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Aminolyses of Monomeric and Polymeric 4-Nitrophenyl Esters of *N*-Methacryloylamino Acids

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SUMMARY:

4-Nitrophenyl esters of *N*-methacryloylamino acids and their copolymers with *N*-(2-hydroxypropyl)-methacrylamide were synthesized. The effect of the ester and amine structure and of the reaction medium on the rate constant of aminolysis was studied.

In the synthesis of pharmacologically active polymers one usually has to choose whether to use a polymeranalogous reaction for binding the biologically active compound to the polymeric carrier or to prepare a polymerizable derivative of the effective drug and incorporate it into the polymeric backbone by copolymerization. It is quite obvious that this question cannot be solved generally once for all, but that each case must be considered separately. The choice of a concrete procedure will depend on the properties both of the polymeric carrier and of the given drug (generally, a biologically active compound).

In our earlier papers we pointed out the possibility of using poly[*N*-(2-hydroxypropyl)methacrylamide][1,2] as blood plasma substitute[3-5] and as a carrier of biologically active compounds[6,7] (BAC). The basic polymeric backbone, poly[*N*-(2-hydroxypropyl)methacrylamide], contains hydroxyl groups which possess weak reactivity[6]. It is, therefore, necessary to modify this backbone by introducing reactive groups. We chose the 4-nitrophenyl ester group whose reactivity is frequently employed in the synthesis of peptides[8,9] and in polymer chemistry[10-16] and which can easily be detected spectrometrically in the UV region. Sterically hindered aliphatic amines were used as models of the biologically active compounds. Reactions between amines, on the one hand, and monomeric and polymeric 4-nitrophenyl esters of *N*-methacryloylamino acids, on the other, can be regarded as model reactions of binding of the biologically active compounds containing the NH_2 group.

We prepared a few 4-nitrophenyl esters of *N*-methacryloylamino acids (**2–7**), (further referred to as ONp esters) in both the monomeric and polymeric form and measured their reaction rate with some amines. We investigated the effect of the structure of ONp ester, amine, reaction medium, and polymeric backbone on the rate of this reaction:

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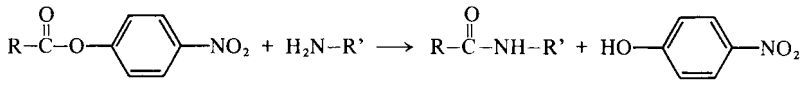

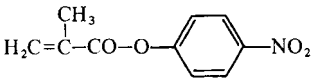

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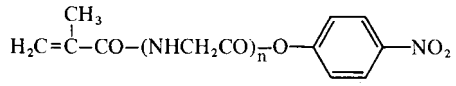

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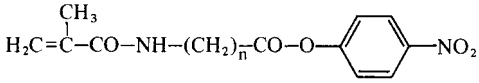

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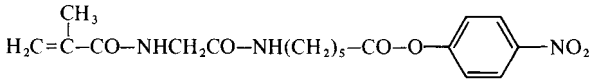

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Experimental Part

Monomers and initiator

Schotten-Baumann's method of acylation with an acylchloride in an aqueous alkaline medium was used for the methacryloylation of amino acids. The general method of preparation of these acids, as well as the subsequent preparation of the esters by means of dicyclohexylcarbodiimide have already been described[7] for the following ONp esters: *N*-methacryloylglycylglycylglycine 4-nitrophenyl ester (**4**), 4-nitrophenyl 6-methacryloylaminocaproate (**6**) and 4-nitrophenyl 6-methacryloylglycylaminocaproate (**7**). The other esters, *N*-methacryloylglycine 4-nitrophenyl ester (**2**), *N*-methacryloylglycylglycine 4-nitrophenyl ester (**3**) and 4-nitrophenyl 3-methacryloylaminopropionate (**5**), were prepared in a similar way. Characteristics of the esters and the abbreviations used are given in Tab. 1.

N-(2-Hydroxypropyl)methacrylamide (*N*-HPMA) was prepared by a known procedure[1]; mp 67°C. *N*-Ethylmethacrylamide was prepared according to ref.[17]; bp 68°C/80 Pa. *N*-Ethylacrylamide was prepared according to ref.[18]; bp 69°C/93 Pa. 2-(2-Hydroxyethoxy)ethyl methacrylate was prepared as in ref.[19]; bp 97–98°C/107 Pa. 2,2'-Azodiisobutyronitrile (AIBN) (from Lachema Brno) was recrystallized from ethanol.

Preparation of the polymers

Homopolymers and copolymers of *N*-HPMA were prepared by radical precipitation polymerization in acetone at 50°C (12,5 wt.-% of monomers, 0,06 wt.-% AIBN, 24 h). After completed polymerization the polymers were filtered off, dissolved in methanol, reprecipitated into acetone, filtered off again, and dried i. vac. to constant weight.

The copolymer from *N*-ethylmethacrylamide and **6** was prepared under similar conditions using a mixture of acetone/diethyl ether (1:3) as precipitant. In the preparation of the copolymer from

Tab. 1. Characteristics of active monomers

Active monomer[a]	Reaction medium	Solvent for crystallization	Yield in % after 2nd cryst.	Mp in °C		Elemental analysis C	H	N	Absorption[b] coefficient in $l\ mol^{-1}\ cm^{-1}$
MA-ONp (**1**)	H_2O	Et_2O/hexane	60	95[c]		—	—	—	9400
MA-Gly-ONp (**2**)	THF	EtOH/hexane	50	101	Calc.	54,55	4,58	10,60	9400
					Found	54,72	4,72	10,45	
MA-$(Gly)_2$-ONp (**3**)	DMF	EtOH/H_2O	70	163	Calc.	52,34	4,71	13,08	9500
					Found	52,52	4,88	12,97	
MA-$(Gly)_3$-ONp (**4**)	DMF	EtOH/H_2O	20	203–204	Calc.	50,79	4,79	14,81	9400
					Found	50,80	4,98	14,88	
MA-β-Ala-ONp (**5**)	CH_2Cl_2	EtOH/hexane	40	65–67	Calc.	56,11	5,07	10,06	9400
					Found	56,05	5,55	10,10	
MA-Acap-ONp (**6**)	$CHCl_3$	EtOH/hexane	50	75–77	Calc.	50,99	6,29	8,75	9500
					Found	60,01	6,48	8,62	
MA-Gly-Acap-ONp (**7**)	THF	EtOH	50	106–107	Calc.	57,28	6,14	11,13	9700
					Found	57,24	6,27	11,03	

[a] MA = Methacryloyl.
[b] Absorption coefficients were determined in DMSO at $\lambda = 274$ nm at 25 °C.
[c] Lit.[20]: mp 95 °C.

Tab. 2. Characteristics of copolymers

M_1[a]	M_2	Mole fraction of M_2 in the initial mixture	Conversion in %	Mole fraction of M_2 in the copolymer[b]	$\frac{[\eta]}{dl\,g^{-1}}$	$\bar{M}_w$[c]
N-HPMA	MA-ONp (**1**)	0,08	47,6	0,124	0,181[d]	56000[d]
N-HPMA	MA-Gly-ONp (**2**)	0,08	55,7	0,058	0,090	20000
N-HPMA	MA-$(Gly)_2$-ONp (**3**)	0,07	59,0	0,080	0,086	19000
N-HPMA	MA-$(Gly)_3$-ONp (**4**)	0,05	55,1	0,036	0,060	11000
N-HPMA	MA-β-Ala-ONp (**5**)	0,08	55,4	0,055	0,083	18000
N-HPMA	MA-Acap-ONp (**6**)	0,05	76,8	0,027	0,085	18500
N-HPMA	MA-Acap-ONp (**6**)	0,15	—	0,092	—	—
N-Ethylmethacrylamide	MA-Acap-ONp (**6**)	0,05	29,0	0,053	0,062	—
N-Ethylacrylamide	MA-Acap-ONp (**6**)	0,05	79,5	0,047	0,116	—
N-2-(2-Hydroxyethoxy)-ethyl methacrylate	MA-Acap-ONp (**6**)	0,055	—	0,033	—	—
N-HPMA	MA-Gly-Acap-ONp (**7**)	0,07	73,0	0,063	0,063	12000

[a] *N*-HPMA: *N*-(2-hydroxypropyl)methacrylamide.

[b] Calc. using the fact that λ_{max} of the ONp group in the monomer and copolymer remains unchanged and assuming that the absorption coefficients are identical.

[c] Calc. from the equation for poly[*N*-(2-hydroxypropyl)methacrylamide][2].

[d] After aminolysis with 1-amino-2-propanol.

N-ethylacrylamide and **6** a mixture of acetone/dibutyl ether (1:5) was used as precipitant, and for the copolymer from 2-(2-hydroxyethoxy)ethyl methacrylate and **6** a mixture of acetone/diethyl ether (1:3) was used as precipitant in the polymerization. The polymer was reprecipitated from an ethanolic solution into a mixture benzene/hexane (1:1).

Characteristics of the copolymers are given in Tabs. 2 and 3.

Tab. 3. Heterogeneous copolymerization of *N*-(2-hydroxypropyl)methacrylamide with *N*-methacryloylglycylglycine 4-nitrophenyl ester (M_2). Conditions of copolymerization: 12,5 weight-% of monomers in the initial mixture, solvent: acetone, temp.: 50°C, polymerization time: 24 h

Mole-% of M_2 in the initial mixture	Weight-% of AIBN[a]	Conversion in %	Mole-% of M_2 in the copolymer	$[\eta]$ [b] / dl g^{-1}	$\bar{M}_w$[c]	$[\eta]$ [b,d] / dl g^{-1}	$\bar{M}_w$[d]
0	0,60	88,5	—	0,199	64500	—	—
1,0	0,60	79,2	1,02	0,136	37000	0,130	34000
5,0	0,60	56,9	5,92	0,091	20000	0,088	19500
0	0,20	87,3	—	0,307	122000	—	—
1,0	0,20	58,2	1,08	0,182	56000	0,152	43000
5,0	0,20	34,7	7,03	0,107	26000	0,093	21000

[a] Per whole mixture.
[b] In 0,1 M KCl at 25°C.
[c] Calc. from equation for poly[*N*-(2-hydroxypropyl)methacrylamide][2].
[d] After aminolysis with 1-amino-2-propanol.

Viscosity measurements

The viscosity of the polymers was determined by a standard procedure in 0,1 M KCl at 25°C. The equation for poly[*N*-(2-hydroxypropyl)methacrylamide] was used in the estimation of $\bar{M}_w$ of the copolymers of *N*-HPMA[2]. Some copolymers were subjected to aminolysis with 1-amino-2-propanol prior to the viscosity measurements (NH_2:ONp = 10:1). After 12 h the polymer was precipitated into acetone, filtered off, dissolved in methanol and precipitated again into an excess of acetone. After removal by filtration the aminolyzed polymer was dried i. vac. to constant weight.

Purification of solvents

Dimethyl sulfoxide (DMSO) was first dried over a molecular sieve, then rectified under nitrogen on a column packed with Helipack at 55°C/533 Pa. The suitability of DMSO for kinetic measurements was verified by measuring the decrease in absorption of the ONp group of solutions of MA-$(Gly)_2$-ONp (**3**). After 60 h at 25°C or after 36 h at 50°C the decrease in the concentration of ONp groups was $\leq 20\%$. Dioxan, ether, and heptane were redistilled on drying with sodium. Dimethylformamide was purified from amine impurities by azeotropic distillation with benzene and water, then it was distilled at 48,5°C/2000 Pa. Amines were purified by distillation.

Measurement of the kinetics of aminolysis

The concentration of the ONp groups in the kinetic measurements was determined spectroscopically from the decrease in the ester absorption at constant λ_{max} with a Cary 14 spectrophotometer. A 0,1 cm cell in a block thermostated to 25°C was used for solutions of ONp esters at a concentration of 10^{-3} mol/l. The course of the aminolysis was compared with control tests in the reaction cell (with stirring), from which samples were taken and diluted with 0,02 M HCl in ethanol. Similar results were obtained in both arrangements. It was verified experimentally that starting from the initial absorption value and up to its final value, when all ONp ester had reacted, the concentration was directly proportional to the absorption.

Hamilton's injection needles were used for dosing solutions of both components into the cell. No more than 5 s passed from the moment when the solutions were mixed with each other to the beginning of measurement.

Results and Discussion

Characteristics of reactive copolymers

Copolymers of 4-nitrophenyl esters of *N*-methacryloylamino acids with *N*-(2-hydroxypropyl)-methacrylamide were prepared by radical precipitation copolymerization up to a high conversion. In order to find out the effect of the structure of a hydrophilic polymeric backbone, copolymers of MA-Acap-ONp (**6**) with *N*-ethylmethacrylamide, *N*-ethylacrylamide and *2*-(2-hydroxyethoxy)ethyl methacrylate were also prepared. The characteristics of the copolymers used in kinetic measurements are given in Tab. 2. By comparing the intrinsic viscosities of these copolymers with those of the homopolymers of *N*-HPMA prepared under the same conditions, one can see that the presence of the 4-nitrophenyl esters in the polymerization mixture reduces both the yield of the polymerization and the molecular weight of the polymers. Similar conclusions were made by *Böhmer* et al.[21] in the copolymerization of styrene and 2-nitrophenyl acrylate. The effect of the 4-nitrophenyl esters on the heterogeneous polymerization is characterized in greater detail in Tab. 3. The drop in the reaction yield and $[\eta]$ of the copolymers of *N*-HPMA with MA-$(Gly)_2$-ONp (**3**) is considerable and increases with increasing content of the active comonomer in the reaction mixture. Since the equation for the homopolymer of *N*-HPMA[2] was used in the calculation of $\bar{M}_w$, $[\eta]$ and $\bar{M}_w$ are given in Tab. 3 both for reactive copolymers and for copolymers formed by the aminolysis with 1-amino-2-propanol. By using the difference between the $\bar{M}_w$ values for polymers before and after aminolysis, a rough estimate can be made of the error of calculation of $\bar{M}_w$ due to the use of the Mark-Houwink equation for the homopolymer.

Aminolyses

A hundredfold amine concentration was always used in the determinations of the rates of aminolyses. Aminolysis can then regarded as a pseudomonomolecular reaction, and can be described by using the equation for the kinetics of first-order reactions, i.e. $\ln(c_0/c_t)=k_1 t$. The second-order rate constant, k_2, was obtained from $k_2=k_1/c_A$, where c_A is the concentration of amine. A proof, justifying the use of this relationship, consists in that the rate constants of aminolyses for various concentrations of ONp ester always at a hundredfold concentration of amine are approximately the same. (The rate constants k_2 of the aminolysis of MA-Acap-ONp with *tert*-butylamine in DMSO for ester concentrations of 10^{-4}, 10^{-3}, and 10^{-2} mol/l, respectively, were 0,023, 0,024 and 0,021 l mol^{-1} s^{-1}; with cells of 1, 0,1, and 0,01 cm).

By determining the rate constants of the aminolyses we wanted to obtain an idea about the reactivity of the 4-nitrophenyl ester groups and about the effects to which they are subjected. The effect of the ester structure is shown in Tab. 4, which contains a comparison of the rate constants of aminolyses of all monomeric and polymeric 4-nitrophenyl esters in the reaction with *tert*-butylamine and diisopropylamine in dimethyl sulfoxide. For better orientation the esters under investigation can be divided into three types: α-acylamino esters, which involve MA-$(Gly)_{1-3}$-ONp (**2–4**), β-acylamino ester, MA-β-Ala-ONp (**5**), and ε-acylamino esters, i.e. MA-Acap-ONp (**6**) and MA-Gly-Acap-ONp (**7**). One can see at first sight that

Tab. 4. Rate constants, k_2, of aminolysis of ONp esters in monomeric and polymeric forms with *tert*-butylamine and diisopropylamine in DMSO at 25°C. Concentration of ONp groups: $1 \cdot 10^{-3}$ mol/l; concentration of amine: $1 \cdot 10^{-1}$ mol/l

ONp Ester	$10^4 \cdot k_2$/l mol^{-1} s^{-1}			
	tert-butylamine		diisopropylamine	
	monomer	copolymer with *N*-HPMA	monomer	copolymer with *N*-HPMA
MA-ONp (**1**)	180	13	2	4
MA-Gly-ONp (**2**)	8000	2000	370	80
MA-(Gly)$_2$-ONp (**3**)	17000	9000	1600	2500
MA-(Gly)$_3$-ONp (**4**)	19000	12000	3000	—
MA-β-Ala-ONp (**5**)	570	360	21	20
MA-Acap-ONp[a] (**6**)	240	150	3	4
MA-Gly-Acap-ONp (**7**)	200	150	4	5

[a] Copolymer with 2,7 mole-% MA-Acap-ONp (**6**) was used.

there is a principal difference between the reactivities of α-acylamino esters on the one hand and of the other acylamino esters and that of **1**, on the other hand, probably due to the induction effect of the carbonyl group of glycine, which increases with increasing number of the glycine repeating units in the molecule of the active ester, in accordance with the increasing values of the respective rate constants of aminolysis. However, other effects, such as e.g. the neighbour group effect, cannot be ruled out either. Aminolyses with *tert*-butylamine present in excess occur with monomeric ONp esters up to 100%, and the dependence of $\ln(c_0/c_t)$ on time is linear within the whole range of conversions. Polymeric ONp esters react slower than the monomeric esters; the final conversion reaches lower values (80–100%). The course of aminolysis satisfies pseudo-first reaction order with the exception of poly(*N*-HPMA-co-MA-ONp), for which the rate of aminolysis decreases, starting from 30% conversion.

All esters react slower with diisopropylamine than they react with primary *tert*-butylamine, but only esters of the type MA-(Gly)$_n$-ONp, both monomeric and polymeric, react according to a kinetic expression for a first-order reaction up to a higher degree of conversion (ca. 60%). For all the others the rate constant was calculated from the initial rate, i.e. approximately up to a 10% conversion (for MA-β-Ala-ONp, to a 30% conversion). Starting from this value onwards the dependence of $\ln(c_0/c_t)$ on time is not linear any more, and the rate of aminolysis decreases. We are fully aware of the fact that in this case the rate constants are only formal and are mainly used for comparing the reaction rates with the other esters. We also do not rule out the possibility of some other reaction mechanisms. The aminolysis with diisopropylamine proceeds in the case of polymers up to a 75–95% conversion, and is in some cases faster with the polymer than with the monomer. One can only guess the reason for this phenomenon. One can imagine that the polymer can cause a concentration fluctuation of diisopropylamine, thus raising its concentration in the proximity of the reaction site. The results indicate that the conformation of the side chains is such that the reactive groups "stick out" from the coil.

Other factors, affecting the rate of aminolysis, were studied only on MA-Acap-ONp which possessed optimal properties from the viewpoint of reactivity and solubility. The reaction

medium strongly affects the rate of aminolysis of 4-nitrophenyl esters[22], in some cases the mechanism of this reaction, as has been proved by *Su* and *Morawetz* in a recent detailed study[23]. The half-times of the reaction of MA-Acap-ONp with *tert*-butylamine in various solvents are given in Tab. 5. Well-ionizing solvents which solvate the reaction components in the transition state reduce the activation energy of aminolysis, thus making it faster.

Tab. 5. Half-time of the reaction of MA-Acap-ONp with *tert*-butylamine in various solvents. Concentration of MA-Acap-ONp: $1 \cdot 10^{-3}$ mol/l; concentration of *tert*-butylamine: $1 \cdot 10^{-1}$ mol/l

Solvent	$t_{0,5}$/min	λ_{max}/nm
Dimethyl sulfoxide	5	274
Dimethylformamide	24	274
50% Aqueous dioxan	0,60[a]	272
Methanol	0,65[a]	268
Dioxane	580	270
Diethyl ether	120[b]	268
Heptane	770[b]	266

[a] Correction for the possible catalyzed hydrolysis or catalyzed methanolysis has not been included in the half-times.

[b] Solution of MA-Acap-ONp in the given solvent was prepared by diluting 100 times the dioxane solution.

The mechanism of aminolysis[9] shows that the amine component will greatly influences the reaction rate. Data on the reactivity of some amines can be found in a paper by *Pless* and *Boissonas*[24]. The rate constants of aminolysis with various amines are summarized in Tab. 6. The results show that in this case steric effects play the most important role. All

Tab. 6. Effect of amine structure on the rate constant of aminolysis of MA-Acap-ONp in DMSO. Concentration of MA-Acap-ONp: $1 \cdot 10^{-3}$ mol/l; concentration of amine: $1 \cdot 10^{-1}$ mol/l

Amine	$10^4 \cdot k_2$/l mol^{-1} s^{-1}
Ammonia	Instantaneous reaction
Butylamine	Instantaneous reaction
Cyclohexylamine	Instantaneous reaction
tert-Butylamine	240
Dibutylamine	670
Diisopropylamine	3
N-Ethyl-*tert*-butylamine	3

monomers and polymers reacted immediately with ammonia with the exception of poly(*N*-HPMA-co-MA-ONp). In this case, the rate of aminolysis could be compared with that of *tert*-butylamine. Owing to the small distance between the active group and the polymeric carrier, the hindering effect of the latter becomes operative in this case. This reasoning is also corroborated by the kinetics of aminolysis with *tert*-butylamine when only this single polymer exhibited a deviation from a pseudo-first order of the reaction.

After having measured the rate constants of aminolyses of poly(*N*-HPMA-co-MA-Acap-ONp), poly(ethylmethacrylamide-co-MA-Acap-ONp), poly(ethylacrylamide-co-MA-Acap-ONp) and poly[2-(2-hydroxyethoxy)ethyl methacrylate-co-MA-Acap-ONp] ($k_2 = 0{,}015$, 0,016, 0,017, and 0,0191 $mol^{-1} s^{-1}$, respectively) with *tert*-butylamine in DMSO, which is thermodynamically a good solvent for these polymers, it can be said that the effect of the structure of the polymeric carrier, as far as the hydrophilic polymeric backbone is concerned, is unpronounced both for the hydrophilic ester and for the hydrophilic amides of methacrylic or acrylic acid. Poly(ethylacrylamide) is more hydrophilic than the other three copolymers under study, but in spite of this the difference in reactivity is not great. A decrease in the rate of aminolysis could probably be observed in the case of hydrophobization of the backbone or if an amine with bulky substituents were used, when the effect of coiling would be more pronounced.

The content of the ONp groups in the copolymers (Tab. 2) lay within the limits allowing to neglect the mutual influencing of the ONp groups. The same rate constant of aminolysis of the *N*-HPMA copolymers with a different content of MA-Acap-ONp (for a copolymer with 2,7 mole-% and for a copolymer with 9,2 mole-%, $k_2 = 0{,}0151\,mol^{-1} s^{-1}$) and the identical course of this reaction within a broad range of conversions gave an experimental proof of this assumption.

It can be summarized, in conclusion, that for fast aminolyses, the half-times of which are counted in seconds, monomeric active esters react faster than the polymeric ones. In this case the aminolysis of the ONp groups in the monomeric and polymeric forms exactly meets the requirement of a pseudo-monomolecular reaction within the whole conversion range. In the case of slow aminolyses, where the half-times are counted in hours, the reaction proceeds as pseudo-monomolecular only within a certain range of conversions, and the degree of conversion is lower than 100.

The structure of the active ester, of the amine, and the reaction medium have a decisive effect on the course of the reaction. Of the active ester under investigation, α-acylamino esters are the most reactive ones, whereas aliphatic unbranched primary amines possess the highest reactivity of amines. The results show that the reaction under investigation can be used in binding compounds which contain primary or secondary amino groups to the polymers under mild conditions. In the case of sterically hindered amines one must bear in mind a lower degree of conversion and remove unreacted ONp groups from the polymer by means of a reactive amine.

The author are indebted to Mrs. *I. Jenčková* for measurements of UV spectra.

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