Synthesis, Exchange Reactions, and Biological Activity of Poly(8-methacryloxyquinoline)

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ABSTRACT: 8-Methacryloxyquinoline (MAQ) was prepared through the reaction of 8-hydroxyquinoline with either methacryloyl chloride or methacrylic acid in the presence of triethylamine or *N,N*-dicyclohexylcarbodiimide, respectively. MAQ was polymerized in dimethylformamide with 2,2-azobisisobutyronitrile as the initiator. The reactions of the resulting polymers with hydroxyl and amino compounds were studied. The polymers were characterized with IR, ^{1}H-NMR, and mass spectroscopy. Some of the synthesized polymers were tested for their antimicrobial activity against bacteria and fungi. Generally, all the polymers were effective against the tested microorganisms, but their growth-inhibition effects varied. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 121: 1160–1165, 2011

Key words: biological applications of polymers; monomers; polymer synthesis and characterization

INTRODUCTION

One promising synthesis strategy for targeted drug delivery involves the use of polymers. One of the most interesting topics in the field of pharmacologically active polymers is the preparation of polymeric drugs: drugs are attached to a polymeric backbone via covalent bonds with limited stability in biological environments.[1,2] If a drug molecule contains hydroxyl or amino groups, a polymeric drug is best prepared through the reaction of the drug with a presynthesized polymer with functional side groups able to react selectively with the aforementioned groups and produce ester or amido bonds.[1,3] Several activated esters and amides of acrylic acid, methacrylic acid, and their polymers have been described.[4–9] In our previous work, we described the synthesis, polymerization, copolymerization, and exchange reactions of acrylic and methacrylic esters.[10–16] Quinoline derivatives are important constituents of several pharmacologically active synthetic compounds.[17–20] This article reports the synthesis and polymerization of 8-methacryloxyquinoline (MAQ or **III**) as well as the exchange reactions of the resulting polymer with aminated and hydroxylated model compounds.

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EXPERIMENTAL

Materials

Methacrylic acid and the free-radical initiator azobisisobutyronitrile (AIBN) were obtained from E. Merck (Darmstadt, Germany). Ethylamine, piperidine, *p*-anisidine, *t*-butanol, phenol, cyclohexanol, and *p*-aminobenzoic acids were acquired from BDH (England). 8-Hydroxyquinoline, triethylamine, *o*-hydroxybenzoic acid, and *p*-hydroxybenzoic acid were used as supplied by Aldrich Chemical Co., Ltd. (Germany). AIBN was purified by recrystallization from absolute alcohol (mp = 102°C). All solvents were reagent-grade and were purified by distillation before use.

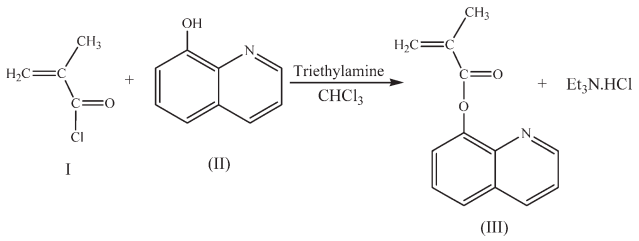
Synthesis

Preparation of MAQ

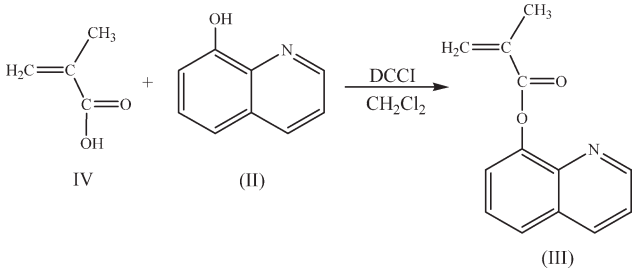
MAQ was prepared through the reaction of 8-hydroxyquinoline with methacryloyl chloride or through the reaction of 8-hydroxyquinoline with methacrylic acid in the presence of *N,N*-dicyclohexylcarbodiimide (DCCI) as a condensing agent according to our previous work.[13–16]

Acid chloride method. Methacryloyl chloride was prepared by the previously reported method[21] and was used for further reactions.

MAQ was prepared as follows. To a cold, well-stirred solution (0–5°) of 8-hydroxyquinoline (0.1 mol) and triethylamine (0.1 mol) in 150 mL of dry chloroform, methacryloyl chloride (0.1 mol) was added dropwise. After the addition of methacryloyl chloride was complete, the reaction mixture was stirred for 4 h



Scheme 1 Preparation of 8-methacryloxyquinoline by acid chloride method.



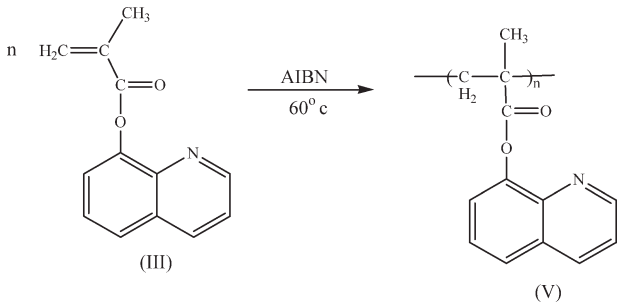
Scheme 2 Preparation of 8-methacryloxyquinoline by DCCI method.

and poured into excess petroleum ether (40–60°C) to reprecipitate triethylamine hydrochloride. Then, the filtrate was extracted with water for the removal of any residual triethylamine hydrochloride and was evaporated to dryness *in vacuo*. The residue was recrystallized from diethyl ether. The yields of the recrystallized products usually ranged from 70 to 85% (mp = 50–52°C, lit. 49°C).[22]

DCCI method. To a cold, well-stirred solution (0–5°C) of 8-hydroxyquinoline (14.51 g, 0.1 mol) and methacrylic acid (8.61 g, 0.1 mol) in 150 mL of DCCI (20.6 g, 0.1 mol), methylene chloride was added with stirring. After 6 h of stirring at room temperature, the precipitated dicyclohexyl urea was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was then recrystallized from diethyl ether. The yield was 75%, and the melting point was 50–52°C.

Polymerization of MAQ

A 10% (w/v) solution of the monomer and AIBN (1 mol %) in dimethylformamide (DMF) was purged



Scheme 3 Polymerization of 8-methacryloxyquinoline.

with deoxygenated nitrogen, and the reaction mixture was allowed to stand at 60°C for 6 h. Poly(8-methacryloxyquinoline) (poly-MAQ or **V**) was obtained by reprecipitation in methanol, collected by filtration, washed, dried, and weighed. The yield was 85%.

Exchange reactions

To a 10% solution of the polymer in DMF, an amine (2 equiv) was added. The reaction mixture was allowed to stand at 60°C for 6 h. The exchange reactions with hydroxylated compounds were carried out similarly, except that triethylamine (2 equiv) was also added to the reaction mixture. In all cases, the products were isolated (the reaction mixture was poured into an excess of diethyl ether, filtered, dissolved in DMF, and reprecipitated with diethyl ether), washed, dried, and weighed.

Characterization

IR spectra (KBr) were recorded on a Pye-Unicam Sp-883 spectrophotometer from PerkinElmer. ^{1}H-NMR spectra were recorded on a Varian Gemini 200-MHz spectrophotometer at Cairo University (Cairo, Egypt). The chemical shifts (δ) are given downfield with tetramethylsilane as the internal standard. Mass spectroscopy (MS) was performed with a Shimadzu GC MS-QP 1000 EX mass spectrometer at the Microanalytical Laboratory of Cairo University. The elemental analysis was also carried out the Microanalytical Laboratory.

TABLE I
IR and ^{1}H-NMR Spectra of Monomer III and Polymer V

	IR			^{1}H-NMR	
Compound	$\nu_{C=O}$ (ester; cm^{-1})	ν_{C-O-O} (cm^{-1})	$\nu_{C=C}$ (cm^{-1})	Segment	δ (ppm)
III	1738	1132, 1165	1630	CH_3—	2.18
				CH_2=C—	6.56, 5.86
				Ar—	7.27–8.94
V	1740	1132, 1165	—OH_3—, —CH_2—C	1.42–1.81	7.27–8.94
				Ar—	

TABLE II
MS Spectrum of Monomer III

m/z	213	128	101	85	69
Abundance %	0.79	8.2	1.44	5.09	100

RESULTS AND DISCUSSION

In this investigation, MAQ was prepared by two routes. The first route for the preparation of MAQ was the reaction of 8-hydroxyquinoline with methacryloyl chloride in the presence of triethylamine according to Scheme 1.

The other route for the preparation of MAQ was the reaction of methacrylic acid with 8-hydroxyquinoline in the presence of DCCI as a dehydrating agent according to Scheme 2.

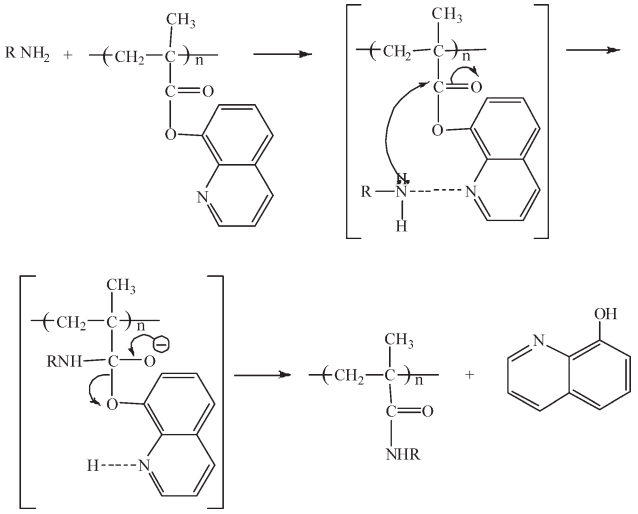
The monomer was a crystalline solid easily dissolved in most organic solvents. It was readily polymerized in solution with AIBN as a free-radical initiator. The polymer was soluble in DMF, dimethyl sulfoxide (DMSO), chloroform, and dioxane but insoluble in water and most organic solvents (Scheme 3).

The structures of the monomer and polymer were established by nitrogen analysis, IR and ^{1}H-NMR spectroscopy (Table I), and MS (Table II).

Exchange reactions

Reactions of poly-MAQ with amines

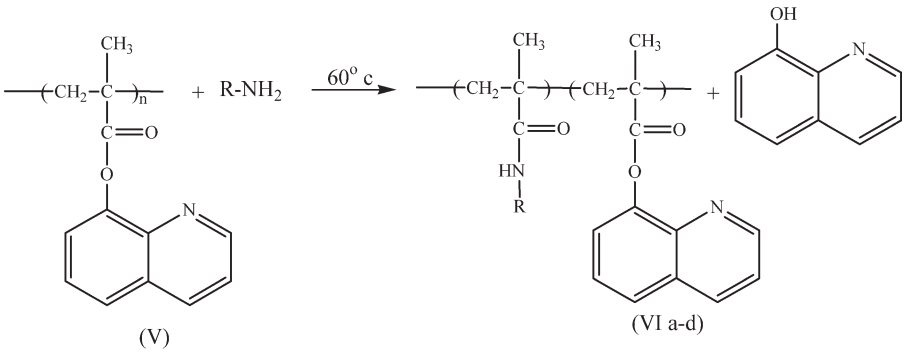
The ability of poly-MAQ to enter an exchange reaction with amines was tested with ethylamine, *p*-toluidine, *p*-anisidine, and *p*-aminobenzoic acid. In a typical experiment, a 10% solution of poly-MAQ in DMF was treated with 2 equiv of amine, and the reaction mixture was allowed to stand at 60°C for 6 h (Scheme 4).



Scheme 5 Mechanism of the reaction of poly(8-methacryloxyquinoline) with amines.

The reaction probably took place according to Scheme 5.

The yield of the exchange reaction was calculated on the basis of ^{1}H-NMR spectroscopy (Table III). This was confirmed with IR spectroscopy. In the spectra of compounds **Va–Vd**, the $\nu_{C=O}$ absorption band of the ester in poly-MAQ became weak after the exchange reactions. At the same time, new bands at approximately 1630–1640 and 1510–1520 cm^{-1}, which were assigned to amide **I** and amide **II**, respectively, appeared. The exchange percentage increased in the following order: ethylamine < *p*-anisidine < *p*-aminobenzoic acid < *p*-toluidine.



(V) (VI a-d)

where:
VI a, R = C_2H_5-
b, = CH_3-C_6H_4-(p)
c, = CH_3O-C_6H_4-(p)
d, = HOOC-C_6H_4-(p)

Scheme 4 Exchange reactions of poly(8-methacryloxyquinoline) with different amines.

TABLE III
^{1}H-NMR Spectral Data for the Exchange Reactions of Polymer V with Amines

Exchange product	Segment	δ (ppm)	Exchange (%)
VIa	CH_3—, —CH_2—	0.9–2.2	52.57
	—OH_2N—	3.4	
	—NH	6.8	
	Ar—	7.0–8.9	
VIb	CH_3—, —CH_2—C—	0.9–1.9	87
	CH_3—	2.2	
	Ar—	6.9–8.84	
	—NH	6.8	
VIc	CH_3—, —CH_2—C–	0.8–2.0	54.2
	—OCH_3	3.4	
	—NH	6.5	
	Ar—	6.8–8.7	
VId	CH_3—, —CH_2—C—	0.8–2.0	72
	—NH	5.8	
	Ar—	6.6–8.8	
	—OH acid	10.5	

Reactions of poly-MAQ with hydroxyl compounds

The ability of poly-MAQ to undergo exchange reactions with hydroxyl compounds was tested with *n*-butanol, cyclohexanol, phenol, salicylic acid, and *p*-hydroxybenzoic acid (Scheme 6).

All the aforementioned exchange reactions took place easily when a 10% solution of poly-MAQ was treated with 2 equiv of a hydroxyl compound and 2 equiv of triethylamine and allowed to stand at 60°C for 6 h. The results are summarized in Table IV. *n*-Butanol was less reactive than both cyclohexanol and phenol, and *o*-hydroxybenzoic acid was less reactive than *p*-hydroxybenzoic acid. The exchange percentage increased in the following

TABLE IV
Analytical Data for the Exchange Reactions of Polymer V with Hydroxyl Compounds

Coreactant	N (%)	Exchange (%)	Time (h)
n-Butanol	5.68	31.1	6
Cyclohexanol	2.80	63.1	6
Phenol	3.39	55.22	6
o-Hydroxybenzoic acid	4.95	25.28	6
p-Hydroxybenzoic acid	4.56	31.31	6

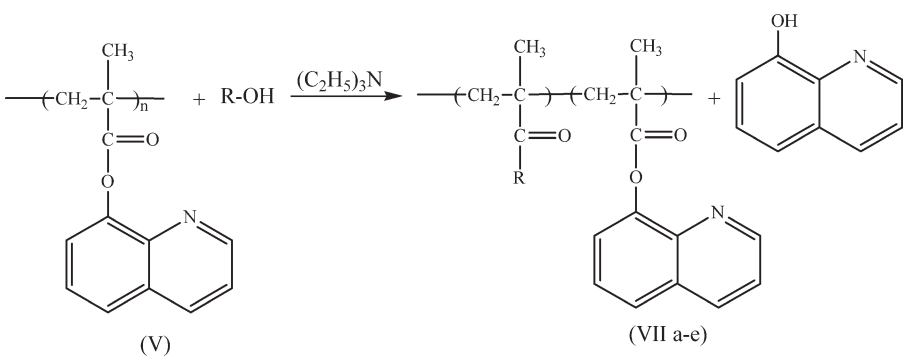
The concentration of N for the unexchanged polymer was 6.55%.

TABLE V
Analytical Data for the Exchange Reactions of Polymer V with Cyclohexanol at 25°C in the Presence of Triethylamine

Reaction time (days)	N (%)	Exchange (%)
1	6.1	9
2	5.85	13
4	5.29	23
8	4.87	31
12	4.57	36
16	4.11	43

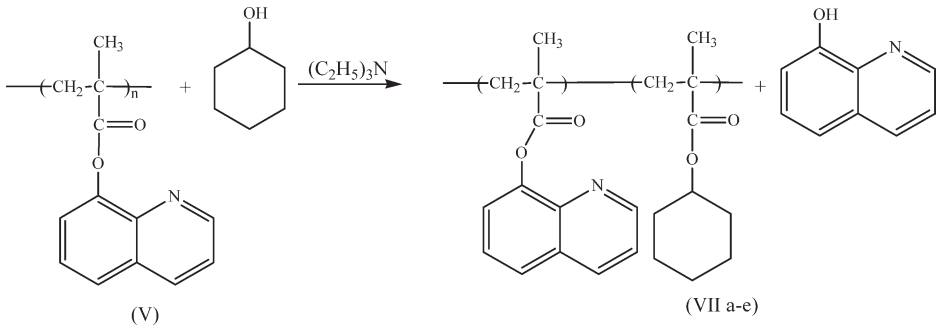
TABLE VI
Analytical Data for the Exchange Reactions of Polymer V with Cyclohexanol at 60°C in the Presence of Triethylamine

Reaction time (min)	N (%)	Exchange (%)
15	6.2	7
30	5.43	21
60	4.89	30
120	4.36	39
240	3.91	46
480	2.71	64



where:
VII a, R = C_4H_{10}-
b, = C_6H_{11}-
c, = C_6H_5-
d, = C_6H_4-COOH(o)
e, = C_6H_4-COOH(p)

Scheme 6 Exchange reactions of poly(8-methacryloxyquinoline) with different hydroxyl compounds.



Scheme 7 Exchange reaction of poly(8-methacryloxyquinoline) with cyclohexanol.

order: *o*-hydroxybenzoic acid < *n*-butanol < *p*-hydroxybenzoic acid < phenol < cyclohexanol.

The exchange reaction of poly-MAQ with cyclohexanol in a DMF solution was further investigated. We were especially interested in cyclohexanol because it is a model for studying polymeric adducts of steroid hormones and prostaglandins.[23]

With equivalent quantities of the polymer, cyclohexanol, and triethylamine, the progress of the reaction (exchange percentage) was recorded against the reaction time at 25 and 60°C. The results are reported in Tables V and VI. Poly-MAQ showed good behavior as a model compound for a long-active polymeric drug (Scheme 7).

Antimicrobial activity

The antimicrobial activity of the synthesized compounds was determined *in vitro* with the hole-plate and filter-paper method[24] against a variety of bacteria and fungi. Comparative studies of the prepared compounds and standard drugs were also carried out. The tested compounds were dissolved in DMSO, and different concentrations were used (125, 250, and 500 μg/mL). The inhibition zones of microbial growth produced by different compounds were measured in millimeters at the end of an incubation period of 48 h at 28°C. DMSO alone showed no inhibition zone. The Gram-positive bacteria were *Staphylococcus aureus* and *Bacillus subtilis*, the Gram-negative bacteria were *Escherichia coli* and *Pseudomonas aeruginosa*, and the fungi were *Aspergillus flavus* and *Candida albicans.* Tetracycline and amphotericin B were used as standards for antibacterial and antifungal activity, respectively. The results are illustrated in Table VII. The investigation of antibacterial and antifungal screening data revealed that all tested compounds showed moderate to good activity in comparison with the standard drugs.

CONCLUSIONS

On the basis of earlier data, new quinoline polymers were synthesized, and their antimicrobial activity was evaluated. All compounds demonstrated moderate to good activity against all tested strains. The importance of such work lies in the possibility that the new polymers might be more efficacious drugs

TABLE VII
Antimicrobial Activity of Some Synthesized Compounds

	Gram-positive bacteria		Gram-negative bacteria		Fungi	
Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. flavus*	*C. albicans*
III	38	35	32	31	17	19
V	29	26	27	26	14	17
VIa	20	23	24	20	18	20
VIb	19	20	21	20	17	17
VIc	18	20	22	23	16	16
VId	20	23	22	29	17	19
VIIa	26	28	29	29	18	18
VIIb	28	23	22	20	20	18
VIIc	11	12	11	13	10	10
VIId	20	23	25	21	15	20
VIIe	27	26	30	29	18	19
DMSO	0.0	0.0	0.0	0.0	0.0	0.0
Tetracycline	31	29	33	30	—	—
Amphotericin B	—	—	—	—	18	20

against bacteria and fungi, and this could be helpful in designing more potent antibacterial and antifungal agents for therapeutic use. Furthermore, similar monomeric quinolines may be synthesized from a number of other hydroxyl or amino compounds and thus provide a wider range of possibilities for the synthesis of pharmacologically active polymers.

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