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COPOLYMERS OF 5-CHLORO-8-QUINOLINYL ACRYLATE AND ACRYLAMIDE: SYNTHESIS, HYDROLYSIS BEHAVIOUR AND ANTIBACTERIAL ACTIVITY

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Abstract—New copolymers of 5-chloro-8-quinolinyl acrylate (AQ) and acrylamide (AM) of various composition were prepared by radical polymerization. The obtained polymers were characterized by spectroscopic methods (IR, ^{1}H and ^{13}C NMR) and differential scanning calorimetry (DSC). Copolymers with AQ content less than 2 mol% are soluble in water. The product of the reactivity ratios is near unity and the monomer pair exhibits a random tendency in copolymerization. The hydrolysis of the copolymers follows pseudo first order kinetics. The hydrolytic release of 5-chloro-8-hydroxyquinoline (HQ) is faster for copolymers of lower AQ content. The antimicrobial activity of some AM–AQ copolymers was tested on Gram-positive and Gram-negative bacteria and the minimum inhibitory concentrations were determined. The tested compounds exhibit comparatively high antibacterial activity.

INTRODUCTION

It is known that 8-hydroxyquinoline derivatives have antibacterial and antimycotic activity [1–3]. Formulations based on them are used as chimiotherapeutic and antiseptic agents. Halogen-containing 8-hydroxyquinoline derivatives have significant activity against a wide variety of bacteria, fungi and protozoa. The chemical anchoring of biocides to polymers is one approach to the problem of the preparation of bioactive materials with potential use in medicine or agriculture. The synthesis of polymeric 8-hydroxyquinoline derivatives by modification of poly(ethylene glycol)s and poly(ϵ-caprolactone)diols with 5-nitro- or 5-chloro-8-hydroxyquinoline was reported previously [4–6].

Another approach for the preparation of polymers bearing groups with antimicrobial activity is the preparation of a polymerizable monomer and its subsequent polymerization or copolymerization with another monomer. There are a few examples for the synthesis and polymerization of vinyl monomers containing the ester-bound quinolinyl group. Methods for the preparation of 5-chloro-8-quinolinyl methacrylate [7], 8-quinolinyl acrylate [8–10] and dihalogen-containing quinolinyl acrylates [11] have been described. The radical copolymerization of 8-quinolinyl acrylate and vinyl acetate or ethyl acrylate [8, 9], methyl methacrylate or butyl acrylate [12] has been described. The antifungal properties of the resulting chemicals have been tested in view of their potential use as antifouling ingredients for marine paints.

Incorporation of different hydrophilic comonomer units into the polymer backbone may be expected to influence significantly the polymer properties. Copolymers containing 8-quinolinyl acrylate and acrylamide containing 13 and 41 mol% quinolinyl groups have been synthesized [10] but data for their characteristics and properties are limited. Recently, we have reported the preparation and characterization of copolymers of 5-chloro-8-quinolinyl acrylate with acrylic acid [13] or *N*-vinyl-2-pyrrolidone [14]. In connection with these studies, copolymers of 5-chloro-8-quinolinyl acrylate (AQ) and acrylamide (AM) of various compositions were prepared. Their synthesis, characterization and hydrolysis behaviour are reported in the present paper. Some of the synthesized copolymers were screened for their antibacterial activity.

EXPERIMENTAL

Materials

5-Chloro-8-hydroxyquinoline (HQ) was purchased from Fluka. Acrylamide (Koch-Light Laboratories Ltd, England) was recrystallized twice from acetone. 2,2′-Azobisisobutyronitrile (AIBN) (Fluka, Switzerland) was recrystallized from ethanol, dried in a vacuum oven and stored at -10°C. The solvents, dimethylformamide (DMF) and dimethylsulfoxide (DMSO), were distilled and stored over 5 Å molecular sieves. All other chemicals were reagent grade and were used without further purification.

Procedures

Preparation of 5-chloro-8-quinolinyl acrylate (AQ). The monomer was prepared similarly to standard procedure [10, 11] by interaction of 5-chloro-8-hydroxyquinoline and acryloyl chloride in benzene in the presence of $(C_2H_5)_3N$ at room temperature, under stirring. The obtained monomer

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was recrystallized from a mixture of diethyl ether and petroleum ether 3:1 v/v); yield 53% (recrystallized product); mp 70–72°C.

Copolymerization of AM and AQ. Copolymerizations were carried out at various feed monomer ratios in DMF or DMSO in sealed glass tubes, after three freeze–thaw cycles, at 60°C for 40 hr. The total concentration of monomers was 1.25 mol/l. The concentration of the initiator (AIBN) was 0.2 wt% based on total monomer content. The polymer products were recovered by precipitation in methanol. They were further purified from unreacted monomers by precipitation from DMSO solution in methanol. The purified products were vacuum-dried at 50°C. The AQ content in the copolymers was determined by UV and ^{1}H NMR spectroscopy in DMSO-d_6.

For calculation of the reactivity ratio of AM and AQ a reaction time of approximately 3 hr was chosen for the copolymerizations in order to achieve a total monomer conversion not higher than 15 wt%. The yields were determined gravimetrically. The composition of the copolymers used for the calculation of the reactivity ratios was determined by UV spectroscopy.

Measurements

IR spectra were recorded on a UR-20 Carl-Zeiss spectrophotometer at room temperature in KBr pellets. UV spectra were taken on a Specord-UV-VIS Carl Zeiss spectrophotometer in DMSO. AQ content in the copolymer was determined using the calibration absorbance of an AQ solution in DMSO at 266 nm vs its concentration. ^{1}H and ^{13}C NMR spectra were taken on a Bruker WM 250 spectrophotometer at 250.13 MHz (^{1}H) and 62.9 MHz (^{13}C) at 25°C in DMSO-d_6, using TMS for reference. The amount of AQ units in the copolymers was calculated from the intensity ratio of $H^e + H^3 + H^6 + H^7$ and H^2 protons using the equation:

$$\frac{2x + 3y}{y} 100 = \frac{I_1}{I_2},$$

where x and y are the number of AM and AQ monomer units, respectively, I_1 is equal to the total integral intensity of $H^e + H^3 + H^6 + H^7$ protons and I_2 is equal to the integral intensity of H^2 protons.

The intrinsic viscosities of the copolymers were measured with an Ubbelohde viscometer in DMSO at 30 ± 0.1°C. The initial polymer concentration was 1.2 or 0.8 g/dl. The glass transition temperatures (T_g) were determined by differential scanning calorimetry (DSC) using Perkin-Elmer DSC7 Delta Series apparatus calibrated with indium. The standard heating rate was 10°C/min.

Hydrolysis experiments were carried out in buffer/ethanol solution (1/1, v/v) because of the low water solubility of HQ. Buffer solutions of pH 4.6 (0.07 M NaOH, 0.136 M CH_3COOH), pH 7.2 (0.05 M KH_2PO_4, 0.0291 M NaOH) and pH 9.2 (0.147 M $NaHCO_3$, 0.0178 M Na_2CO_3) were used. The copolymers were ground and sieved (100 mesh). A copolymer sample containing 1.22×10^{-2} mol 5-chloro-8-quinolinyl groups was placed in cellulose membrane dialysis tubing (molecular weight cut-off 1000). After adding 10 ml solution, the sample was dialysed against the same solution. The total solution volume was 100 ml. Hydrolysis was performed at 25 or 37°C. Periodically, a 0.5 ml sample was withdrawn from the outer solution and replaced with 0.5 ml of fresh solution. The concentration of HQ released was determined by UV spectroscopy.

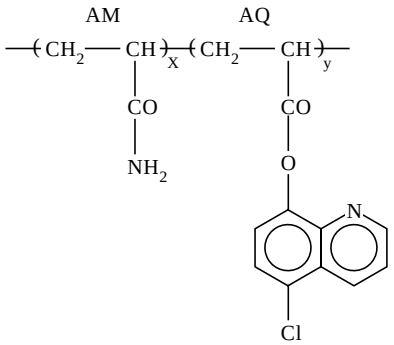
Microbiological screening for the determination of minimum inhibitory concentration (MIC) was carried out on the following bacterial strains: *Y. enterocolitica*, *S. aureus*, *S. typhimurium*, *P. vulgaris* and *L. monocytogenes*. Bacteria were suspended in meat-peptone broth to provide inocula containing approximately 1.2×10^6 cells/ml (determined optically using a standard). The tested compounds were dissolved in DMSO at an initial concentration of 0.1 g/ml 5-chloro-8-quinolinyl acrylate for AQ and P(AM_{68}-co-AQ_{32}) and 0.033 g/ml for P(AM_{95}-co-AQ_5). Solutions were prepared by the serial dilution method and were incubated at 37°C for 24 hr.

*The subscripts indicate AM and AQ content (in mol%) in the copolymers.

RESULTS AND DISCUSSION

Preparation and characterization of the copolymers of AM and AQ

Copolymers of AM and AQ [P(AM-co-AQ)] were prepared by radical copolymerization in DMF or DMSO with initiator AIBN.



P(AM-co-AQ)

The data given in Table 1 demonstrate that copolymers of AM and AQ of various compositions have been successfully prepared. The obtained copolymers are soluble in DMSO. Copolymers of AQ content 38 and 32 mol% are soluble in DMF. Copolymers of AQ content less than 2 mol% (samples 6 and 7, Table 1) are soluble in water. Copolymers of AM and AQ are insoluble in ethanol, methanol, toluene, chlorinated hydrocarbons and tetrahydrofuran.

The copolymers of AM and AQ, as well as their corresponding homopolymers, are amorphous. The glass transition temperatures (T_g) of poly(5-chloro-8-quinolinyl acrylate) and poly(acrylamide) prepared under the same experimental conditions as the copolymers differ significantly (118.4 and 217°C, respectively). The glass transition temperature of copolymers rich in AM units is close to the T_g of poly(acrylamide). For example, the T_g values of P(AM_{86}-co-AQ_{14})*,* P(AM_{95}-co-AQ_5) and P(AM_{99}-co-AQ_1) are in the range 190.0–198.5°C.

The obtained copolymers were characterized by ^{1}H NMR spectroscopy in DMSO-d_6 (Fig. 1). The signals towards the high field are due to the main chain methylene and methine protons [-CH_2-, (a) and (c); -CH-, (b) and (d)]. On increasing the content of AQ units in the copolymer, these resonance signals become broad and not well resolved. The signals of H^c and H^d protons are partially overlapped by those of the solvent. On increasing the AM content in the copolymers, the signals of H^a and H^b protons are shifted towards the low field and their resonance values are very close to the resonance values of the

Table 1. Composition, yield and intrinsic viscosity of the copolymers of AM and AQ [copolymerization conditions: solvent DMSO, initiator AIBN (0.2 wt% based on total monomers), 60°C, 40 hr]

No.	Copolymer[a]	n[b]	AQ in feed (mol%)	Yield (%)	AQ in the copolymer (mol%) UV	^{1}H NMR	$[\eta]$[c] (dl/g)
1	$P(AM_{62}\text{-co-}AQ_{38})$	2	50	70	38.2	38.6	0.39
2	$P(AM_{67}\text{-co-}AQ_{33})$	2	33	75	32.5	33.7	0.34
3	$P(AM_{86}\text{-co-}AQ_{14})$	6	20	72	14.3	15.3	0.41
4	$P(AM_{92}\text{-co-}AQ_{8})$	13	9	84	7.5	8.3	1.08
5	$P(AM_{95}\text{-co-}AQ_{5})$	19	6	88	5.1	4.3	1.14*
6	$P(AM_{99}\text{-co-}AQ_{1})$	80	2	95	1.2	1.3	0.92*
7	$P(AM_{99.3}\text{-co-}AQ_{0.7})$	146	1	95	0.7	1.0	0.83*

[a]The subscripts indicate AM and AQ content (in mol%) in the copolymers. The value of AQ content is determined by UV; the value for AM is calculated from the difference to 100%.

[b]n is the number of AM units for one AQ unit.

[c]Values marked by an asterisk were determined at an initial copolymer concentration of 1.2 g/dl; other values determined at initial concentration of 0.8 g/dl.

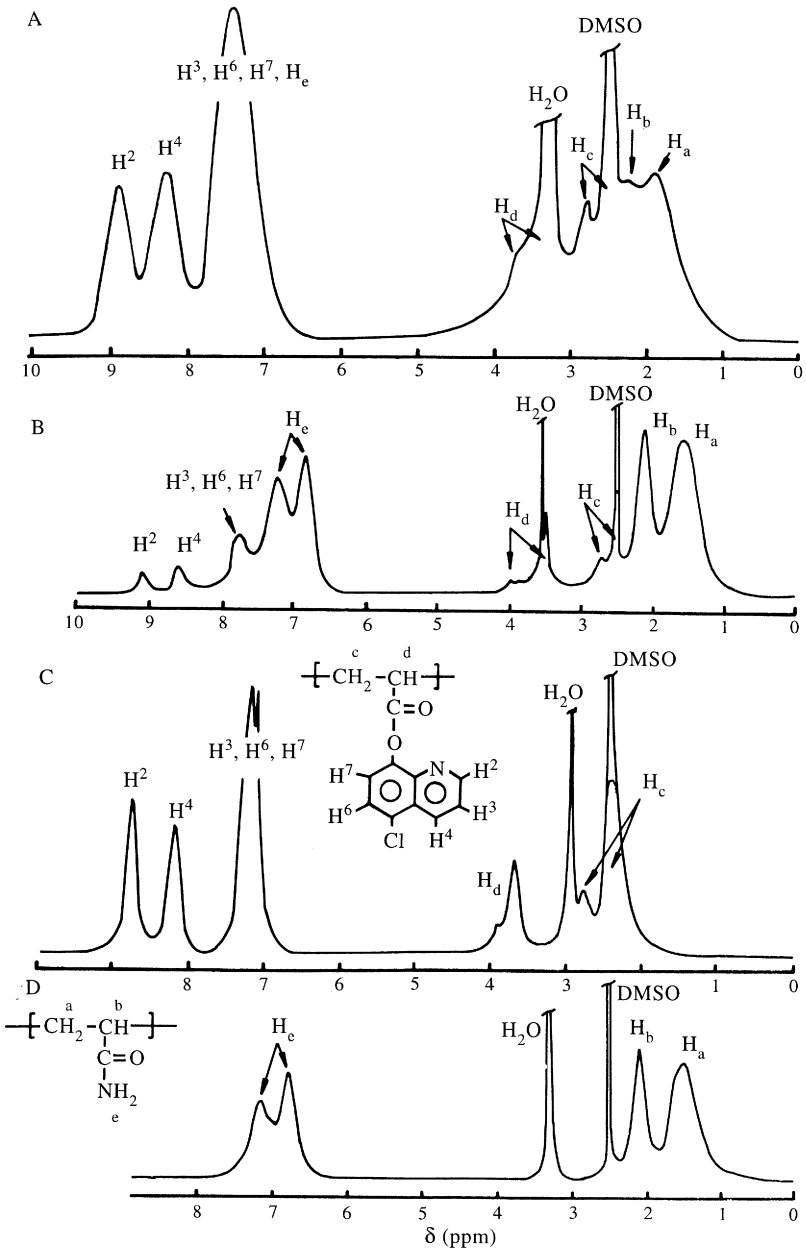


Fig. 1. ^{1}H NMR spectra of: (A) $P(AM_{62}\text{-co-}AQ_{38})$; (B) $P(AM_{92}\text{-co-}AQ_{8})$; (C) poly(5-chloro-8-quinolinylacrylate); and (D) poly(acrylamide), DMSO-d_6.

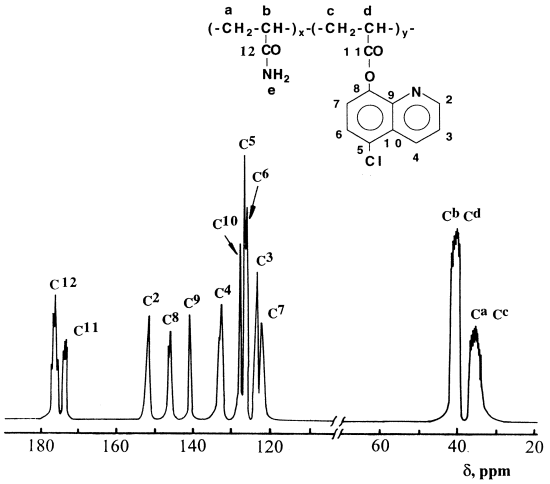


Fig. 2. ^{13}C NMR spectrum of P(AM_{67}-co-AQ_{33}), DMSO-d_6.

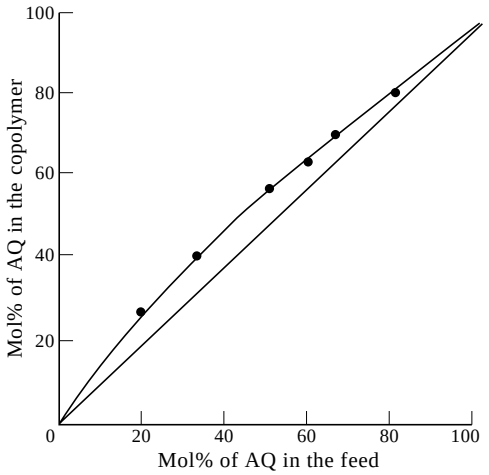


Fig. 4. Copolymer composition as a function of feed composition for the copolymerization of AM and AQ (DMSO, AIBN, 60°C).

same protons for poly(acrylamide). For example, the resonance of H^a and H^b protons are at: (δ) 1.90 ppm and 2.26 ppm for P(AM_{62}-co-AQ_{38}); 1.62 ppm and 2.12 ppm for P(AM_{86}-co-AQ_{14}) and P(AM_{93}-co-AQ_7); 1.56 ppm and 2.10 ppm for P(AM_{95}-co-AQ_5); and 1.48 ppm and 2.08 ppm for poly(acrylamide), respectively. The resonance signals towards the low field revealed the presence of quinolinyl groups. The signals of the amide protons of AM units are also in this region. The aromatic AQ protons in the copolymers are deshielded in comparison with those of poly(5-chloro-8-quinolinylacrylate). The deshielding becomes greater on decreasing the content of AQ in the copolymers. For copolymers with high AQ content, the resonances of the NH_2 protons of AM units overlap with those of the aromatic H^3, H^6 and H^7 protons and appear at the same position as that of NH_2 protons of poly(acrylamide). These features observed in the ^{1}H NMR spectra of the synthesized products and comparison with the ^{1}H NMR spectra of the corresponding homopolymers, confirm that copolymers of AM and AQ were obtained. The greater the AM content in the copolymers, the more probable is the presence of longer sequences built by consecutive AM units.

The structure of the copolymers was confirmed by ^{13}C NMR spectroscopy. A typical ^{13}C NMR spectrum of AM–AQ copolymer is given in Fig. 2. The signals for the ester carbonyl carbon of AQ monomer and the amide carbonyl carbon of AM monomer are at (δ) 164.6 and 167.5 ppm, respectively. The resonances of the carbonyl carbons of AQ and AM units in the copolymers are appreciably shifted downfield. They are at 173.3 ppm (C^{11}, Fig. 2) and 176.3 ppm (C^{16}, Fig. 2). Two types of ^{13}C NMR signals are observed towards the high field, which are due to the main chain methylene (C^a and C^c) and methine (C^b, C^d) carbon atoms. The signals of the two types of monomer units are overlapping, which results in

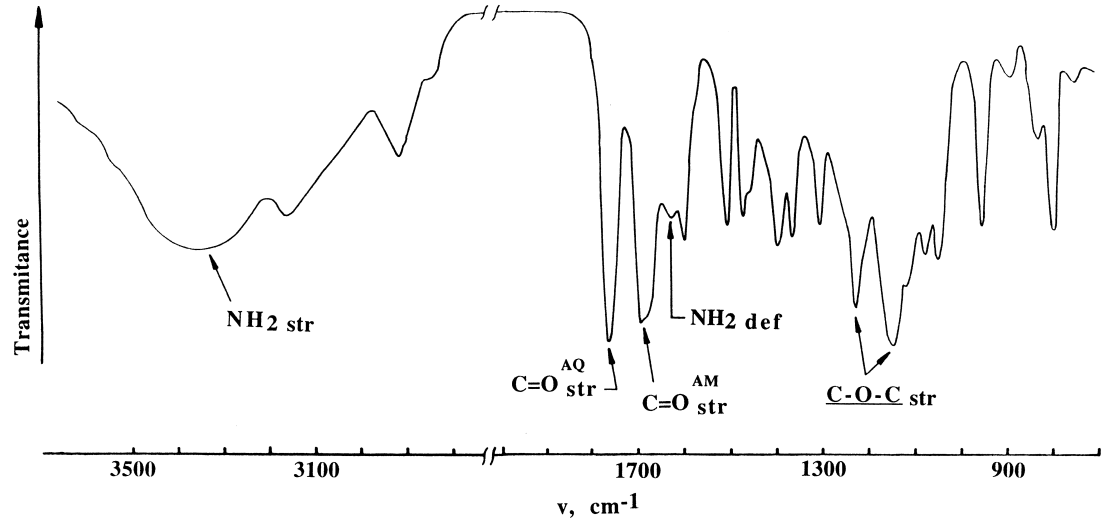


Fig. 3. IR spectrum of P(AM_{62}-co-AQ_{38}), KBr pellet.

Table 2. Microstructural characteristics of P(AM-co-AQ) copolymers[a]

Polymer[b]	Blockiness AM–AM	Blockiness AQ–AQ	Alternation AM–AQ	Mean sequence length μ_{AM}	Mean sequence length μ_{AQ}
$P(AM_{62}\text{-co-}AQ_{38})$	17.14	30.91	51.94	1.66	2.19
$P(AM_{67}\text{-co-}AQ_{33})$	34.14	14.93	50.94	2.34	1.59
$P(AM_{86}\text{-co-}AQ_{14})$	53.47	6.03	40.50	3.64	1.30
$P(AM_{92}\text{-co-}AQ_{8})$	75.91	1.33	22.74	7.68	1.12
$P(AM_{95}\text{-co-}AQ_{5})$	83.25	0.61	16.14	11.32	1.08
$P(AM_{99}\text{-co-}AQ_{1})$	94.17	0.07	5.76	33.68	1.02
$P(AM_{99.3}\text{-co-}AQ_{0.7})$	97.01	0.02	2.96	66.55	1.01

[a]Blockiness and alternation in mol%.
[b]The subscripts indicate AM and AQ content (in mol%) in the copolymers. The value of AQ content is determined by UV; the value for AM is calculated from the difference to 100%.

signals that are too broad and complicated. The resonances in the region 120.0–152.0 ppm are assigned to the carbons of the quinolinyl groups, as shown in Fig. 2.

The IR spectra of the copolymers (Fig. 3) show the absence of absorption bands for the double bond ($\nu_{C=C}$) and for the vinyl methylene group ($\nu_{=CH_2}$) characteristic of the monomers. The ester carbonyl band for AQ units in the copolymers is shifted to shorter wavelengths and is at 1765 cm^{-1} (i.e. $\Delta\nu_{C=O} = 25\ cm^{-1}$). The absorption band at 1685 cm^{-1} is assigned to the C=O vibration of AM units and the absorption band of low intensity at 1620 cm^{-1} is due to NH_2 deformation vibrations of units of the same type. On decreasing the AQ content in the copolymers, the intensity of the band at 1765 cm^{-1} decreases as compared with that at 1685 cm^{-1}. This appears as a shoulder for copolymers with high AM content. Such a result is expected and confirms the fact that copolymers of AM and AQ of various composition have been prepared.

Copolymerization reactivity ratios and microstructure studies

The reactivity ratios of AM and AQ in DMSO were calculated by Fineman–Ross [15] and Kelen–Tüdos [16] methods. Series of copolymerization reactions were carried out, varying the AQ content in the feed from 20 to 80 mol%. Fig. 4 shows the copolymer composition as a function of feed composition for the copolymerization of AM and AQ. The Fineman–Ross plot for AM (M_1) and AQ (M_2) yields reactivity ratios of $r_1 = 0.69$ and $r_2 = 1.22$ (correlation coefficient 0.983). The plot according to the Kelen–Tüdos method gives values of $r_1 = 0.63$ and $r_2 = 1.16$ (correlation coefficient 0.982). For the comonomer pair AM–AQ, r_1 and r_2 values are near unity and $r_1 \times r_2 \approx 1$. This suggests that AM and AQ exhibit a random tendency in copolymerization. The reactivity ratio product for the AM–AQ pair is closer to unity than that reported for the AM–8-hydroxyquinolinylacrylate pair [10], thus showing that the behaviour of the AM–AQ pair in copolymerization is closer to the ideal. Calculation of Q and e values by the two low-conversion methods and the known Q and e values of AM [17, 18] gave $Q = 0.95$ and $e = 0.699$ for AQ.

Microstructural calculations were carried out to estimate the degree of blockiness and alternation. The statistical distribution of the monomer sequences AM–AM, AQ–AQ and AM–AQ was calculated. Monomer sequence lengths, μ, were calculated according to the literature [19–21] from the determined reactivity ratios for the comonomer pair. The data are listed in Table 2. The values of mean sequence length for the AM–AQ pair vary considerably with composition. On increasing AM content in the feed, the probability of AM–AM bond formation increases, thus decreasing the probability of AM–AQ and AQ–AQ bond formation.

Hydrolysis behaviour

It is interesting to study the hydrolysis behaviour of the copolymers since it might be expected that the hydrolysis of the ester bonds is related to the

Table 3. Rate constants of hydrolysis of P(AM-co-AQ) copolymers

Polymer	Hydrolysis rate constants × 10^7 (sec^{-1}) pH 4.6 25°C	pH 7.2 25°C	pH 7.2 37°C	pH 9.2 25°C
$P(AM_{62}\text{-co-}AQ_{38})$	nd	4.40	11.76	15.75
$P(AM_{86}\text{-co-}AQ_{14})$	3.78	5.29	21.12	111.11
$P(AM_{92}\text{-co-}AQ_{8})$	nd	18.90	79.28	203.70

nd = not determined.

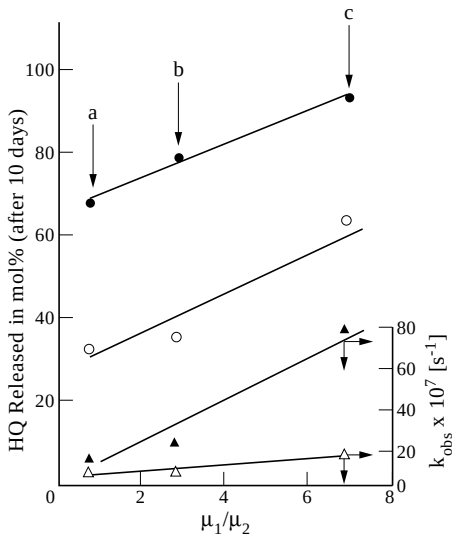
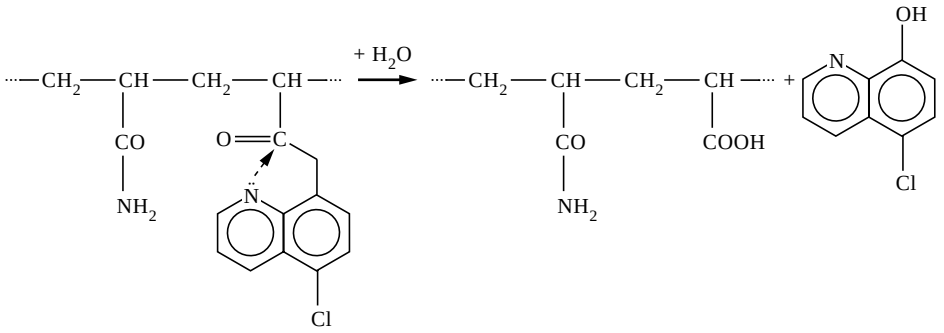


Fig. 5. Plot of mean sequence length ratio (μ_{AM}/μ_{AQ}) for AM–AQ copolymers vs release concentration of HQ at (○) 25°C and (●) 37°C, and vs hydrolysis rate constants at (△) 25°C and (▲) 37°C, pH 7.



Scheme 1. P(AM-co-AQ).

biological activity of the copolymers. The hydrolysis rate depends on a number of factors, such as the pH of the medium, the temperature and accessibility of the nucleophile to the hydrolysis site; the last point is connected with the copolymer microstructure, neighbouring groups effects and hydrophilic–hydrophobic ratio.

The 5-chloro-8-hydroxyquinoline (HQ) release was followed as a function of time for copolymers of different AQ content at different pH values at 25 and 37°C. The results fit best with pseudo first order hydrolysis kinetics. The rate of HQ release increases with increasing pH and temperature. The hydrolysis rate constants k_{obs} are calculated from the slope of a plot of $\ln(C_o/C)$ against time and are presented in Table 3. The rate of HQ release decreases in the order $P(AM_{92}\text{-co-}AQ_8) > P(AM_{86}\text{-co-}AQ_{14}) > P(AM_{62}\text{-co-}AQ_{38})$.

As seen from Fig. 5, there is good correlation between the results for copolymer microstructure and hydrolysis behaviour. The hydrolysis rate constants and the amount of HQ released increase with the μ_{AM}/μ_{AQ} ratio (corresponding to increase in hydrophilicity). The determined hydrolysis rate of AM–AQ copolymers is much higher than the reported one [22] for similar copolymers containing bulky hydrophobic ester-bound aromatic residues. This may be explained by the structure of the quinolinyl group favouring the release of the aromatic residue (see Scheme 1).

Antibacterial activity

The antibacterial activity of copolymers $P(AM_{68}\text{-co-}AQ_{32})$ and $P(AM_{95}\text{-co-}AQ_5)$ against Gram-positive (*S. aureus*, *L. monocytogenes*) and Gram-negative (*Y. enterocolitica*, *S. typhimurium*, *P. vulgaris*) bacteria was tested. A comparative study of the biological activity of AQ was conducted, as its antibacterial activity has not been reported to date. The results for the minimum inhibitory concentrations (MIC) are summarized in Table 4. It can be seen that all tested compounds exhibit relatively high biological activity. AQ and its polymer derivatives are more effective against Gram-positive bacteria than against Gram-negative bacteria. The copolymer $P(AM_{95}\text{-co-}AQ_5)$, with a lower content of bioactive residues than $P(AM_{68}\text{-co-}AQ_{32})$, exhibits higher activity. It is suggested that these differences in copolymer activity are due to differences in hydrolysis behaviour.

Table 4. Minimum inhibitory concentration (MIC) of AQ and copolymers of AM and AQ

Strain	Minimum inhibitory concentration[a] (μg/ml) AQ	$P(AM_{68}\text{-co-}AQ_{32})$[b]	$P(AM_{95}\text{-co-}AQ_5)$[b]
Y. enterocolitica	12	98	25
S. aureus	25	12	12
S. typhimurium	49	770	98
P. vulgaris	98	385	25
L. monocytogenes	12	49	6

[a]The MIC values given are the lowest concentrations giving complete inhibition of visible growth. MIC values have been calculated taking into account the active substance (5-chloro-8-quinolinoxy groups).

[b]The subscripts indicate AM and AQ content (in mol%) in the copolymers. AQ content is determined by UV; the value for AM is calculated from the difference to 100%.

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