Hofmann Degradation of Acrylamide Copolymer: Synthesis of Amine Functionalized Thermoplastic Hydrogel

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SYNOPSIS

The amine functionalization of an acrylamide copolymer was achieved via Hofmann degradation. The starting material, poly(acrylamide-co-methyl methacrylate), was synthesized by radical precipitation polymerization. Using this copolymer, Hofmann degradation at 0°C in a water–dioxane mixture was done using sodium hypochlorite and NaOH. The resulting hydrogel could be dissolved in water–tetrahydrofuran mixtures, and the cast film had a water content of 73%. It was found that the conversion to primary amine was lower, and the extent of a side reaction was higher, compared to those of an acrylamide homopolymer. This was presumed to be due to the lack of the neighboring group effect among acrylamide units since it was a random copolymer. Further modification of this polymer by reacting the amine group is considered to obtain the desired properties for biomedical applications. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

Hydrogels have been used for a variety of biomedical applications. Their high water content has been exploited for controlled release (high permeability)[1,2] and more generally as biomaterials.[3] A hydrogel made from a hydroxyethyl methacrylate–methyl methacrylate (HEMA–MMA) copolymer has been used to microencapsulate mammalian cells to isolate these cells from the immune system and permit their implantation.[4] For this application, the polymer needs to dissolve in a cell compatible solvent but must not dissolve when implanted.

The HEMA–MMA copolymer satisfies the permeability and biocompatibility constraints, although higher permeability and more control of the tissue reaction would be features of any improved material. To achieve this we are working toward preparing a polymer with a high water content with "reactive" side groups that can be used for further modification of the thermoplastic hydrogel. An amine-containing hydrogel is one such material, in which the high reactivity of the primary amine allows for the incorporation of various additional moieties. The vinyl amine (VA) is the simplest polymer structure conceivable; but so far, there are no reports of a successful direct polymerization method. Rather, it has been synthesized indirectly by various polymer reactions.[5-8] Among them, Hofmann degradation of polyacrylamide is one of the simplest methods: It uses a readily available monomer and can result in a high amine content.[9] Hofmann degradation has been done in a homogeneous solution and also on the surface of latex particles.[10]

We have chosen poly(acrylamide-co-methyl methacrylate-co-vinyl amine), poly(AM-co-MMA-co-VA), as the target material. The synthesis scheme is shown in Figure 1. The hydrophilicity of amide and amine is expected to give a high water content; yet, the product will be water insoluble because of the physical crosslinks formed by hydrophobic methyl methacrylate. The advantage of Hofmann degradation is that, even if we vary the amount of primary amines introduced to the polymers, products are expected to possess a high water content because of the unreacted AM. Free amines are expected to used for further modification; this will be reported separately.

Step1 - synthesis of poly(AM-co-MMA)
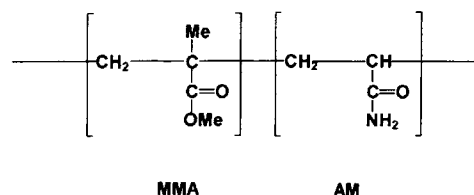
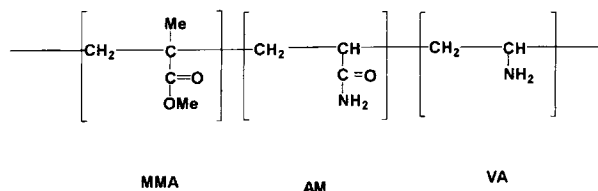Step2 - modification of polymer
Hofmann degradation

Figure 1 Synthesis scheme of poly(AM-co-MMA-co-VA).

EXPERIMENTAL

Materials

AM (Schwarz/Mann Biotech, Cleveland, OH) was recrystallized from methanol. Azobis(isobutyronitrile), (AIBN, Polysciences Inc., Warrington, PA) was recrystallized from a 50% aqueous methanol solution. MMA (Aldrich, Milwaukee, WI), ethanol, and acetone were purified by distillation. Dioxane was dried by Na_2SO_4 and then distilled. Sodium hypochlorite ($0.67M$ of NaOCl, BDH, Dermstadt, Germany), tetrahydrofuran (THF, Aldrich), pyridine (Aldrich), chloroform-d (Aldrich), polyAM (MW 5–6,000,000, Polysciences, Inc.), polyMMA (MW 100,000, Polysciences, Inc.), and standard $0.1M$ HCl solution (Fisher Scientific, Nepean, ON) were used as received.

Polymerization

A random copolymer of poly(AM-co-MMA) was prepared by radical precipitation polymerization. Various ratios of AM and MMA (0.08 mol in total) were dissolved in 200 mL of solvent (water, ethanol, or dioxane); ethanol was preferred. Polymerization was initiated by 0.2 g (1.8 mol % to the total monomer feed) of AIBN and was carried out under nitrogen at 70°C for 4 h. Polymer was purified by washing in distilled water, collected by centrifugation, and vacuum dried. Yield was about 30%.

Hofmann Degradation

Primary amine was introduced to the poly(AM-co-MMA) by Hofmann degradation. Polymer made from 60% MMA and 40% AM monomer feed was dissolved in 8 mL of 50% aqueous dioxane and cooled to 0°C. Various amounts (9.5–57.0 mL) of ice-cooled sodium hypochlorite ($0.67M$) was added to the polymer solution and stirred. After 5 min, 21 mL of ice-cooled $7.6M$ aqueous NaOH solution was added to the mixture. The reaction was carried out at 0°C for 1 to 6.5 h. One sample was reacted at 70°C for 6.5 hours in a similar manner. After the reaction, excess $NaHSO_4$ was added to the polymer solution in order to reduce the residual chlorine, followed by the addition of $2M$ HCl solution for neutralization. The polymer was separated by centrifugation and washed in distilled water. Polymer was collected by centrifugation and freeze-dried. Yield was about 50%.

After the Hofmann degradation, one modified polymer sample was treated further with concentrated hydrochloric acid. The modified polymer, 0.6 g, was dissolved in 50% aqueous pyridine, and 10 mL of hydrochloric acid (35.4%) was added. The polymer solution was stirred and refluxed at 50°C for 26 h. Polymer was purified and collected in a similar manner as for the Hofmann degradation and freeze-dried.

Homopolymers of AM and MMA were exposed under the same reaction conditions (1-h reaction, 28.5 mL NaOCl). Afterward, the polyAM product was purified by dialysis and polyMMA product was purified by reprecipitation from acetone.

Polymer Characterization

Qualitative and quantitative analysis of synthesized and modified polymers were done by IR spectroscopy (KBr disc) using Nicolet 8210E FTIR (4 cm^{-1} resolution) and elemental analysis (Galbraith Laboratories, Inc., Knoxville, TN, or Guelph Chemical Laboratories Ltd., Guelph, ON), respectively. Proton NMR of polyMMA was taken in chloroform-d with 400 MHz XRS (Varian).

Quantification of Functional Groups

Amounts of primary amine and carboxylic acid were quantified by potentiometric titration. After grinding to a powder, 0.2 g of the modified polymer was measured and suspended in 35 mL of $0.2M$ aqueous KCl solution. 138 μL of $8.0M$ aqueous KOH was added to raise the pH to 12. Standard $0.1M$ HCl was added using a 10 μL Eppendorf pipette, and pH was
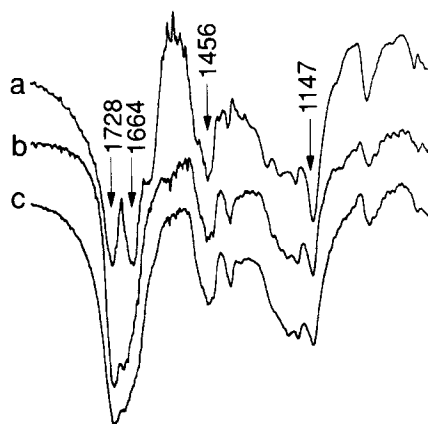
Figure 2 Transmittance IR spectrum of poly(AM-co-MMA) and poly(AAc-co-AM-co-MMA-co-VA). Numbers represent wave number in cm^{-1}. (a) Poly(AM-co-MMA), made from 60% AM monomer feed (0 h Hofmann degradation). (b) Poly(AAc-co-AM-co-MMA-co-VA) after 1 h Hofmann degradation (0°C, 9.5 mL NaOCl). (c) Poly(AAc-co-AM-co-MMA-co-VA) after 6.5 h Hofmann degradation (0°C, 9.5 mL NaOCl). After Hofmann degradation, decrease in amide absorbance (1664, 1456, and 1147 cm^{-1}) was observed.

measured after each addition by a pH meter equipped with a combination electrode (Cole-Parmer Instrument, Chemcadet®). HCl was added until the pH was about 2.5. Measurements were done at 25.0 ± 0.3°C under nitrogen gas. Approximately two minute intervals between the additions of HCl were used to let the polymer equilibrate. All measurements were completed within an hour.

Water Content

Films of poly(AM-co-MMA) were cast from a 5% (w/w) in water–acetone on to glass plates and dried in a chamber saturated with acetone vapor. Films were submerged in methanol before drying completely to prevent cracking. Films were equilibrated

in deionized distilled water for 3 days and weighed. Films were then vacuum dried and weighed once again. For the modified polymer (sample made by 1 h reaction and 57 mL NaOCl), a water-THF mixture was used to dissolve the polymer, and films were dried in air; methanol was not needed to prevent cracking and was not used.

RESULTS

Synthesis of Poly(AM-co-MMA)

Poly(AM-co-MMA) was synthesized by radical precipitation polymerization. Different solvents were tested in order to use solution polymerization, but the polymer precipitated in all three solvents chosen. Ethanol was finally used due to its easy handling and because it would still allow the desired amount of AM in the final copolymer by changing the monomer feed composition. 50% aqueous dioxane, 50% aqueous acetone, and 50% aqueous pyridine were found to be the best solvents for the products.

A typical IR spectrum is shown in Figure 2. The absorption band near 1728 cm^{-1} was assigned to the C=O stretch of the methyl ester of the MMA units. The absorption band near 1664 cm^{-1} was assigned to the C=O stretch of the amide group of the AM units. The intensity of those absorption bands was different for each monomer feed ratio and was consistent with the amount of AM feed. Copolymer composition was calculated using the result of elemental analysis and the theoretical atomic ratios. Results are summarized in Table I.

Hofmann Degradation

After Hofmann degradation, the modified copolymer was soluble in the reaction medium (water/dioxane) but it started to precipitate during neutralization with HCl, indicating that the product was pH sen-

Table I   Copolymer Composition of Poly(AM-co-MMA)

Monomer Feed AM/MMA	Elemental Analysis (Wt %)			AM Units in Polymer (Mol %)[a]
	C	H	N	
70/30	51.5	8.2	7.4	46.2
60/40[b]	54.9 ± 1.3	8.0 ± 0.5	6.0 ± 0.5	38.0 ± 1.6
50/50	53.2	8.3	4.9	32.1

Ethanol was used as a solvent during polymerization.
[a] AM units (mol %) were calculated according to the C : N and H : N ratios and averaged.
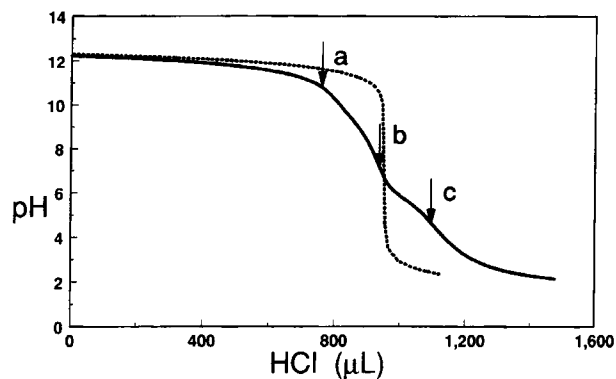[b] Average of n = 4, expressed as ±SD.

Figure 3 Typical titration curve of poly(AAc-co-AM-co-MMA-co-VA) (1 h reaction, 57 mL NaOCl). 0.2 g of polymer sample was titrated with $1M$ HCl after pH was raised. The following three inflection points were found: (a) $NH_2 \rightarrow NH_3^+$, determined by comparing with a blank titration curve; (b) main inflection point, determined by first derivative method; and (c) $COO^- \rightarrow COOH$, determined by first derivative method; (-, polymer; $\cdots$, blank.)

Figure 4 Amount of functional groups introduced by Hofmann degradation. Reaction conditions were 0°C, 9.5 mL NaOCl, and reaction time was varied. Amount of carboxyl acid increased by increasing the reaction time. ($\square$, NH_2; $\square$, COOH.)

sitive. Solvents for this product were found to be $\sim 50\%$ aqueous dioxane, $\sim 50\%$ aqueous THF, and 50% aqueous pyridine. The 50% aqueous acetone, which was the solvent for the original copolymer, did not dissolve the modified polymer. The product remained water insoluble as expected.

A typical IR spectrum is shown in Figure 2. Comparing it with the spectrum of the original copolymer, it is obvious that the absorption band near 1664 cm^{-1} assigned to $C=O$ stretch of the amide group has disappeared. Another distinct change was the decrease of the absorption near 1456 cm^{-1} ($C-N$ stretch of the primary amide). The absorption near 1147 cm^{-1} also decreased, but both AM and MMA units have absorption bands near this region. It was difficult to find an increase in an absorption band characteristic of the primary amine group because the absorption bands (e.g., $C-N$ stretch at 1040–1250 cm^{-1} or $N-H$ stretch at 3400–3500 cm^{-1}) were similar to those of AM or MMA.

Quantitative analysis was done by potentiometric titration. The typical titration curve is shown in Figure 3. It shows three end points: (A) one above pH 7.0, (B) the main inflection point, and (C) one near pH 4. The first (A) was from the protonation of the free amine, the second (B) was from the acid-base equivalence point, and the third (C) was from the protonation of the carboxylate anion. In most cases, it was difficult to determine the end point (A) by the first derivative method; therefore, it was done by comparison with the titration curve of the blank solution. The copolymer was found to undergo hydrolysis during titration, producing additional car-
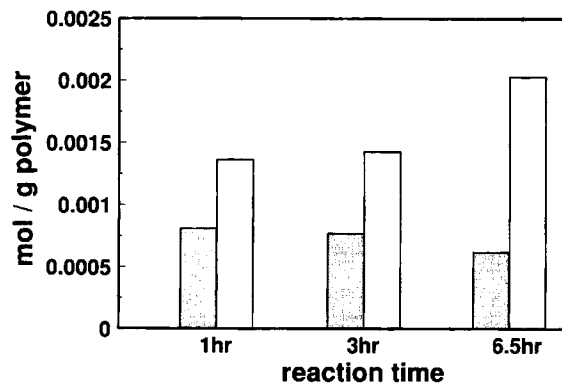
boxylic acids. This was taken into account by calculating the amount of carboxyl groups that were formed during the titration of the original copolymer, poly(AM-co-MMA), of known composition; this amount was subtracted from each of the modified polymer samples. The amount of free amine and carboxyl group in each polymer is shown in Figures 4 and 5. The final composition of the modified polymer and the fraction conversion (Table II) were also calculated.

The effect of reaction time on conversion is shown in Table III, in terms of the amide band absorbance. Decrease of these absorption bands depended on the length of reaction; the longer the reaction, the weaker the absorption. It was initially considered that this decrease was caused by the conversion of amide groups to primary amine, but the titration
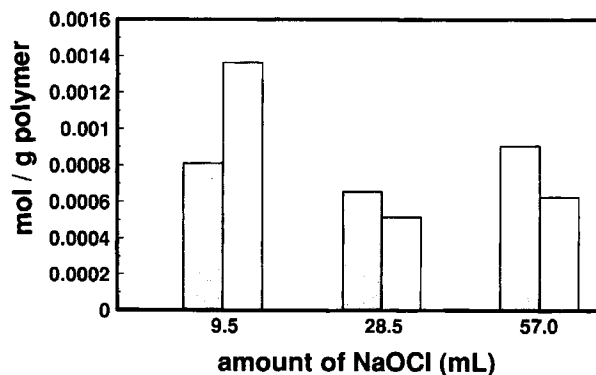

Figure 5 Amount of functional groups introduced by Hofmann degradation. Reaction conditions were 1 h, 0°C, and amount of NaOCl was varied. Side reaction of carboxyl acid was suppressed by increasing the NaOCl. ($\square$, NH_2; $\square$, COOH.)

Table II   Composition of Modified Polymer [poly(AAc-*co*-AM-*co*-MMA-*co*-VA)]

| | Reaction Conditions | | | | | | | |
| Temp (°C) | Time (h) | NaOCl Amount | | MMA[a] (%) | AM[b] (%) | Primary Amine[b] (%) | Carboxylic Acid[b] (%) | Conversion to Primary Amine[c] (%) |
		mL	NaOCl : AM					
0	6.5	9.5	0.7	60.8	15.6	5.5	18.1	14.0
0	3	9.5	0.7	60.8	19.6	6.8	12.7	17.4
0	1	9.5	0.7	60.8	19.9	7.2	12.2	18.3
0	1	28.5	2.4	64.5	21.8	8.1	5.6	22.9
0	1	57.0	4.8	64.5	25.0	5.9	4.6	16.6
70	6.5	57.0	4.4	61.7	19.2	1.9	17.2	4.4

[a] Based on elemental analysis of poly(AM-*co*-MMA). Difference was due to different batches of poly(AM-*co*-MMA).
[b] Based on potentiometric titration, after Hofmann degradation.
[c] Calculated as (mole of primary amine) × 100/(mole of initial AM).

results showed that there was a significant amount of carboxyl groups formed due to the side reaction. It was found that increasing the reaction time did not increase the amount of primary amine introduced, but rather increased the amount of carboxyls (Fig. 4). The effect of increasing the amount of NaOCl is shown in Figure 5. The degree of side reaction was greatly suppressed by increasing the amount of NaOCl. Reaction at high temperature (70°C) did not increase the amount of primary amine (Table II), and Figure 6 shows that a side reaction leading to functional groups other than carboxyl acid was present (absorbance at 1567 cm⁻¹). Acid treatment of the modified polymer did not show any change in the IR spectrum (spectrum not shown).

Reactions of Homopolymers

In order to understand the source of the carboxyl groups, homopolymers of both AM and MMA were exposed to the Hofmann degradation reaction condition. For polyMMA, the untreated and treated

Table III   Decrease of AM Units During Hofmann Degradation[a] Based on IR

Reaction Time (h)	Ratio of 1456 cm⁻¹ [b]	Ratio of 1147 cm⁻¹ [b]
0	0.45	0.70
1	0.39	0.59
3	0.27	0.45
6.5	0.28	0.48

[a] Results of 9.5 mL sodium hypochlorite (NaOCl : AM = 0.7).
[b] Values are the ratio of the absorbance of AM (at 1456 or 1147 cm⁻¹) to absorbance of MMA (at 1728 cm⁻¹).

polyMMA had the same ratio of methyl ester to α-methyl group (from proton NMR), and it was found that no hydrolysis occurred during the one hour reaction period.

PolyAM was only partly soluble in the water-dioxane mixture used for reaction. The IR spectrum of the treated material is shown in Figure 7. The amide carbonyl absorbance (1680 cm⁻¹) was found, but the acid absorbance (expected at 1720 cm⁻¹) was not found. Titration of treated material to quantify the amine content was not successful because the pH drifted continuously during the measurement.

Water Content of Polymers

Water content of both the original copolymer and the modified polymer was obtained from the hydra-
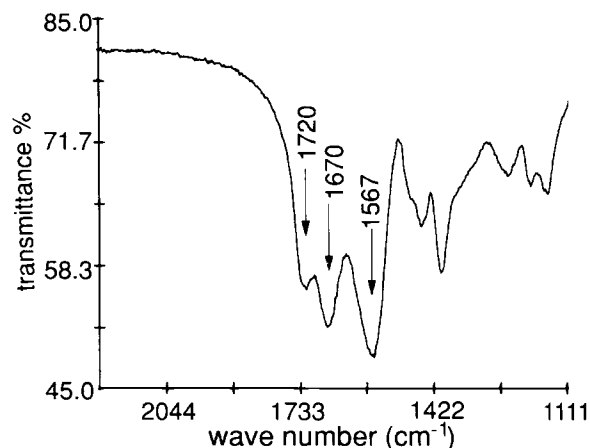
Figure 6   IR spectrum of poly(AAc-*co*-AM-*co*-MMA-*co*-VA). Hofmann degradation at high temperature (6.5 h, 70°C, 57 mL NaOCl). A side reaction besides carboxyl acid was found.
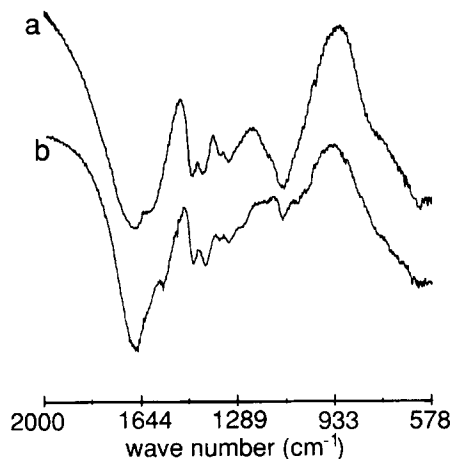
Figure 7 Transmittance IR spectrum of polyAM before (a) and after (b) Hofmann degradation. Acid carbonyl absorbance was not found after Hofmann degradation.

tion of cast films. As expected, the modified polymer had a higher water content than the original copolymer (Table IV).

DISCUSSION

Polymer Synthesis

In studying the effect of using different solvents for the polymerization of AM with MMA, dioxane was found to result in more AM units in the copolymer compared to that polymerized in ethanol at the same monomer feed.[11] Nevertheless, ethanol was chosen as a solvent here, and our results were similar to the reported values[11] using ethanol. Polymers were prepared here with up to 46% AM in copolymer with a 70% AM monomer feed. It was possible to prepare polymers up to 80% AM in ethanol,[11] but these high AM polymers were expected to be water soluble and were therefore avoided in this research. Some MMA was considered necessary so that hydrophobic interactions would produce an adequate degree of physical cross-links. Aqueous dioxane, aqueous pyridine, and aqueous acetone mixtures were found to be useful solvents for the product as expected; water is a good solvent for polyAM, and dioxane and acetone are good solvents for polyMMA.

About half of the polymer was lost during the Hofmann degradation. Some weight loss had been expected since the VA unit has a lower molecular weight than an AM unit; yet judging from the extent of conversion, the weight loss was considered to be due to the partial dissolution of the polymer in distilled water during purification. Chain scission has

been observed in the case of Hofmann degradation of polyAM,[9] and since it was to occur in our case as well, low molecular weight fragments were probably lost, resulting in the low yield. Since we were only interested in a water insoluble polymer, the soluble fraction was deliberately discarded. After Hofmann degradation, the vinyl amine copolymer became insoluble in aqueous acetone and soluble in aqueous THF. The modified polymer also had a higher water content (Table IV), presumably because of the presence of amines and carboxyl groups in addition to the amide groups. The modified polymer was also partly charged and showed a pH dependent solubility; it dissolved completely at basic pH and precipitated at acidic pH. This solubility behavior was the result of the balance between the electrostatic effect of anion and cation and the hydrophobic interaction with MMA. Depending on the pH or ionic strength of the solvent, the anion and cation might form an intra/intermolecular complex as well. It is necessary to consider these effects of the acid content in the further chemical modification (using the primary amine) because the modified polymer was found to be a polyampholyte.

Hofmann Degradation Conditions

The titration result showed that there were significant amounts of carboxyls introduced to the polymer as the result of a side reaction (Table II). Therefore, the modified polymers consisted of four monomeric units: the acid group [considered to be acrylic acid, (AAc)], AM, MMA, and VA. In Hofmann degradation of AM homopolymer in water, the amount of carboxyls formed was small.[12] This was not considered to be the effect of the mixed solvent (i.e., the presence of dioxane) since Hofmann degradation of AM homopolymer in water-dioxane mixture did not result in a distinctive amount of carboxyl formation. Similarly, MMA was not considered to be a source of the acid since the Hofmann degradation conditions were insufficient to obtain detectable hydrolysis in our case; however, hydrolysis of polyMMA under alkaline conditions has been reported with a maximum of 9% of MMA units in the homopolymer hydrolyzed to methacrylic acid, which increased with the addition of a comonomer (styrene).[13] Our results, using the homopolymer of both AM and MMA, did not show the distinct formation of carboxyls; yet we believe that AM was probably their source and it formed acrylic acids, as follows.

Carboxylic acid formation was likely to be caused by the effect of using an acrylamide copolymer, con-

verting acrylamide to acrylic acid. Since the reactivity ratios of two monomers in ethanol were 0.53 (AM) and 3.00 (MMA),[14] the original copolymer probably consisted of long MMA and short AM blocks, despite the relatively large amount of AM. Thus, the neighboring group of the AM groups was quite different in the copolymer than in the AM homopolymer, and this may lead to quite different behavior. The neighboring group effect plays an important role in the Hofmann degradation reaction mechanism of polyAM.[15] It was found[15] that the rate of reaction for polyAM, in spite of a higher activation energy, was an order of magnitude greater compared to low molecular weight amide compounds and suggested the presence of neighboring group effect that was in favor of this reaction. The fact that would support their theory was the reaction temperature; Hofmann degradation of polyAM was possible to be achieved at a low temperature, such as 0°C, while low molecular weight amide compounds usually require 70–100°C. The initial step in the reaction is the chlorination of amide (Figure 8). Once amide had been chlorinated, it was considered that it would not hydrolyze to produce carboxyl acid.[15] Our results suggest that only a few amide were chlorinated due to the lack of a neighboring group effect and this led to the low conversion of primary amine. The remaining nonchlorinated amides were considered to be the source of the carboxyl group.

Hofmann degradation of a poly(AM-co-styrene) copolymer has been done on the surface of latex particles, and this was able to introduce a sufficient amount of primary amines.[16] The majority of AM units in the particles were expected to be on the surface,[17] giving a high local concentration of AM, leaving them susceptible to the neighboring group effect; it was possible to obtain a high conversion of primary amine. On the other hand, our copolymer was dissolved in a solvent, and the AM blocks were considered to be short so that there was no local
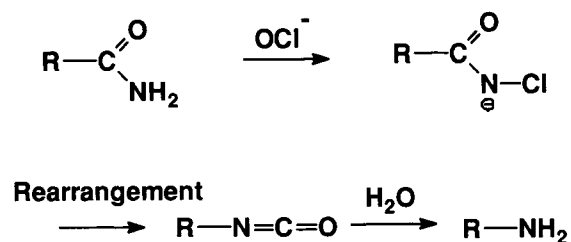

Figure 8   Reaction mechanism of Hofmann degradation.

concentration of AM, thus leading to a low conversion.

We found that by increasing the reaction time, the amount of carboxyls increased, but not the amount of primary amines (Fig. 4). This suggested that both the primary amines and carboxyls were formed during the early stage of Hofmann degradation; but after that period, only carboxyls were formed. These few chlorinated amides, mentioned previously, were formed early and presumably proceeded to amines at an early stage of the reaction. As the reaction proceeded, all of these chlorinated amides were consumed, and only the hydrolysis of remaining nonchlorinated amides was observed to increase the amount of carboxyls as the reaction time increased.

We found that the side reaction was suppressed by increasing the amount of NaOCl (Fig. 5), as well as decreasing the concentration of NaOH. Others found that the side reaction producing carboxyls was independent of the ratio of NaOCl to AM[16] or the concentration of NaOH.[15] When increasing the NaOCl, we also observed no increase in primary amines, although an increase was observed by others.[16] The reason for the differences here is not clear. Our results showed that only a small fraction of the NaOCl was effective in converting the amides to amines. This supports the previous hypothesis that the initial chlorination of amides was not very great in our case, leading to a low conversion to amines.

Table IV   Water Content of Polymers

Polymer Sample	Water Content[a]	Standard Deviation	n
Original copolymer [poly(AM-co-MMA)]	44	4.1	5
Modified polymer [poly(AAc-co-AM-co-MMA-co-VA)]	73	2.1	5

[a] Calculated as

$$\frac{(\text{Weight of Hydrated Polymer}) - (\text{Weight of Dry Polymer})}{(\text{Weight of Hydrated Polymer})} \times 100.$$

Side products other than carboxyl acid are known for Hofmann degradation. Intramolecular cyclizations, such as the urea linkage formed from amine and isocyanate (reaction intermediate), or the lactam formed from carboxyl acid and amine, are possible.[15,18] In our case, reactions carried at 0°C did not apparently show these side products in the IR spectrum. Another possible side product is a carbamate that is easily hydrolyzed by an acid to give amine.[19] This side reaction was considered negligible in our case for reaction at 0°C because the IR spectrum showed no difference before and after the acid treatment of the modified polymer. The reaction at 70°C showed a 1567 cm^{-1} absorption in Figure 6, which was not seen for reactions at 0°C. This could be from the carbamate or secondary amide formed either by intermolecular reactions (branching) or by intramolecular cyclization having a large ring (i.e., not 5- or 6-membered ring).

CONCLUSION

Synthesis of poly(AAc-co-AM-co-MMA-co-VA) was achieved by Hofmann degradation of poly(AM-co-MMA). The source of acid was considered to be AM; thus, it was assumed that the modified polymer contained acrylic acid groups. The product that was obtained was a hydrogel with a maximum of 8% primary amine and water content of 73%. The conversion to primary amine was low, and the side reaction of carboxylic acid formation was extensive compared to results of Hofmann degradation of polyAM and copolymer latex. This was considered to be caused by the use of a copolymer that lacked the neighboring group effect among amide groups. Further modification of this polymer using reactions of amines is currently being examined.

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