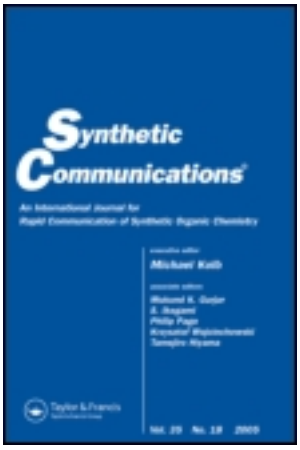


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# Method for a Convenient and Efficient Synthesis of Amino Acid Acrylic Monomers with Zwitterionic Structure

Shoji Nagaoka [a] , Atsuomi Shundo [b] , Takao Satoh [b] , Kazuhiko Nagira [c] , Ryoich Kishi [d] , Katsuhiko Ueno [d] , Kokoro Iio [d] & Hirotaka Ihara [b]

[a] Kumamoto Industrial Research Institute, Kumamoto, Japan

[b] Department of Applied Chemistry and Biochemistry, Faculty of Engineering, Kumamoto University, Kumamoto, Japan

[c] Dojindo Laboratories, Kumamoto, Japan

[d] National Institute of Advanced Industrial Science and Technology, Ibaraki, Japan

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# Method for a Convenient and Efficient Synthesis of Amino Acid Acrylic Monomers with Zwitterionic Structure

**Shoji Nagaoka**
Kumamoto Industrial Research Institute, Kumamoto, Japan

**Atsuomi Shundo and Takao Satoh**
Department of Applied Chemistry and Biochemistry, Faculty of Engineering, Kumamoto University, Kumamoto, Japan

**Kazuhiko Nagira**
Dojindo Laboratories, Kumamoto, Japan

**Ryoich Kishi, Katsuhiko Ueno, and Kokoro Iio**
National Institute of Advanced Industrial Science and Technology, Ibaraki, Japan

**Hirotaka Ihara**
Department of Applied Chemistry and Biochemistry, Faculty of Engineering, Kumamoto University, Kumamoto, Japan

**Abstract:** Ampholyte monomers with zwitterionic moiety derived from $\alpha$-amino acid, that is, L-lysine and L-serine, were obtained using a method in which their copper complexes could be produced in simple steps. The *N*-acryloylation of L-lysine and L-serine was carried out by reaction between their copper complexes and acryloyl chloride. Specifically, the removal of copper from the copper complex of acryloyl amino acid through the use of 8-hydroxyquinoline as an organic chelate precipitant

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Address correspondence to Shoji Nagaoka, Kumamoto Industrial Research Institute, Higashimachi, Kumamoto 862-0901, Japan. Tel.: +81-96-365-5172; Fax: +81-96-365-5172; E-mail: nagaoka@kmt-iri.go.jp

increased the yield of the ampholyte monomers with zwitterionic moiety. These syntheses were easily carried out in a three-step procedure.

**Keywords:** Amino acid copper complex, 8-hydroxyquinoline, zwitterionic monomer



The hydrogel structure formed on the surface of zwitterionic amino acid moiety, for example, *O*-methacryloyl L-serine and ε-methacryloyl L-lysine, is a suitable biocompatible material.[1–3] Sugiyama et al. reported that copolymers containing the zwitterionic L-serine moiety greatly inhibit the aggregation of platelet-rich plasma (PRP). The zwitterionic monomer was prepared through a complex three-step procedure involving the esterification of the hydroxyl group in *N*-*t*-butoxycarbonyl L-serine using methacryloyl chloride, followed by laborious treatment with trifluoroacetic acid as a deblocking reagent, which resulted in 25% yield.[4] We have sought a convenient and efficient synthetic method without need for the organic blocking reagent and deblocking reagent, which are highly acidic substances, in order to increase the yield of the zwitterionic monomer derived from L-serine.

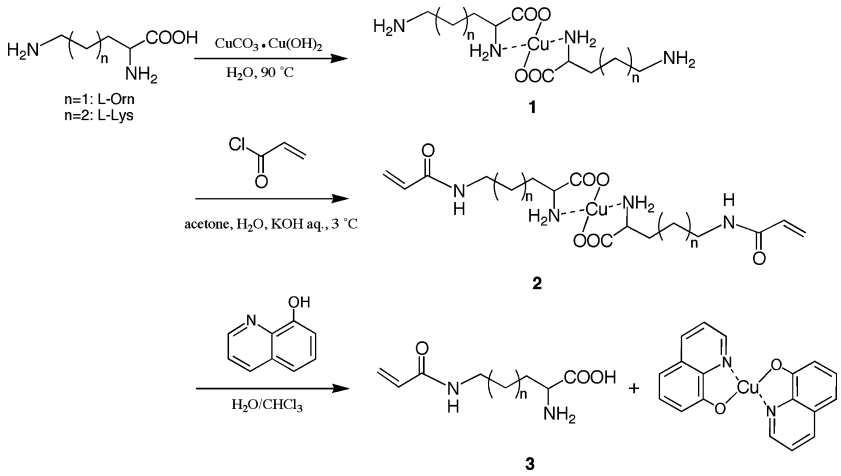
We noticed the reaction between the amino acid copper complex and acryloyl chloride. Morawetz et al. have obtained a zwitterionic monomer containing the L-lysine side chain group using the following procedures: (1) they synthesized the methacryloyl L-lysine copper complex and (2) they passed hydrogen sulfide through a suspension of the copper complex in an aqueous methanol solution to remove copper from the copper complex. However, the resulting yield was only 1%.[5]

In an attempt to create a convenient and efficient collection method without using hydrogen sulfide, we developed the following simple procedure: (1) the acryloylation of α-amino acid copper complexes (i.e., L-lysine copper complexes, Scheme 1, or L-serine copper complexes, Scheme 2), and (2) the extraction of copper from their copper complexes using 8-hydroxyquinoline as an organic chelate precipitant.[6]

Stirring L-lysine hydrochloride with basic cupric carbonate in water at 90°C gave the copper complex **1** of L-lysine. After KOH aqueous solution and acetone were added to the aqueous solution of the copper complex of L-lysine, acryloyl chloride and KOH aqueous solution were added in four doses at 3°C. The precipitates of *N*-acrylamide cupric complex **2** of L-lysine were obtained in a 78% yield by filtrating and washing successively with water, methanol, and ether.

In addition, *O*-acryloyl L-serine copper complex **5** was produced by the esterification of the hydroxyl group of L-serine copper complex **4** by the same procedure as used in the synthesis of **2**. The yield was 50%.

The acryloyl copper complexes of the respective amino acids were then dispersed in water and the chloroform solution of 8-hydroxyquinoline was added. After shaking in a separation funnel, a green precipitate was produced

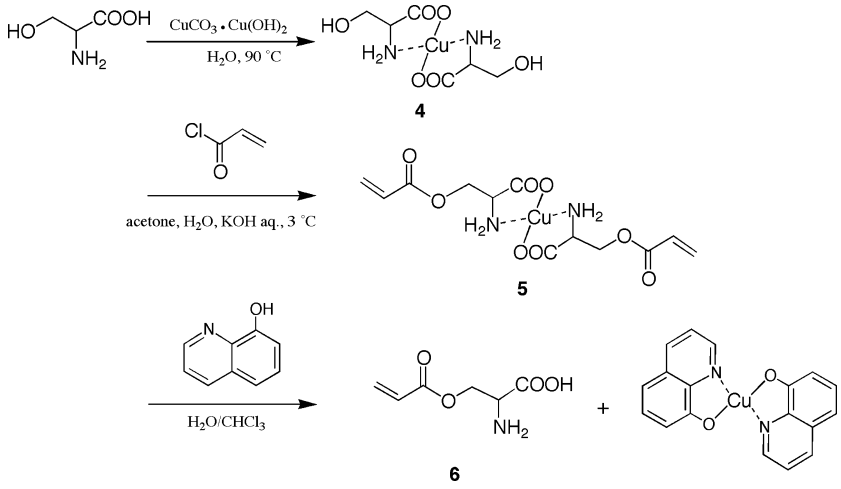



*Scheme 1.*

in the chloroform layer, and this was removed by filtration. The product in water was recrystallized from teterahydrofuran. The yield of the ε-acryloyl L-lysine (LysAAm) **3** monomer estimated from L-lysine as the starting material was 74%. It is clear that the yield of **3** was much higher than that reported by Morawetz et al.[5]

In addition, δ-acryloyl L-ornitine (OrnAAm) could be produced by the same procedure used for the synthesis of **3** in good yields.

However, the 50% yield of **5** estimated from the amount of L-serine was lower than that of the copper complex of basic amino acids, L-lysine and




*Scheme 2.*

L-ornitine. This phenomenon is caused by L-serine's neutrality as an amino acid. However, the yield of *O*-acryloyl L-serine **6** obtained by the extraction of copper using 8-hydroxyquinoline is estimated to be 92%, based on the amount of its copper complex. The yield of **6** estimated from the amount of L-serine is 46%. It is clear that the yield of **6** was higher than that reported by Sugiyama et al.[4]

We developed a simpler method for the synthesis of ampholyte monomers with a high yield starting from basic amino acids, L-lysine and L-ornithine, and even starting with a neutral amino acid such as L-serine. These syntheses were easily carried out using a three-step procedure. The yield of the ampholyte monomers with zwitterionic moiety could be easily increased by extracting the copper from the acryloyl amino acid copper complexes using the 8-hydroxyquinoline–chloroform solution.



## EXPERIMENTAL

### General

$^1$H NMR spectra were recorded with a JEOL GX-400 spectrometer. IR spectra were measured as KBr disks with diffuse reflectance infrared Fourier-transform (DRIFT) spectroscopy (JASCO FT/IR-700).

### ε-Acryloyl L-Lysine Copper Complex 2

L-Lysine hydrochloride (100 g, 548 mmol) was dissolved in water (1200 ml) at 90°C. Basic cupric carbonate (66.6 g, 301 mmol) was added slowly to the solution and stirred for 10 min. After cooling and filtering the insoluble residue, 580 ml of acetone was added. After 274 ml of 2.0 M KOH aqueous solution were added into solution of the copper complex of the L-lysine, acryloyl chloride (13.8 ml, 171 mmol) and 77 ml of 2.0 M KOH aqueous solution was added every 5 min at 3°C. This procedure was repeated four times. After stirring for 12 h, the precipitates of the acrylamide cupric complex of the L-lysine were filtrated and washed successively with water, methanol, and ether. The yield was 98.7 g (78%). Their structure was confirmed by their IR spectra. IR ($cm^{-1}$): 3100–3400, $\nu_{N\text{-}H}$ (amide, amine); 2880–2960, $\nu_{C\text{-}H}$; 1660, $\nu_{C=O}$ (amide I); 1620, $\delta_{N\text{-}H}$ (amide II); 670, $\delta_{N\text{-}H}$ (amide V). Elemental analysis (%) calcd. for $C_{18}H_{30}N_4O_6Cu$: C, 46.80; H, 6.55; N, 12.13. Found: C, 45.00; H, 6.52; N, 11.81.

### ε-Acryloyl L-Lysine (LysAAm) 3

The solid of **2** (21.0 g, 45.5 mmol) was dispersed in water (300 ml), and a chloroform solution (300 ml) of 8-quinolinol (7.91 g, 54.5 mmol) was added.

After shaking for 12 h in a separation funnel, a green precipitate in the chloroform layer was produced, and this was removed by filtering. Three extractions with chloroform were performed to remove traces of 8-hydroxy quinoline. The water layer was concentrated to 50 ml after the removal of 8-hydroxyquinoline. The white precipitate was recrystallized from teterahydrofuran. The yield was 17.1 g (94%). The structure was confirmed by its $^1$H NMR and IR spectra. The $^1$H NMR spectrum of the monomer was measured in $D_2O$. $^1$H NMR ($D_2O$, $\delta$ ppm): 1.42 (m, 2H, $CH_2$), 1.60 (m, 2H, $CH_2$), 1.86 (m, 2H, $CH_2$), 3.26 (t, 2H, $CH_2$), 3.73 (t, 2H, $CH_2$), 5.75 (d, 1H, $CH_2$═CH[trans]), 6.18 (d, 1H, $CH_2$═CH[cis]), 6.21 (dd, 1H, $CH_2$═CH). IR ($cm^{-1}$): 3350, $\nu_{N\text{-}H}$ (amide); 2880–2960, $\nu_{C\text{-}H}$; 2200–3200, $\nu_{N\text{-}H}$ ($NH_3^+$); 2000–2222, $\delta_{N\text{-}H}$ ($NH_3^+$); 1660, $\nu_{C=O}$ (amide I); 1620, $\delta_{N\text{-}H}$ (amide II); 670, $\delta_{N\text{-}H}$ (amide V). Elemental analysis (%) calcd. for $C_9H_{16}N_2O_3$: C, 53.22; H, 7.72; N, 13.80. Found: C, 53.98; H, 8.05; N, 13.99.

## δ-Acryloyl L-Ornithine (OrnAAm)

δ-Acryloyl L-ornithine copper complex was produced from L-ornithine hydrochloride (100 g, 594 mmol) using the same procedure as that for L-lysine. The yield was 91.0 g (71%). The structure was confirmed by IR spectra. IR ($cm^{-1}$): 3100–3400, $\nu_{N\text{-}H}$ (amide, amine); 2880–2960, $\nu_{C\text{-}H}$; 1660, $\nu_{C=O}$ (amide I); 1620, $\delta_{N\text{-}H}$ (amide II); 670, $\delta_{N\text{-}H}$ (amide V). Elemental analysis (%) calcd. for $C_{16}H_{26}N_4O_6Cu$: C, 44.29; H, 6.04; N, 12.91. Found: C, 42.35; H, 6.15; N, 12.78.

In addition, L-OrnAAm was produced from δ-Acryloyl L-ornithine copper complex (32.1 g, 74.1 mmol) using the same procedure as that for the synthesis of L-lysAAm. The yield was 25.2 g (92%). The structure was confirmed by its $^1$H NMR and IR spectra. The $^1$H NMR spectrum of the monomer was measured in $D_2O$. $^1$H NMR ($D_2O$, $\delta$ ppm): 1.63 (m, 2H, $CH_2$), 1.88 (m, 2H, $CH_2$), 3.30 (t, 2H, $CH_2$), 3.74 (t, 2H, $CH_2$), 5.76 (d, 1H, $CH_2$═CH[trans]), 6.19 (d, 1H, $CH_2$═CH[cis]), 6.21 (dd, 1H, $CH_2$═CH). IR ($cm^{-1}$): 3350, $\nu_{N\text{-}H}$ (amide); 2880–2960, $\nu_{C\text{-}H}$; 2200–3200, $\nu_{N\text{-}H}$ ($NH_3^+$); 2000–2222, $\delta_{N\text{-}H}$ ($NH_3^+$); 1660, $\nu_{C=O}$ (amide I); 1620, $\delta_{N\text{-}H}$ (amide II); 670, $\delta_{N\text{-}H}$ (amide V). Elemental analysis (%) calcd. for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15. 04. Found: C, 51.14; H, 7.33; N, 15.04.

## *O*-Acryloyl L-Serine Copper Complex 5

L-Serine (5.0 g, 47.6 mmol) was dissolved in water (50 ml) at 90°C. Basic cupric carbonate (5.90 g, 26.2 mmol) was added slowly to the solution and stirred for 10 min. After filtering the insoluble residue, washing with hot water (30 ml), and cooling, acetone (10 ml) was added. After 27.1 ml of 2.0 M KOH aqueous solution were added into the solution of the copper complex

of L-serine, acryloyl chloride (4.8 ml, 59.5 mmol) in acetone (30 ml) was added over 5 min. After stirring for 12 h, the precipitate of the acryloyl cupric complex of the obtained serine was filtrated and washed successively with water, methanol, and ether. The yield was 50% (4.83 g). The structure was confirmed by their IR spectra. IR ($cm^{-1}$): 3160–3320, $\nu_{N\text{-}H}$ (amine); 2880–2960, $\nu_{C\text{-}H}$; 1725, $\nu_{C=O}$ (ester). Elemental analysis (%) calcd. for $C_{12}H_{16}N_2O_8Cu$: C, 37.95; H, 4.25; N, 7.38. Found: C, 37.34; H, 4.33; N, 7.22.

### *O*-Acryloyl L-Serine (SerAE) 6

In addition, L-SerAE was produced from **5** (4.83 g, 12.7 mmol) using the same method as that used for L-LysAAm. The yield was 92% (3.79 g). The structure was confirmed by its $^1H$ NMR and IR spectra. The $^1H$ NMR spectrum of the monomer was measured in $D_2O$. $^1H$ NMR ($D_2O$, $\delta$ ppm): 4.11 (m, 2H, $CH_2$), 4.58 (t, 2H, $CH_2$), 6.03 (d, 1H, $CH_2$═CH[trans]), 6.21 (dd, 1H, $CH_2$═CH), 6.44 (d, 1H, $CH_2$═CH[cis]). IR ($cm^{-1}$): 2200–3200, $\nu_{N\text{-}H}(NH_3^+)$; 2880–2960, $\nu_{C\text{-}H}$; 1725, $\nu_{C=O}$ (ester). Elemental analysis (%) calcd. for $C_6H_9NO_4$: C, 45.28; H, 5.7; N, 8.80. Found: C, 43.65; H, 5.56; N, 8.71.

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