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# AMINOLYSES OF REACTIVE MONOMERS AND POLYMERS—I

## 4-NITROPHENOL ESTERS

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**Abstract**—A series of 4-nitrophenol esters of *N*-methacryloylated ω-amino acids were prepared and copolymerized with methyl methacrylate and *N*-(2-hydroxypropyl) methacryl amide. The rates of aminolyses of monomers and copolymers were compared.

### INTRODUCTION

Active esters, which also include 4-nitrophenol esters, are able to react selectively with the amino group. To investigate the rate of the aminolytic reaction of 4-nitrophenol esters incorporated in soluble polymers, a number of polymerizable monomers were prepared, having side chains of various length and structure. 4-Nitrophenol esters of *N*-methacryloylated ω-amino acids have already been used in polymer chemistry [1–3] e.g. for the binding of papain on an insoluble macroporous copolymer [4]. Soluble copolymers with side-chains of various lengths and structures were used in the investigation of the mobility of a stable free radical, 4-amino-2,2,6,6-tetramethylpiperidine-*N*-oxyl, bound to the end of the side-chain by polymer-analogous reaction [5, 6].

### EXPERIMENTAL

*Chemicals and monomers*

ω-Amino acids were denoted by a numerical system analogous to the letter code used for α-amino acids. The number denotes the number of carbon atoms in the amino acid.

Amino acids H-2-OH, H-3-OH, H-4-OH and H-6-OH were Fluka products. Acids H-5-OH, H-7-OH, H-8-OH and H-12-OH were obtained by acid hydrolysis of the appropriate lactams (Fluka). The physical properties of derivatives are summarized in Table 1.

The acids H-2-6-OH and H-2-2-6-OH were prepared by the sequence

$$\text{H-6-OH} \xrightarrow{\text{ClAcCl}} \text{ClAc-6-OH} \xrightarrow{NH_4OH} \text{H-2-6-OH} \xrightarrow{\text{ClAcCl}}$$

$$\text{ClAc-2-6-OH} \xrightarrow{NH_4OH} \text{H-2-2-6-OH}.$$

6-Chloroacetylglycylaminohexanoic acid (ClAc-2-6-OH): 0.2 mol 6-glycylaminohexanoic acid (31.6 g) and 0.2 mol NaOH (8 g) were dissolved in 150 ml water, and 0.2 mol chloroacetyl chloride (20.8 g) and 0.2 mol NaOH (8 g) in 30 ml water were added dropwise with stirring and cooling. After stirring for two hours at room temperature, the reaction mixture was acidified with 25 ml of conc. HCl. The product was recrystallized from water.

6-Glycylglycylaminohexaonic acid (H-2-2-6-OH): 0.1 mol 6-chloroacetylglycylaminohexanoic acid (26.4 g) was dissolved in 200 ml conc. ammonia. After 5 days the reaction mixture was evaporated to dryness. The solid residue was dissolved twice, each time in 200 ml water, and evaporated. Dry crystals were extracted with 100 ml of boiling methanol. The residue was crystallized from aqueous methanol.

Methacryloyl derivatives of amino acids (MA-): Methacryloylation was performed under Schotten–Bauman conditions.

12-Methacryloylaminododecanoic acid (MA-12-OH): 25 mmol 12-aminododecanoic acid (5.3 g) and 25 mmol NaOH (1 g) were dissolved in a mixture of 150 ml dioxan and 70 ml water. 50 mmol Methacryloylchloride (2.6 g) and 50 mmol NaOH (2 g) in 10 ml water were added simultaneously with stirring and cooling to 5°. After stirring for 2 hr at room temperature, the reaction mixture was acidified with conc. HCl (5 ml), diluted with 100 ml water and the filtrate was shaken with 150 ml methylene chloride. After evaporation of the solvents, the semisolid residue was crystallized from a mixture ethyl acetate–hexane.

6-Methacryloylaminohexanoylglycine (MA-6-2-OH), was prepared according to the scheme

$$\text{MA-6-OH} + \text{H-2-OME} \rightarrow \text{MA-6-2-OMe} \rightarrow \text{MA-6-2-OH}$$

6-Methacryloylaminohexanoylglycine methyl ester (MA-6-2-OMe): 0.1 mol 6-methacryloylaminohexanoic acid (20 g) was dissolved in 100 ml chloroform; 0.1 mol triethylamine (10.1 g) was added; the mixture was cooled to −10° and stirred and 0.1 mol ethylchloroformiate (10.8 g) was added dropwise. A suspension of 0.12 mole glycine methyl ester hydrochloride (16.4 g) and 0.12 mol triethyl amine (12.3 g) in 50 ml chloroform was added after 60 min. The product was recrystallized from ethanol-hexane mixture. The methyl ester was hydrolysed by boiling in 20% methanolic KOH for 4 min.

4-Nitrophenol esters (Np) of ω-methacryloylated amino acids:

MA-2-OH through MA-8-OH and MA-12-OH were prepared using dicyclohexylcarbodiimide in methylene chloride. The other esters were prepared by using mixed anhydride. The physical constants of Np esters are summarized in Table 2.

4-Nitrophenyl ester of 6-methacryloylglycylglycylaminohexanoic acid (MA-2-2-6-ONp): 10 mmol of 6-methacryloylglycylglycylaminohexanoic acid (3.1 g) was suspended in a mixture of 15 ml DMF and 10 ml THF and cooled to −10°; 10 mmol triethyl amine (1.0 g) and 10 mmol ethyl chloroformiate (1.08 g) were gradually added. After stirring and cooling for 90 min (−10°), 12 mmol 4-nitrophenol (1.7 g) was added. After 24 hr, 20 ml methylenechloride was added, and the reaction was extracted five times with 5% $NaHCO_3$ solution (100 ml), 1% acetic acid solution, and water. The product was crystallized from ethanol-hexane mixture.

Table 1. Amino acids derivatives

| Compound | R = H m.p. C | Yield. % | R = Np m.p. C | Yield. % | $\epsilon.10^{-4}$ |
|---|---|---|---|---|---|
| MA-OR [11] | — | — | 94–5 | 83 | 0.98 |
| MA-2-OR [1] | 101–3 | 75 | 101 | 42 | 0.92 |
| MA-3-OR [1] | 75 | 70 | 63–5 | 40 | 0.97 |
| A-4-OR [2]* | 99–100 | 80 | 116 | 35 | 1.02 |
| MA-5-OR | oil | 92 | 115–17 | 35 | 1.05 |
| MA-6-OR [1. 4. 12] | 50–1 | 50 | 75–7 | 65 | 0.93 |
| MA-7-OR | oil | 90 | 64–5 | 35 | 0.94 |
| MA-8-OR | oil | 90 | 78–9 | 30 | 1.01 |
| MA-12-OR | 68–70 | 74 | 88–91 | 53 | 0.94 |
| MA-2-2-OR [1] | 195–7 | 60 | 163–5 | 45 | 0.95 |
| MA-2-2-2-OR [1] | 195–200 | 74 | 202–5 | 15 | 0.96 |
| ClAc-6-OR | 82–4 | 72 | — | — | — |
| H-2-6-OR | 197–9 | 55 | — | — | — |
| MA-2-6-OR [1] | 99–101 | 51 | 106–7 | 71 | 0.97 |
| ClAc-2-6-OR | 113–115 | 73 | — | — | — |
| H-2-2-6-OR | 196–7 | 65 | — | — | — |
| MA-2-2-6-OR | 181–3 | 67 | 150–2 | 72 | 0.97 |
| MA-6-2-OR | 108 | 47 | 132–4 | 25 | 0.98 |

* Acryloyl. Microanalyses corresponded to the suggested compounds.

*Copolymerization*

*N*-(2-hydroxypropyl)methacrylamide (HPMA) was prepared as described above [10]. Methyl methacrylate (MMA) was fractionated before use.

HPMA was copolymerized with 4-nitrophenol esters of $\omega$-methacryloylated amino acids by radical precipitation copolymerization in acetone at 60° (15% wt monomers, 5 mol. % monomer $M_2$, 0.1% wt AIBN, 7 hr). The polymers were reprecipitated from methanolic solution into acetone.

Copolymers of MMA with 4-nitrophenol esters of $\omega$-methacryloylated amino acids were prepared by solution copolymerization in acetone under the same conditions. Reprecipitation of the copolymers was performed from acetone solution into methanol. The characteristics of copolymers are given in Table 2.

*Copolymerization parameters*

The pair of monomers HPMA ($M_1$) and MA-6-ONp ($M_2$) was chosen for preliminary determination of the copolymerization parameters. The copolymers were prepared as indicated in the preceding section up to ~10% conversion. The copolymers were prepared only to a content of $M_2 \simeq 10$ mol.%; products with a higher content of $M_2$ do not precipitate from acetone. The Fineman and Ross [14] method led to $r_1 \simeq 2$ and $r_2 \simeq 0.15$. The values were treated by the linear regression method. Molecular weights were measured with a Photo-Gonio Diffusometer Sofica 42.000 apparatus. The solvents for MMA and HPMA were dioxan and dimethylformamide respectively.

*Aminolyses of monomers and polymers*

The time dependence of concentration of bound activated esters was determined spectroscopically from decrease in the absorption at constant wavelength with a Cary 14 spectrophotometer. The measurement was carried out with a 1 mm cell at (22 ± 0.1) . The concentration of 4-nitrophenol esters was $1.8 \times 10^{-3}$ mol/l, and that of amine was 0.18 mol/l in DMSO.

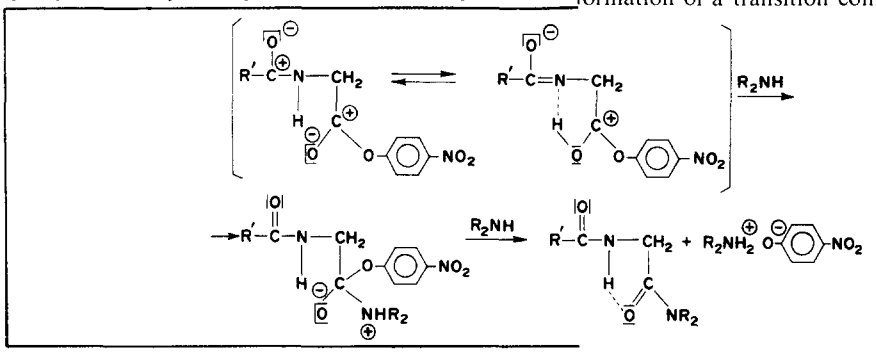
The solutions were dosed with high-precison syringes; 10 sec at most was the interval between mixing and the beginning of measurement. The rates of aminolysis of monomers and polymers were compared using of the time value for splitting of one half of acylated 4-nitrophenol ester ($t_{1/2}$). The end of aminolysis was verified each time by addition of ammonia.

Table 2. Characteristics of copolymers with 4-nitrophenyl esters

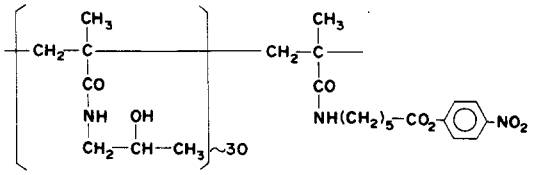
| Monomer | Conversion. % | Copolymers HPMA Content of Np (mol. %) | HPMA Mol. weight ($M_w$) | MMA Conversion (%) | MMA Content of Np (mol. %) | MMA Mol-weight ($M_w$) |
|---|---|---|---|---|---|---|
| MA-ONp | 64 | 4.02 | 39.000 | 65 | 3.27 | 42.000 |
| MA-2-ONp | 75 | 3.45 | 42.000 | 73 | 2.28 | 43.000 |
| MA-3-ONp | 71 | 3.19 | 37.000 | 72 | 2.44 | 46.500 |
| A-4-ONp | 81 | 2.6 | 40.000 | 68 | 2.98 | 41.000 |
| MA-5-ONp | 56 | 2.95 | 34.000 | 73 | 3.2 | 41.500 |
| MA-6-ONp | 61 | 3.24 | 37.000 | 53 | 2.73 | 42.000 |
| MA-7-ONp | 59 | 3.1 | 41.000 | 62 | 2.07 | 25.000 |
| MA-8-ONp | 80 | 3.02 | 42.000 | 72 | 2.8 | 42.000 |
| MA-12-ONp | 65 | 2.9 | 37.000 | 81 | 2.15 | 40.000 |
| MA-2-2-ONp | 63 | 3.0 | 27.000 | 65 | 1.55 | — |
| MA-2-6-ONp | 78 | 3.3 | 31.000 | 71 | 1.77 | 38.000 |
| MA-2-2-6-ONp | 65 | 3.15 | 33.000 | 78 | 1.05 | — |
| MA-2-2-2-ONp | 40 | 0.9 | — | — | — | — |

## DISCUSSION

A series of 4-nitrophenol esters of methacryloylated ω-amino acids and copolymers with methyl methacrylate (MMA) and *N*(2-hydroxypropyl)methacrylamide (HPMA) were prepared. The rate of aminolytic reaction of monomers and copolymers (cf. Table 3) due to methyl methacrylate (MMA) and *N*-(2-hydroxypropyl)methacrylamide (HPMA) was measured. Amines with a sterically hindered amino group were used, because aminolysis, with unscreened amines (pentyl amine, cyclohexyl amine) was too rapid. The

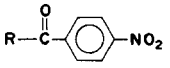


average content of incorporated 4-nitrophenol esters was 3 mol.% (spectroscopically). The length of sequences of the individual monomeric units for calculated from the monomer reactivity rates for HPMA/MA-6-ONp, giving the probable structure of the copolymer

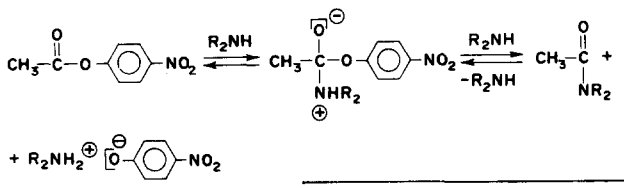


This provides sufficient distance between the individual reactive groups for them to be regarded as isolated. Since the other monomers are analogous, similar structures may be assumed for their copolymers.

In the case of 4-nitrophenyl esters, the activation of the ester bond (and thus also easy aminolysis) is due to the inductive effect of the 4-nitrophenyl group.



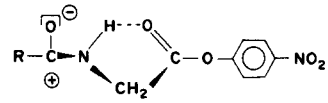
The aminolysis of 4-nitrophenyl acetate and 4-nitrophenyl methacrylate proceeds only with the help of the inductive effect of the 4-nitrophenyl group via the following mechanism:



The different rates of aminolysis of 4-nitrophenyl acetate observed with the individual amines may be explained by the different basicities of the amines and by the steric effect of the alkyl group (or of two alkyl groups in the case of tertbutyl ethyl amine). With 4-nitrophenyl methacrylate, there is moreover the negative steric effect of the branched acyl group.

When comparing the rates of aminolysis in the homologous series of 4-nitrophenol esters having an amide group at the end of the acyl chain, one can see a striking increase in the rate of aminolysis of the first members of the series. This finding may be explained by a cooperative effect of the amide group on the activation of the ester bond undergoing aminolysis. For the monomer MA-2-ONp one may consider a cyclic mechanism of activation, and thus an easier formation of a transition complex with amine:

The rate of aminolysis of this monomer is raised by the steric order of the five-membered ring formed in the reaction, which facilitates the nucleophilic attack of the ester group. The inductive effect of the amide bond itself may also operate in the activation. The same mechanism may be valid for the aminolysis of MA-2-2-ONp, MA-2-2-2-ONp and MA-6-2-ONp.



For the monomer MA-3-ONp, it is possible to consider a cooperative effect of the amide bond which forms a hydrogen bond in the six-membered ring with the ester carbonyl. For steric reasons, the carbonyl carbon atom of the ester group in the six-membered ring is less accessible to nucleophilic attack by the amine group containing a bulky substituent than that in the five-membered ring. The inductive effect of the amide group is already insignificant in this case, and it may also contribute to the decrease in the rate of aminolysis compared with the monomer MA-2-ONp.

The i.r. spectra for the monomers MA-2-ONp, MA-3-ONp and A-4-ONp in an inert solvent show that the formation of an intramolecular bond clearly predominates in the monomer MA-2-ONp (cf. Figs 1 and 2) while the monomer MA-3-ONp exhibits a marked decrease in intramolecular bonds with pre-

dominating free amide bond. With the monomer A-4-ONp, distinct intermolecular hydrogen bonds can be seen.

The same mechanism can also be considered for polymers. Differences between the rates of aminolysis

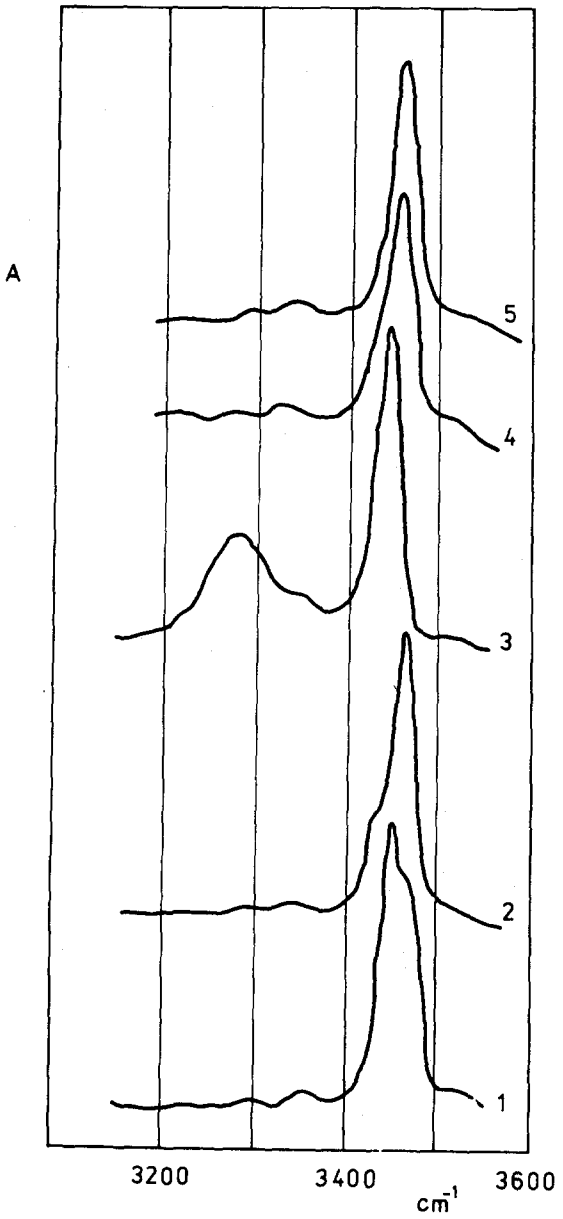



Fig. 1. i.r. Spectra of monomers: (1) MA-2-ONp; (2) MA-3-ONp; (3) A-4-ONp; (4) MA-6-ONp; (5) MA-12-ONp in $CCl_4$ at 22°, concentration $10^{-3}$ M, cell 2 cm.

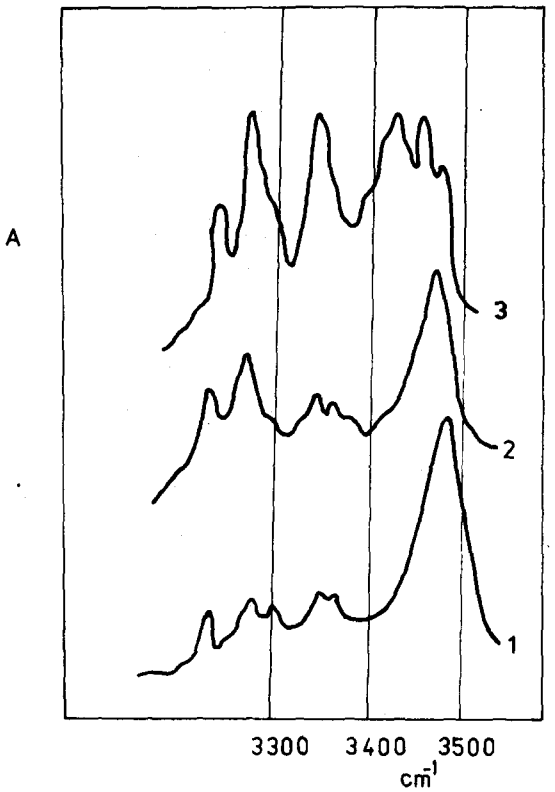



Fig. 2. i.r. Spectra of monomers: (1) MA-2-ONp; (2) MA-3-ONp; (3) A-4-ONp measured in a KBr pellet.

Table 3. Half-times (sec) of aminolyses of 4-nitrophenyl esters in DMSO A: ammonia B: tert-butyl amine C: tert-butyl ethyl amine. D: Tris(hydroxymethyl)aminomethane. Measured at 274 nm. 22

| Monomer (Type of side chain) | Aminolyses of monomers | | | Aminolyses of copolymers with HPMA | | | MMA | |
|---|---|---|---|---|---|---|---|---|
| | B | C | D | B | C | D | A | B |
| Ac-ONp | 140 | 1800 | 890 | — | — | — | — | — |
| MA-ONp | 300 | 2400 | 1750 | 1920 | * | * | 250 | * |
| MA-2-ONp | 8 | 70 | 70 | 35 | 75 | 195 | 28 | 85 |
| MA-3-ONp | 110 | 450 | 900 | 105 | 2200 | 650 | 35 | 750 |
| A-4-ONp | 165 | 2100 | 960 | 350 | 4200 | 1020 | 46 | 1500 |
| MA-5-ONp | 250 | 3300 | 990 | 265 | 4600 | 1300 | 50 | 1680 |
| MA-6-ONp | 260 | 3150 | 980 | 350 | 4650 | 1600 | 60 | 1720 |
| MA-7-ONp | 285 | 3200 | 1000 | 330 | 4600 | — | 65 | 1800 |
| MA-8-ONp | 290 | 3290 | 980 | 320 | 4500 | — | 72 | 1770 |
| MA-12-ONp | 340 | 3300 | 980 | 385 | 4580 | 1750 | 68 | 1860 |
| MA-2-2-ONp | 8 | 60 | 57 | 12 | 19 | 45 | 9 | 55 |
| MA-2-2-2-ONp | 8 | 55 | 58 | 10 | 18 | 38 | — | — |
| MA-2-6-ONp | 270 | — | — | 340 | 3000 | — | 50 | 1770 |
| MA-2-2-6-ONp | 285 | — | — | 230 | 2900 | — | 50 | 1780 |
| MA-6-2-ONp | 8 | — | — | 8 | 50 | 40 | — | — |

* Does not react up to 20 min.

may be assigned to steric effects of the polymer chain and to the possibility of formation of intermolecular hydrogen bonds both with the solvent and with the polymer chain.

A pronounced effect of the polymer chain on the rate of aminolysis can be seen for the copolymers MMA-Np esters, where the methyl methacrylate polymer chains in DMSO are coiled and shield bulky alkyl amines from the ester group.

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