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Polymeric Antimicrobial *N*-Halamine Epoxides

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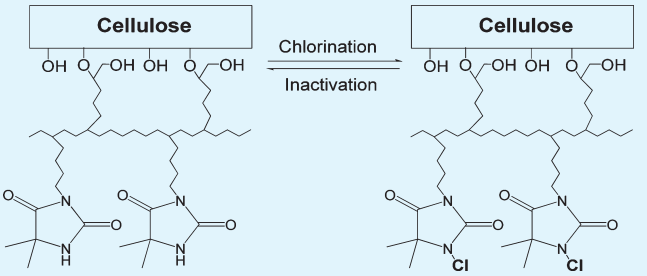
Supporting Information

ABSTRACT: A new N-halamine copolymer has been prepared, characterized, and evaluated for antimicrobial efficacy, stability toward hydrolyses, and stability toward UVA degradation when covalently bound to cellulose fibers. A copolymer of 3-chloro-2-hydroxypropylmethacrylate and glycidyl methacrylate was coated onto cotton, and, after curing, was treated with an aqueous solution containing the potassium salt of 5,5-dimethylhydantoin to form a coating which became antimicrobial upon exposure to household bleach (sodium hypochlorite). The coating inactivated *S. aureus* and *E. coli* O157:H7 within minutes of contact time and was quite stable toward washing and UVA photodegradation.



KEYWORDS: antibacterial polymer, N-halamine, hydantoin, epoxide, cellulose

INTRODUCTION

Extensive work on *N*-halamine antimicrobial compounds has been reported from these laboratories for three decades.[1−3] The work began with disinfection in aqueous solution[1] and was then extended to antimicrobial polymers for use in potable water disinfection[2] and antimicrobial textiles.[3] *N*-halamine materials have been also investigated extensively in other laboratories.[4−9] Quaternary ammonium salts,[10−13] metal ions,[14−16] and light-activated coatings[17,18] are also being evaluated as antimicrobial agents in infection control. Among these antimicrobial materials, *N*-halamine compounds are advantageous because of their long-term stabilities, nontoxicities to humans, biocidal functions against a broad range of microorganisms, and regenerable properties upon exposure to household bleach.

Antimicrobial *N*-halamine moieties have been attached to surfaces such as cellulose fibers by several grafting,[4] tethering,[19,20] and copolymerization[21,22] methods. One of the more successful methods[20] has been to bond the *N*-halamine precursors (e.g., hydantoin derivatives) to epoxides which can then tether to a surface such as cellulose fiber through covalent ether linkages (see Figure 1). The effort in this regard was the reaction of the sodium salt of 5,5-dimethylhydantoin with epichlorohydrin, followed by curing onto cellulose fibers; chlorination with dilute household bleach then produced antimicrobial fibers which were capable of producing 6-log inactivations of *Staphylococcus aureus* and *Escherichia coli* O157:H7 within 10 min of contact time and withstanding 50 machine washes without losing their biocidal efficacies.[20] Although other monomeric epoxide derivatives have been subsequently developed and applied onto various surfaces such as polyester,[23] one of the drawbacks of epoxide **M** (Figure 1) was the inability to obtain loadings of Cl^+ greater than 0.15 wt % on cotton without employing tedious chromatographic techniques for purification of **M**. Generally a Cl^+ loading of 0.3 to 0.4 wt % is employed for good antimicrobial performance.

Because epoxide linkages provide superior physical properties such as washing stability for the monomeric **M**'s,[20] an investigation of polymeric *N*-halamine epoxides was undertaken in hopes of enhancing chlorine loadings on cellulose fibers so as to improve antimicrobial efficacies. In this study, we synthesized a new copolymer by the free radical polymerization of two commercially available monomers 3-chloro-2-hydroxypropyl-methacrylate (**CM**) and glycidyl methacrylate (**GM**) as shown in Scheme 1. The copolymer was successfully coated onto cotton fabric and then treated with 5,5-dimethylhydantoin potassium salt to produce *N*-halamine precursor moieties on the surface. The monomeric hydantoin epoxide **M** was also prepared for comparison of the stabilities, UV resistances, and antibacterial activities of the epoxide derivatives.

EXPERIMENTAL SECTION

Materials. Chemicals were purchased from Sigma-Aldrich (Saint Louis, MO) and used without further purification unless otherwise stated.

Instrumentation. NMR spectra were obtained using a Bruker 400 MHz spectrometer; ^1H and ^{13}C spectra were recorded with 16 and 1024 scans, respectively. FTIR data were obtained with a Nicolet 6700 FT-IR spectrometer with an ATR (Attenuated Total Reflectance) accessory, recorded with 64 scans at 2 cm^{-1} resolution.

Preparation of 3-Glycidyl-5,5-dimethylhydantoin (M). 3-Glycidyl-5,5-dimethylhydantoin was prepared according to a procedure

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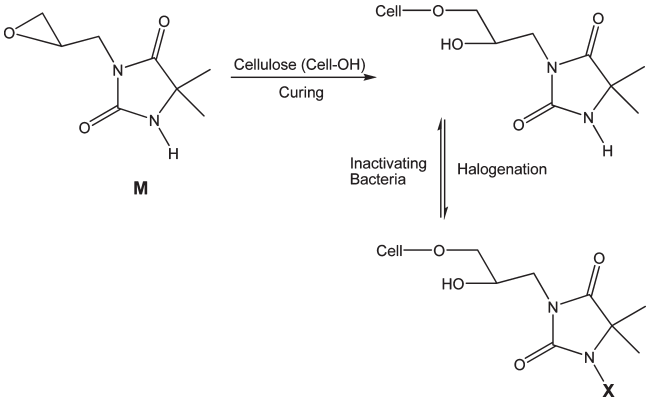
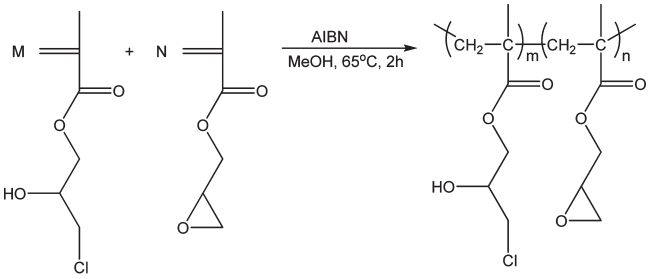


Figure 1. Preparation of **M**-based antimicrobial cellulose (X = Cl, Br).

Scheme 1. Structure of the Synthesized Copolymer



outlined previously.[20] Briefly, the sodium salt of 5,5-dimethylhydantoin was prepared by reacting 5,5-dimethylhydantoin with an equimolar quantity of NaOH in water at ambient temperature for 10 min. Then preparation of **M** was accomplished by subsequent addition of epichlorohydrin and stirring for 10 h. Following the reaction, water was removed by vacuum evaporation, and the product was dissolved in acetone. Then the byproduct sodium chloride was removed by filtration, and the acetone was removed by evaporation to obtain the product. The structure was confirmed by NMR and FTIR analysis.[20]

Synthesis of the Copolymer (P). The copolymer of 3-chloro-2-hydroxypropylmethacrylate (**CM**) and glycidyl methacrylate (**GM**) was synthesized by free radical polymerization. In a 100 mL round-bottom flask, 4.47 g (25 mmol) of **GM**, 3.55 g of (25 mmol) **CM**, and 0.08 g of AIBN (2,2′-Azobis(2-methylpropionitrile)) were dissolved in 20 mL of methanol. Nitrogen was bubbled through the solution for 15 min to remove any dissolved oxygen before initiating the reaction and continued during the reaction. The mixture was stirred at 65 °C for 2 h. The copolymer was precipitated during cooling of the mixture. The copolymer was separated from the mixture and washed with methanol several times to remove unreacted monomers. The methanol was evaporated under reduced pressure at room temperature, and the copolymer was recovered as pellets with a yield of 78%. It was not possible to completely remove all traces of methanol from the copolymer, as application of heat during the evaporation process was accompanied by undesirable cross-linking. Also, heat could accelerate a side reaction of the epoxide with the trace methanol concentration. The intrinsic viscosity of the copolymer was 0.79 dL/g (in dimethylsulfoxide, 25 °C).

Coating and Chlorination Procedures. **M** and **P** were first dissolved in acetone, and the mixture was stirred for 15 min to produce a uniform solution. Cotton swatches (style 400 bleached 100% cotton print cloth from Testfabrics, Inc., West Pittston, PA) in the size of 300 cm^2 were soaked in the coating solution (25 g) for 15 min, then

Table 1. Coating onto Cotton at Different Concentrations of the Coating Solutions

compd	concentration of the coating solution (wt %)	weight gain of the fabric (wt %)	Cl^+%
M[a]	5	1.16	0.14
	10	1.33	0.15
P[b]	1.5	1.48	0.16
	2	2.08	0.22
	3	3.10	0.32
PH[c]	5	5.19	0.55

[a] 3-Glycidyl-5,5-dimethylhydantoin. [b] Copolymer of 3-chloro-2-hydroxypropylmethacrylate and glycidyl methacrylate. [c] The highest concentration of copolymer **P** included in the study.

uniformly padded through a laboratory wringer (Birch Brothers Southern, Waxhaw, NC), and then cured at 165 °C for 1 h. This procedure also removed any residual methanol present in **P**. After curing, the swatches were soaked in a 0.5% detergent solution for 15 min, rinsed several times with water, and conditioned in a standard environment (21 °C, 65% RH). The weight gains on the fabrics after the coating procedure are summarized in Table 1. For the monomeric coating, the weight gain on the fabric did not increase significantly by increasing coating solution concentration. This was a result of every monomeric epoxide moiety requiring one hydroxyl group on the cellulose surface to bind, and the sites of attachment were saturated at 5 wt %. However, for the polymeric epoxide the weight gain, and therefore the chlorine loading, increases by increasing coating solution concentration because epoxide groups can be attached as large macromolecules containing multiple hydantoin moieties onto to the cellulose surface. This represents an advantage of **P** over **M** in the coatings because higher chlorine loadings can be obtained for **P**. The same chlorine loading for **P** as for **M** was obtained at a coating concentration of only 1.5 wt % for **P** as compared to 5 wt % for **M**.

The copolymer-coated fabrics were then immersed into 0.5 M 5,5-dimethylhydantoin potassium salt solution in EtOH for 5 min while under reflux (see Figure 2). The fabric became stiffer and slightly yellow during the immersing treatment because of KCl salt formation on the fabric surface; however, immediately after rinsing with tap water the fabric became softer and white. There were insignificant changes in the feel of the fabric samples after the coating process was complete.

The treated fabrics were chlorinated by soaking in a 1% aqueous solution of household bleach (6% sodium hypochlorite) at pH 7 (adjusted with 6 N HCl) for 60 min. After rinsing with tap and distilled water, the swatches were then dried at 45 °C for 1 h to remove any occluded chlorine from the material. The chlorine concentrations loaded onto the coated samples were determined by a iodometric/thiosulfate titration procedure. The weight percent Cl^+ on the samples was calculated by the following formula

$$Cl^+\% = [(NV35.45)/(2W)]100 \quad (1)$$

where Cl^+ % is the weight percent of oxidative chlorine on the samples, N and V are the normality (equiv/L) and volume (L) of the titrant sodium thiosulfate, respectively, and W is the weight of the sample in g.

Stability Testing. The stability and rechargeability of chlorine on the samples were evaluated by using a standard washing test according to AATCC Test Method 61. The cotton samples were washed for the equivalents of 5, 10, 25, and 50 machine washes in a Launder-Ometer. The Cl^+ % loadings on the samples before and after the washings were determined by the titration procedure mentioned above.

UVA light stability of the bound chlorine and the coatings on cotton fabric samples were determined using an Accelerated Weathering Tester

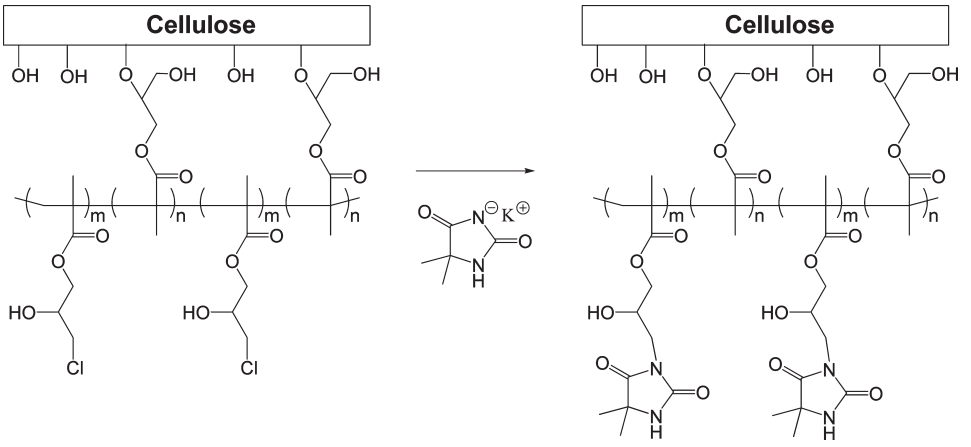


Figure 2. Hydantoin treatment of the copolymer coated cotton fabric.

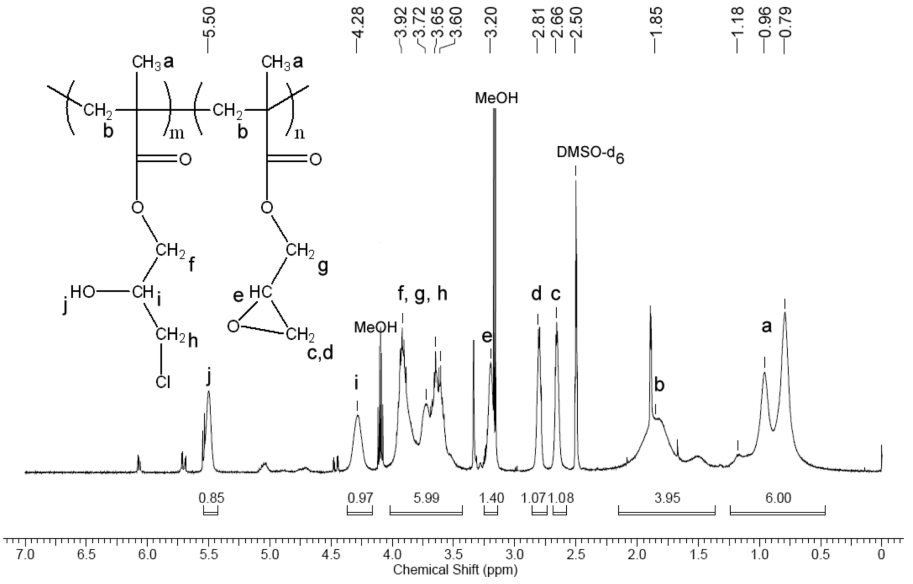


Figure 3. ^{1}H NMR spectra of the synthesized copolymer (solvent: DMSO-d_6).

(The Q-panel Company, Cleveland, OH, USA). The samples were placed in the UV (Type A, 315−400 nm) chamber for contact times ranging up to 24 h. After specific times of exposure to UVA irradiation, the samples were removed from the UV chamber and titrated, or rechlorinated and titrated. The temperature was 37.6 °C, and the relative humidity was 17% during the UVA light irradiation.

Biocidal Efficacy Testing. A "sandwich test" was used to evaluate the biocidal efficacies. Both chlorinated and unchlorinated coated cotton samples were challenged with *S. aureus* (ATCC 6538) and *E. coli* O157: H7 (ATCC 43895) bacterial suspensions in pH 7 phosphate buffer solution (100 mM). Suspensions (25 μL) of the bacterial solution were added to the center of a 2.54 cm square fabric swatch, and a second identical swatch was placed on top of the first swatch. A sterile weight was used to ensure sufficient contact of the swatches with the inocula. The contact times for the bacteria with the swatches were 5, 10, and 20 min. At those contact times the fabric swatches were quenched with 0.02 N sodium thiosulfate solution to remove any oxidative chlorine which could cause extended disinfection. Serial dilutions of the solutions contacting the surfaces were plated on Trypticase agar, incubated for 24 h at 37 °C, and colony counts were made to determine the presence or absence of viable bacteria. Unchlorinated control samples were treated in the same manner.

RESULTS AND DISCUSSION

Synthesis and Characterization of the Copolymer. **GM** was copolymerized with **CM** in equimolar amounts, and the resulting copolymer consisted of almost equimolar comonomer units. The amount of the **CM** in the copolymer composition contributes to the halogen loading capability (antimicrobial property); whereas the tethering epoxide monomer (**GM**) contributes to the adhesion property of the copolymer. NMR and FTIR analyses were used to confirm the structure of the synthesized copolymer. A ^{1}H NMR spectrum of the copolymer is shown in Figure 3; the primary evidence for the polymer formation is the disappearance of the vinyl proton signals between 5.5 and 6.5 ppm. The signals at 2.66 and 2.81 ppm can be assigned to the protons of the epoxide group,[24] indicating tethering functionality remains after polymerization. The resonance signal of the methyl groups is split into three peaks at 0.79, 0.96, and 1.18 ppm that are assigned to syndiotactic, heterotactic, and isotactic structures, respectively.[24] The signal at 0.79 ppm with the highest intensity indicates that the copolymer is predominantly syndiotactic.

The average composition of the monomers in the copolymer was determined from the corresponding ^{1}H NMR spectrum

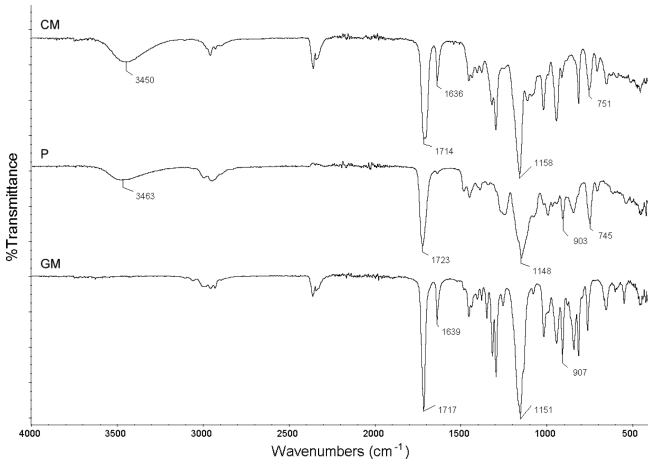


Figure 4. FTIR spectra of the synthesized copolymer and the two monomers.

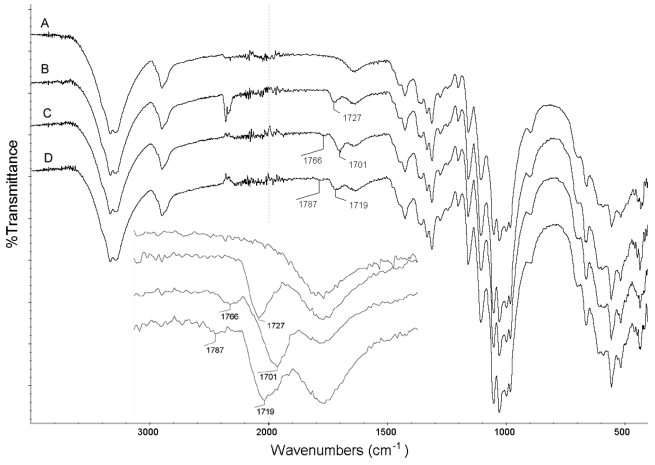


Figure 5. FTIR spectra of (A) cotton, (B) copolymer-coated cotton at 1.5 wt %, (C) hydantoin treated copolymer-coated cotton, and (D) chlorinated hydantoin treated copolymer-coated fabrics.

shown in Figure 3. Assignments of the signals for the copolymer were based upon comparison with the corresponding signals in the NMR of the two monomers (see the Supporting Information Section). The mole fraction of **CM** in the copolymer was calculated by comparing the signal area of an epoxide methylene proton (Figure 3, c, 2.66 ppm) of **GM** to the hydroxyl proton signal area (Figure 3, j, 5.50 ppm) of **CM**. Consequently, the reactivity ratio of **GM** was slightly higher than **CM**, resulting in a slightly lower **CM** amount ($m/(m+n) = 0.47$) in the copolymer as compared to its feed ratio ($M/(M+N) = 0.50$).

The FTIR spectrum of the synthesized copolymer in Figure 4 (**P**) was also suggestive of the copolymer formation by disappearance of the vinyl bond stretching vibration at around 1640 cm^{-1}. The bands at 1723 and 1148 cm^{-1} correspond to ester group vibrational modes, while the bands at 903 and 745 cm^{-1} can be assigned to epoxide[24] and CH_2-Cl group[25] vibrations, respectively.

Figure 5 shows the FTIR spectra of cotton fabric and the additional processes to produce a biocidal cotton fabric. There is an additional band for the copolymer-coated fabric (B) at 1727 cm^{-1}, which is assigned to ester group vibrations of the copolymer. After the treatment with 5,5-dimethlhydantoin potassium salt (C), two additional bands appeared at 1701 and 1766 cm^{-1}, which can be assigned to the carbonyl groups of the amide structure on the hydantoin moiety. These bands shifted to 1719 and 1787 cm^{-1} (respectively) after chlorination (D), indicating disruption of N−H···O═C hydrogen bonding as conversion of N−H to N−Cl occurred. The N−H stretching band for (C) above 3000 cm^{-1} was obscured by the intense O−H bands for the coated cellulose.

Table 2. Stability toward Washing of Coatings on the Cotton (Cl^+ % remaining)[a]

	M[c]			**P**[c]		
MW[b]	C	R	U	C	R	U
0	0.13			0.15		
5	0.01	0.11	0.12	0.14	0.15	0.15
10	0.01	0.11	0.11	0.12	0.15	0.15
25	0	0.11	0.11	0.11	0.14	0.14
50	0	0.11	0.11	0.08	0.13	0.15

[a] The error in the measured Cl^+ weight percentage values was ±0.01. [b] MW, machine washes. [c] C, chlorinated before washing; R, chlorinated before washing and rechlorinated after washing; U, unchlorinated before washing, but chlorinated after washing.

Stability toward Washing and Ultraviolet Light Irradiation. The stabilities toward machine washing of coated fabric swatches are presented in Table 2. Three types of washing experiments were performed: prechlorinated coatings at the concentration levels indicated at 0 machine washes Table 2C, prechlorinated and rechlorinated after a given number of machine washes (R), and unchlorinated until after a given number of machine washes (U). The initial chlorine loadings of the coated fabrics (0 machine washes) were almost equal at 0.13 and 0.15 wt % for the monomer (**M**) and the copolymer (**P**) coated fabrics, respectively, so that a direct comparison of the two types of coatings could be made. Several observations can be made pertaining to the data in Table 2. First, **M** lost all of the bound chlorine within 25 cycles, whereas almost half of the initial chlorine still remained on **P** coated fabric even after 50 cycles (Table 2C). This could be due to more hydrophobic character of the polymeric coating as compared to the monomeric coating. Moreover, these rates of loss are not a result of the dissociation of tethering groups (epoxide) from cotton because rechlorination of the coated fabrics provided chlorine loadings at approximately their initial values (Table 2R). The unchlorinated coatings (U) were also very resistant toward washing cycles.

Table 3 illustrates the stabilities of the coatings (**M** and **P**) and chlorinated coatings (**M**−**Cl** and **P**−**Cl**) on cotton toward UVA light degradation following a series of rechlorinations after successive exposures; the data for **M** and **P** represent chlorination after UVA exposure of the unchlorinated samples at the indicated UVA contact times. Several conclusions can be drawn from these data. First, both coatings lost oxidative chlorine upon exposure to UVA photons slowly within 24 h, and the UVA exposed samples were almost completely rechlorinated after 24 h (R_1). However, following UVA exposure cycles, and rechlorinations (R_2-R_5), a progressive decline in chlorine loading occurred upon rechlorination which was more dramatic for the polymeric coating. This could be due to the more UV sensitive ester structures in the polymeric epoxide coating. Polymeric esters have been reported to be subject to photooxidative degradation upon UV irradiation.[26] On the other hand, unchlorinated coatings on cotton exhibited no significant decomposition in the presence

Table 3. Effect of UVA Irradiation on the Coatings (Cl^+ % remaining)

time (h)[a]	M−Cl	M	P−Cl	P
0	0.14		0.15	
0.5	0.13		0.15	
1.5	0.10		0.14	
6	0.08		0.09	
24	0.03		0.04	
$24R_1$	0.13	0.14	0.13	0.15
48	0.01		0.02	
$48R_2$	0.11	0.15	0.13	0.14
72	0.01		0.01	
$72R_3$	0.11	0.14	0.11	0.15
96	0.01		0.01	
$96R_4$	0.10	0.14	0.07	0.14
120	0.01		0.01	
$120R_5$	0.08	0.14	0.03	0.14

[a] R_1−R_5 indicate rechlorination of samples after UVA exposure for the specified time intervals.

of the UVA irradiation over the entire 120 h of exposure, so the presence of the N−Cl functionality seems to have an observable effect on the photodegradation process. This also was observed for N-halamine siloxanes.[27] The stabilities were quite remarkable given that a six hour exposure in the UV chamber was equivalent to the same time in direct midday summer sunlight.

Antimicrobial Efficacies. The treated cotton swatches were challenged with *S. aureus* and *E. coli* O157:H7 at concentrations of about 10^7 CFU (colony-forming units), as summarized in Table 4. The biocidal efficacy of the monomeric coating **M** as compared to the polymeric coating **P** with similar chlorine loading (0.14 and 0.15 wt %, respectively) onto cotton fabric was evaluated. In addition, a cotton fabric containing a higher amount of the polymer on the surface (**PH**), providing a higher chlorine loading (0.55 wt %), was also tested in order to ascertain whether chlorine loading was an important variable in determining inactivation rates. Unchlorinated control samples (**M**, **P**, and **PH**) provided only about 0.50 log reductions, due to the adhesion of bacteria to the cotton swatches, within 20 min contact time intervals. All of the chlorinated coated samples inactivated all *S. aureus* with log reductions of ca. 6.3−6.7 in a contact time of 5 min, in the repeated experiments. On the other hand, a longer period of contact time 10 min was required to inactivate all Gram-negative bacteria (*E. coli*) for **M-Cl** and **P−Cl** for a chlorine loading of ca. 0.15% onto cotton in Experiment 1. The cotton fabric coated with a higher amount of the polymer (**PH**), providing a higher chlorine loading (0.55%), inactivated all *E. coli* within 5 min of contact time. In Experiment 2, however, *E. coli* was inactivated (6.7 logs) within 5 min contact for all of the chlorinated samples. It is not unusual to observe such inconsistencies in repeated experiments in this type of experiment. It might be beneficial to examine shorter contact times for further discrimination of the samples, but surface disinfection times of 5 min on cellulose are quite remarkable for antimicrobials, and experiments with contact times of less than 5 min for cotton swatches are difficult to perform in the laboratory. It would appear that the chlorine concentration on the fibers (0.15 as compared to 0.55%) was not a critical variable in attaining excellent biocidal results.

Table 4. Biocidal Tests

		Exp1[a]		Exp2[b]	
sample Cl^+%	contact time (min)	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*
M	20	0.25	0.42	0.37	0.05
P	20	0.19	0.28	0.36	0.04
PH	20	0.14	0.52	0.56	0.02
M−Cl 0.14	5	6.25	4.60	6.73	6.75
	10	6.25	6.72	6.73	6.75
	20	6.25	6.72	6.73	6.75
P−Cl 0.15	5	6.25	4.42	6.73	6.75
	10	6.25	6.72	6.73	6.75
	20	6.25	6.72	6.73	6.75
PH−Cl 0.55	5	6.25	6.72	6.73	6.75
	10	6.25	6.72	6.73	6.75
	20	6.25	6.72	6.73	6.75

[a] Exp 1: The inoculum concentrations were 6.25 and 6.72 logs or *S. aureus* and *E. coli*, respectively. [b] Exp 2: The inoculum concentrations were 6.73 and 6.75 logs for *S. aureus* and *E. coli*, respectively.

CONCLUSIONS

It can be concluded from this work that N-halamine-functionalized epoxides, when tethered to cellulose fibers, provide a very effective antimicrobial property, with disinfection capability within a few minutes of contact time. Also, when included in a copolymer that may have multiple attachment points to the cellulose, the N-halamine groups are more stable toward a laundering process and are capable of loading a higher amount of oxidative chlorine, rendering them more effective in antimicrobial activity. Both monomeric and polymeric N-halamine epoxides bound to cellulose lose chlorine over an extended period of time when exposed to UVA irradiation, but they can be rechlorinated after the exposure. The copolymer synthesized in this study possesses considerable potential for use in the health care industry for fabrics or other surfaces containing functional groups that can be reacted with the epoxide moieties.

ASSOCIATED CONTENT

Supporting Information. Additional NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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