gel sample.

the environment at pH3 to pH11 as seen in Figure 4. At pH=11, the volume of the gel was about twice that in acidic solution. This may be attributed to the electrostatic repulsion between carboxylate anions in the side chains generated by dissociation of the carboxylic acid in alkaline solution.

Figure 5 indicates the gel shape before and after applying an electric field, in which the left-hand side is the anode and the right-hand side is the cathode. As clearly seen in this picture, the gel bends with the anode side under an electric field. Response time is greatly dependent on the conditions, and it takes only a few minutes in 1.0 wt% NaCl aqueous solution, but about 4 h in distilled water. This may be explained by gel ionization.²⁰ The gel swelling upon ionization gradually occurs in distilled water mainly because of the slow increase of the osmotic pressure exerted by mobil counterions. In NaCl aqueous solution, however, the anode side is smoothly acidified with chloride ions, whereas the cathode side is alkalized with sodium ions. This brings about rapid change in anion and cation distribution around the gel, followed by increase in osmotic pressure of the external solution and electrostatic screening of the gel charges leading to the gel shrinkage in the anode side and the swelling in the cathode side. Shrinking and swelling on each side force the gel to bend as seen in Figure 5.

Figure 5. Variation in gel shape with application of an electric field of 30 V. Before (A) and after (B) application of the electric field.

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