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Studies on the Synthesis of Protein Analogus (Part IV)

Polymerisation of Glycine*

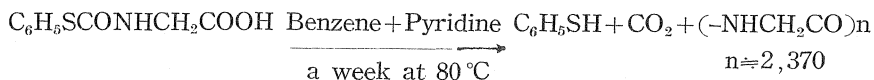
By

Junzo NOGUCHI, Masatomo ASAI, Shohei ISHINO and

Tadao HAYAKAWA

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The only method for preparing the polyglycine having several ten thousands molecular weight was that of α -amino-N-carboxylic acid anhydride.¹⁾ Applying to glycine our N-carbothiophenyl method²⁾ which is a new synthetic method of polypeptide, we could prepare polyglycine having high molecular weight of about 135,200.



Solvent effect is remarkable in this reaction. After heating the monomer in benzene for a week at 80°C, no remarkable change occurred and unchanged carbothiophenyl-glycine was recovered almost quantitatively, while in benzene containing a small amount of pyridine, white gelatinous polymer began to precipitate uniformly in the solvent after heating for one day at 80°C.

The polymerisation was carried out at the heating of 80°C for 170 hours in benzene containing about ten moles pyridine to the sample. That was the best condition and the best concentration of the solution in the case of polymerizing DL-phenylalaine³⁾, too.

The polymer was white powder and the rate of polymerisation was about 89% of the theoretical. The analytical value corresponded to polyglycine $(-\text{NHCH}_2\text{CO}-)_n$, and clear Biuret's reaction was proved. It is insoluble in cold or hot water, alcohol, benzene, acetic acid, formic acid, pyridine and alkali, hardly soluble in the mixture of glacial acetic acid and monochlor acetic acid (1 : 1) and soluble in dichlor-acetic acid. The molecular weight and the polymerisation degree were measured by the osmotic method in dichlor-acetic acid solution.

Molecular weight M. W. = 135, 200

Polymerisation degree $n \approx 2,370$

The intrinsic viscosity was determined by the viscosity of dichloracetic acid solution at 30°C.

intrinsic viscosity $[\eta] = 0.530$ (g/100 cc unit)

After the polymer was centrifuged, the mother liquor was concentrated to dryness

* It was published in the Jan. of the Chem. Soc. of Japan **75**, 642—643 (1954) (in Japanese).

1) H. Leuchs, Ber. **39**, 857 (1906), R. B. Woodward, C. H. Schram, J. Am. Chem. Soc. **69**, 1551 (1947).

2) J. Noguchi, Jan. of the Chem. Soc. of Japan **74**, 961 (1953).

3) J. Noguchi, K. Miyamori, S. Ishio, ibid. **75**, 641 (1954).

and the residue was purified with alcohol and water, then white powder was obtained, m. p. 59°C. It did not contain any nitrogen, but sulphur about 29.2%. So it might be dithiophenol, m. p. 59–60°C.

Carbothiophenyl-glycine decomposed slightly at about 120–130°C and vigorously at 150–170°C to polymerise. The polymer, which was obtained by block polymerisation at 150°C and washed with alcohol and ether, may not be of high polymerisation degree, to judge from its solubility and from the fact that its nitrogen content was lower than the theoretical. It had no trace of thiophenol when tested with lead acetate after treatment of alkali. In such conditions, we thought, there must be some subreaction beside the normal polymerisation, and it was confirmed by the next reaction that some branched chain polymer would be formed in the block polymerisation. Carbothiophenyl-glycine ethylester was mixed with carbobenzoxy-glycine, and heated at 120°C for 7 hours. We could not obtain the expected carbobenzoxy-glycylglycine ethylester, but we could obtain white crystal. (m. p. 73°C, N=8.29%). After hydrolysis of it by 0.5 N-NaOH, another new crystal (m. p. 162°C) was obtained. The nitrogen content and the molecular weight correspond to the following formula, but it is just a speculation at this stage, so more detailed evidences are necessary for confirming it.



After all, the method of the block polymerisation of carbothiophenylglycine is improper for the preparation of polyglycine, while the solution polymerisation can afford the high polymer.

Experimental

N-carbothiothiophenyl-glycine (m. p. 153°C), which was used in experiments, was prepared by treating glycine ester with carbothiophenylchloride as described by A. Lindenmann, etc.⁴⁾

Polyglycine—N-carbothiophenyl-glycine 2.11 g (0.01 moles) was dissolved in benzene 70 cc and pyridine 8.0 cc (0.1 moles) and polymerized in a sealed tube at 80°C for a week. The polymer began to precipitate uniformly in the solution as white gel after 24 hours. After polymerizing for a week, it was centrifuged, washed with benzene, alcohol and ether until the pyridine smell was lost completely, and dried in vacuum. White powder was obtained. Yield 520 mg. (88.5% of the theoretical). Strong clear Biuret's reaction was shown.

N analysis found N = 24.27%

For $(\text{C}_9\text{H}_9\text{ON})_n$ calc. N = 24.56%

Molecular weight : It was measured at 30 ± 0.01 °C by osmotic method with Meshizuka's apparatus.⁵⁾ The sample 0.05032 g was dissolved in dichlor-acetic acid and diluted to

4) A. Lindenmann, N. H. Khn, K. Hofmann, J. Am. Chem. Soc. **74**, 476 (1952).

5) G. Meshizuka, The Chemistry of Highpolymer **6**, 305 (1949)

10 cc.

Concentration $c=5.032$ g/L, Specific gravity $\rho=1.494$

Osmotic press. $\pi=0.64$ cm= 9.25×10^{-4} atm.

Molecular weight M. W. = 135,160 \approx 135,200

Polymerisation degree $n=2,370$

Viscosity : It was measured at $30 \pm 0.1^\circ\text{C}$ by Ostwald's viscosimeter.

$C=0.5032$, $\eta_{sp}/c=0.213$

$C=0.3018$, $\eta_{sp}/c=0.295$

$C=0.1812$, $\eta_{sp}/c=0.419$

intrinsic viscosity $[\eta]=[\eta_{sp}/c]_{c \rightarrow 0}=0.530$

Fused reaction with N-carbothiophenyl-glycine ester and N-carbobenzyloxyglycine

—N-carbothiophenyl-glycine ethyl 1.00 g and N-carbobenzyloxy-glycine 0.88 g were heated in a test tube at 120°C for 7 hours and then, in 12 mm Hg vaccum for 7 hours. The thiophenol decomposed was almost completely distilled. The residue was extracted with ether. The ether solution was concentrated and recrystalized with ether. White crystal was obtained. Yield 550 mg. (m.p. 73°C). found N=8.29%. The crystal 0.30 g was dissolved in the mixture of 0.5 N-NaOH 2 cc, water 3 cc and alcohol 10 cc, which was kept at room temperture for a few days, until the sample was completely dissolved. Then it was neutralized with 0.5 N-HCl 2.2 cc and concentrated in vaccum. Pure crystal was obtained by several recrystalizations of the residue with water. Yield 210 mg. (m.p. 162°C).

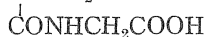
N analysis

found N=11.46%

Molecular weight by Rust's method using campher.

found M=363

for $\text{C}_6\text{H}_5\text{CH}_2\text{OCONHCH}_2\text{CON}-\text{CH}_2\text{COOH}$



calc. N=11.44%

calc. M=367