Preparation and Evaluation of Nonionic Amphiphilic Phenolic Biocides in Urethane Hydrogels

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ABSTRACT: Phenols are rarely used in the preparation of polyurethanes because of the inherent competitive reaction of the phenolic moiety with isocyanates. This work represents a successful application of the combination of phenols with isocyanates toward the development of phenolic-based antimicrobial urethane coatings for niche applications. In this effort, a series of nonionic amphiphilic phenolic molecules were prepared by condensation of 4-hexylresorcinol with the corresponding hydroxyl-terminated monomethyl poly(ethylene glycol) in the presence of a catalytic amount of acid in refluxing toluene. These new molecules were evaluated against a variety of Gram-positive and Gram-negative bacteria for their antimicrobial activity in minimum inhibitory concentration solution testing. The same amphiphilic molecules were also incorporated into a hydrophilic polyurethane hydrogel and dispensed as films for evaluation of surface activity with a newly developed protocol. All samples possessed some degree of surface antimicrobial activity, which was expressed as a log kill reduction in colony-forming units starting from an initial bacterial concentration of 10^7 CFU, and structural features of the phenolic compound were found to contribute significantly to the observed antimicrobial activity. The highest activity was observed in samples containing the phenolic compound with the shortest ethylene oxide polar structural feature and therefore highest mobility in the highly polar urethane resin. © 2007 Wiley Periodicals, Inc.† J Appl Polym Sci 107: 2089–2094, 2008

Key words: additives; biomaterials; hydrogels; polyurethanes; self-organization

INTRODUCTION

Phenolic compounds are common, naturally occurring, biologically active agents and often represent a large fraction of the extracts obtained from natural products.[1] These compounds are now finding applications as antimicrobial additives to coatings and films for a variety of markets, such as the food industry. A specific example includes a clever introduction of essential oil extracts of oregano to an alginate-based film applied to beef muscle slices for enhanced preservation.[2] In addition to their broad applications as biocides and as synthetic intermediates in the preparation of pesticides, phenolic-based materials are also added liberally to coatings as antioxidants, such as the monomer 2,4-di-*tert*-butylphenol and oligomeric compound nonylphenol disulfide (Ethanox 323), which are available commercially.[3] Recent studies by Boudjouk et al.[4] and Yoon et al.[5] have reported the use of phenolic biocides in the preparation of active antimicrobial coatings. Specifically, the Thomas group incorporated Triclosan [5-chloro-2-(2,4-dichlorophenoxy)phenol] as a functional pendant group into the silicone backbone for use in the preparation of new antifouling coatings, and Yoon's group polymerized vinyl monomers having phenol pendant groups to produce antimicrobial polymers.

As a matrix material, versatile, inexpensive, and readily available polyurethane has found wide use in the preparation of antimicrobial films and coatings, and several excellent recent studies exist. A polyether-type polyurethane film containing well-dispersed silver nanoparticles was prepared by Hsu et al.[6] and found to impart increased biostability when implanted in a rat subcutaneous model. Similarly, Piozzi[7] developed a dual-antimicrobial agent polymer system composed of a new silver-complexing polyurethane and ciprofloxacin antibiotic additive for coating medical devices. Most recently, the Piozzi group[8] reported the preparation of antibiotic-releasing polyurethane coatings for central venous catheters, which may ultimately prevent bacterial

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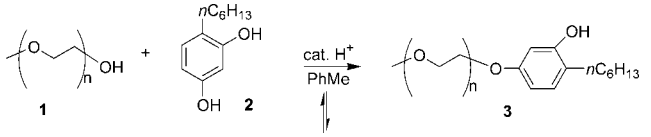

Figure 1 Synthetic scheme for the amphiphilic phenol biocide series.

colonization and the emergence of bacterial resistance. In an elegant application of surface-active biocides, block urethane polymers were synthesized by the Wynne group containing pendant hydantoin groups that are readily converted to the active biocidal compound when treated with hypochlorite.[9]

Our interest lies in the synthesis, characterization, and evaluation of custom antimicrobial compounds designed for both high biocidal activity at the surface against a variety of pathogens and compatibility with commercial carrier liquids and common polymer resins.[10] In this work, a polyurethane hydrogel was chosen as the polymer matrix because of its exceptional versatility and unique water absorption characteristics, and the specific urethane hydrogel employed is capable of absorbing 5–25% water by weight. The phenolic biocidal compounds possess polar polyether segments to promote water solubility and resin compatibility along with nonpolar alkyl chains to promote orientation and present the phenolic OH at the air–surface interface. Coatings having these unique characteristics are suitable for eventual use in food service and storage areas and in hazardous waste containment and temporary storage vessels to deter bacterial growth.

RESULTS AND DISCUSSION

We report the synthesis and evaluation of a novel series of amphiphilic phenolic biocides. Each biocide was first evaluated for the minimum inhibitory concentration (MIC) with a standard aqueous solution test protocol.[11] Each of the biocides was then blended into a hydrophilic urethane hydrogel in tetrahydrofuran, and coatings were solvent-cast and analyzed for antimicrobial activity. This is the first report of a series of amphiphilic phenolic biocides blended within a urethane hydrogel. Biocidal activity results from film studies were obtained with a new film testing protocol and subsequently compared to solution MIC values.

Because of their broad spectrum of antimicrobial activity, benign environmental impact, and current commercial utility, a nonionic amphiphilic phenol biocidal moiety was selected for this study. The amphiphilic biocides were synthesized by condensation of 4-hexylresorcinol with the corresponding hydroxyl-terminated monomethyl poly(ethylene glycol) (PEG) in the presence of a catalytic amount of acid in refluxing toluene (Fig. 1). Although this reaction was predicted to afford a mixture of products, the desired product (**3**) was obtained as the major product along with the disubstituted and alternate trisubstituted products in greatly diminished quantities. It is believed that the steric effects of the *n*-hexyl substituent of the resorcinol selectively directed condensation to the one position, resulting in the formation of **3** almost quantitatively. The byproducts, acid catalyst, and unreacted starting materials were removed by flash column chromatography, and this resulted in the isolation of the desired product in significant purity.

All newly prepared amphiphilic phenolic biocides [2-hexyl-5-(2-methoxy-ethoxy)-phenol (**3a**), 2-hexyl-5-[2-(2-methoxy-ethoxy)-ethoxy]-phenol (**3b**), 2-hexyl-5-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-phenol (**3c**), 2-hexyl-5-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-phenol (**3d**), and 2-hexyl-5-[poly(ethylene glycol) monomethyl ether]-phenol (**3e**)] were subjected to MIC evaluations against both Gram-positive and Gram-negative bacteria (Table I). Although in general all were effective in the lysing of bacteria, none of the phenols (**3a–3e**) were outstanding performers when directly compared to published MIC data for commercial phenolic biocides.[12] However, recent findings in our laboratory suggest that one must be cautious in dismissing the utility of an apparently high-MIC biocide, as there is often a poor correlation of solution antimicrobial activity and the effectiveness of the same biocide in a film/coating.[13] All phenols are inactivated by inclusion in

TABLE I
MIC (μg/mL)[a] of Aqueous Phenolic Biocides

Entry	**1**	Product	Yield (%)	*S. aureus* (Gram-positive)	*B. anthracis* (Sterne; Gram-positive)	*E. coli* (Gram-negative)	*S. typhimurium* (Gram-negative)
1	$n = 1$	**3a**	73	124	170	52	173
2	$n = 2$	**3b**	78	113	165	67	186
3	$n = 3$	**3c**	64	75	167	47	143
4	$n = 4$	**3d**	55	83	189	81	132
5	$n = 16$	**3e**	48	102	174	94	129

[a] Milligrams of biocide required to neutralize 1 mL of the respective bacteria at 10^5 CFU/mL.

TABLE II
Biological Activity Results for Phenolic Biocides in Polyurethane Hydrogels[a]

Film containing biocide	Loading (w/w %)	*E. coli* (Gram-negative)	*S. aureus* (Gram-positive)	*S. typhimurium* (Gram-negative)	*B. anthracis* (Sterne; Gram-positive)
3a	0.25	4	3	3	2
3b	0.25	4	4	2	2
3c	0.25	4	4	3	2
3d	0.25	3	3	2	2
3e	0.25	3	4	2	3
3a	0.5	6	7	5	4
3b	0.5	5	5	5	3
3c	0.5	5	6	4	4
3d	0.5	5	5	4	4
3e	0.5	5	6	3	5
3a	1.0	6	7	5	3
3b	1.0	6	5	4	3
3c	1.0	5	6	4	4
3d	1.0	4	5	3	3
3e	1.0	5	6	3	5
3a	2.0	5	6	5	3
3b	2.0	6	5	3	2
3c	2.0	4	4	4	3
3d	2.0	4	5	3	2
3e	2.0	5	5	2	4

[a]Values 1–7 describe the log reduction from a starting concentration of 10^7 CFU/cm^2.

micelles, which can occur in solutions when the detergent/surfactant (nonionic and anionic) concentration exceeds the critical micellization concentration.[1] We believe that the elevated MIC data reflect the presence of solution micellar formation in competition with antimicrobial activity performance. However, it should be noted that the MIC data of the new biocides reflected the significantly enhanced activity against *Escherichia coli*, the Gram-negative bacterium, over the Gram-positive bacteria examined. Phenolic biocidal compounds have been reported to be membrane-active agents,[5,14] ultimately rupturing the cell membrane and releasing the intracellular constituents.

Phenolic biocides **3a–3e**, used in the MIC study, were also incorporated into a hydrophilic polyurethane and evaluated as an antimicrobial film additive against the same bacteria used in solution testing. The choice and compatibility of the polymer matrix are critical to the success of the resulting active coating because the antimicrobial activity of compounds in polymers has been shown to depend on molecular diffusion of the antimicrobial agents in the matrix.[15] Selection of the urethane was based on the desire to have a one-component hydrophilic urethane with a relatively low glass-transition temperature. Glassy polymers are considered inferior matrix materials. In addition, phenolic biocidal compounds are incompatible with the reactive isocyanates that are inherently present in the two-component system. The biological activity of our custom phenols when incorporated into urethane hydrogels is summarized in Table II, in which the numbers 1–7 represent the log kill reductions in colony-forming units when we start with a 10^7 concentration. For example, a log 4 kill represents a reduction of 99.99% in bacteria capable of forming colonies. Because there are currently no standard antimicrobial coating test methods, our antimicrobial activities were evaluated with a new method developed in our laboratory. Standard test methods exist to evaluate fabrics against a variety of bacteria at concentrations of 10^5/cm^2; however, the different scope of our application has required modification of this original procedure. In this work, we wished to demonstrate antimicrobial activity that one would likely encounter in a biological attack and therefore increased the bacteria loading to $\sim 10^7$ CFU/cm^2. The coatings were inoculated, allowed to incubate for 2 h, and evaluated by swabbing followed by serial dilution and incubation.

Upon analysis of the data shown in Table II, it was concluded that compound **3a** exhibited the best overall antimicrobial action (Fig. 2). Although for *Bacillus anthracis* the performance of **3e** was greater, it was concluded that the increase in the ethylene oxide length had a more dramatic effect on the antimicrobials when subjected to *B. anthracis* over the other bacteria examined. For all biocides examined, there appeared to be a slight increase in activity when the phenolic biocide concentration was increased from 0.25 to 0.5 and 1% (w/w); however, increasing the phenolic biocide concentration above 1 wt % resulted in very little increase in activity. This plateau of biocidal activity at higher agent concentrations is not entirely understood. A recent report[12] speculates that the reduced kill at higher concentrations results from the formation of micelles,

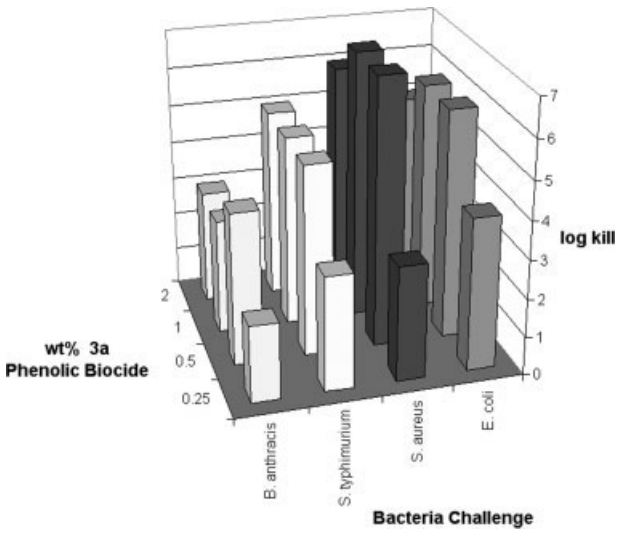

Figure 2 Antimicrobial action versus challenge for amphiphilic phenolic biocide **3a** in a polyurethane hydrogel.

which place limits on solution biocidal activity or in this case aggregate and concentrate at the urethane–air interface, thus inhibiting coating surface activity.

In the challenge with the Gram-negative bacteria, *E. coli*, optimum results were obtained in films containing 0.5 and 1% loadings of an amphiphilic phenolic biocide. Diminished activity resulted from both higher and lower weight percentage loadings. Compound **3a** showed superior overall activity among the group of biocidal compounds tested. Three common pathogenic Gram-positive bacteria were also evaluated, including the spore former *B. anthracis* (Δ Sterne). The amphiphilic phenol biocides were more active against both *Staphylococcus aureus* and *Salmonella typhimurium* than *B. anthracis*. This is to be expected because phenols are known to be less active toward spore-forming bacteria. Although the results from the exposure of films to *S. typhimurium* were slightly diminished compared with those of *S. aureus*, trends were similar and the effects of loading were comparable for all samples examined.

Structural features of the amphiphilic phenolic biocides, such as the length of the tethered PEG chain, were found to significantly affect the antimicrobial activity of the resulting biocide. Biocidal testing results indicate that a lengthening of the PEG chain results in significantly diminished antimicrobial activity. This reduced activity was attributed to agent mobility and solubility: specifically, the ability of the phenol to remain mobile within the curing resin and present its active phenolic OH subunit at the surface. The longer, more hydrophilic PEG chain, as observed in compound **3e**, is believed to remain deeper in the bulk of the coating rather than self-stratifying to the air–coating interface, as was desired for making surface-active biocidal coatings. The Yoon group observed a similar effect in a biocidal system, and the relative biocidal activity among a series of structurally similar agents was attributed at least in part to the compound's hydrophilic nature and ease of diffusion in media.[5] The hydrophobic hexyl alkyl chain substituent is believed to assist in the mobilization of the biocidal moiety to the coating–air interface, thus resulting in the increased bioactivity. Less hydrophilic tethers, as observed in phenols **3a–3d**, provide more flexibility and consequently greater freedom for movement within the coating upon application and curing. This increased flexibility allows for maximum orientation of the active functional group with respect to surface-residing contamination/bacteria and thus may actually promote self-concentration at the surface, ultimately resulting in a more viable and effective antimicrobial coating.

EXPERIMENTAL

General methods

Moisture-sensitive reactions were conducted in oven-dried glassware under a nitrogen atmosphere. Analytical thin-layer chromatography was performed on precoated silica gel sheets, and flash column chromatography was accomplished with silica gel (60 Å, 200–400 mesh). External elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). All melting points are uncorrected. Unless otherwise noted, ^{1}H-NMR and ^{13}C-NMR spectra were taken in $CDCl_3$ at 300 and 75 MHz, respectively, with a TMS internal standard. Chemical shifts are reported in units downfield from tetramethyl silane (TMS). Coupling constant (*J*) values are reported in hertz. The polyurethane hydrogel, Hydrothane, was purchased from Cardiotech International.

Film forming and characterization

Films were prepared by the combination of 0.80 g of Hydrothane with 25 mL of freshly distilled tetrahydrofuran and stirring for 4 h, at which time the polymer completely dissolved. To the dissolved Hydrothane, a solution consisting of 0.008 g of **3** dissolved in 1 mL of di-H_2O was added dropwise, resulting in a final loading of $\sim$ 1 wt % (w/w) with respect to polymer solids. The final solution was allowed to stir for an additional 30 min, and films were solvent-cast by the addition of a 1-mL solution via a pipette to a precleaned microscope glass slide. The glass slide was held overnight in a sterilized, covered Petri dish to slow the rate of evaporation. The resulting films were rinsed with 5 mL of di-H_2O to clean the surface of any unincluded ammonium salt before subsequent examination and antimicrobial testing.

General antimicrobial testing

The general procedure for the preparation of growth media was as follows. To a 1-L Erlenmeyer flask equipped with a stirring bar were added 25.7 g of Letheen broth (Difco Laboratories, Detroit, MI) and 1 L of Milli-Q filtered water. The mixture was stirred over low heat for 30 min. Aliquots (4.5 mL) of the resulting solution were added to autoclavable culture tubes ($\sim$ 200) to be used in subsequent serial dilutions. The test tubes were covered with plastic lids and autoclaved at 121°C (and 15 psi) for 25 min. Letheen broth was selected for its ability to neutralize the biocidal effect of phenols with sorbitan monooleate, so that continued antibacterial action would not occur after the serial dilution step. For the preparation of bacteria, *S. aureus* (ATCC 12598), *E. coli* (ATCC 0157 : H7), *S. typhimurium* (ATCC 14028), and *B. anthracis* (ATCC 34F2) cells were each grown in our laboratory according to standard microbiological techniques. Bacteria were harvested from an agar plate by the removal of a single colony-forming unit with a sterile inoculating loop and its placement in Letheen broth. The culture was incubated at 28–30°C overnight in a shaking incubator. The cells were then pelleted by centrifugation at 3000 rpm and 18°C. The cells were then resuspended in a 0.5% saline solution to achieve a density of about 10^9 CFU/mL as determined by McFarland turbidity standards.

Procedure for coating challenge tests

This method of evaluation is a well-established serial dilution screening that has been employed previously.[16,17] A 1-μL aliquot was taken from a solution of each bacterium (concentration = 10^9) and applied directly to the coating on a microscope slide, resulting in the delivery of 10^7 CFU/cm^2. The slides were placed in sterile Petri dishes with a piece of hydrated filter paper in the bottom of each dish. The use of the hydrated filter paper prevented the death of the bacteria by desiccation. After the slides were allowed to incubate for 2 h, the coating surface was thoroughly swabbed with two sterile swabs and vortexed in a 4.5-mL solution of previously sterilized Letheen broth. Letheen broth was selected because it contains sorbitan monooleate, which would neutralize the antimicrobial activity of any phenol that may have been extracted by aggressive swabbing, thus preventing additional kill once recovered. The initial tube was then serially diluted by the extraction of 0.5 mL and its placement into the subsequent tube for a total of seven tubes. The tubes were allowed to incubate at 35°C for 24 h before they were read. Positive growth was indicated by the presence of stringlike, filamentous growth of colonies of bacteria in solution, not mere murkiness, which may result from other forms of contamination. All data reported are averages of triplicates, and data are reported as a log reduction from a starting concentration of 10^7 CFU/mL.

General procedure for preparation of 3

In a 25-mL, round-bottom flask equipped with a magnetic stirring bar, Dean–Stark trap, and condenser were placed 4-hexyl-benzene-1,3-diol (4-hexylresorcinol; 0.59 g, 6.25 mmol), an ethylene oxide monomethyl ether (6.25 mmol), *p*-toluenesulfonic acid (0.01 g, 0.008 mmol), and 20 mL of toluene. An additional 7 mL of toluene was placed in the Dean–Stark trap to prevent the pot volume from becoming too low. The solution was allowed to reflux vigorously for 24 h in an oil bath. The resulting solution was allowed to cool to room temperature and concentrated with the rotary evaporator. The resulting oil was eluted through a silica gel column with a hexane/EtOAc (1 : 1) solvent system, and the desired product eluted in the first fraction.

3a

Fourier transform infrared (FTIR): 3362, 2950, 2930, 2858, 1606, 1519, 1463, 1376, 1297, 1221, 1162, 1114, 1055, 972 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 6.91 (d, J = 9, 1H), 6.34 (d, J = 2, 1H), 5.76 (d, J = 5, 2H), 3.54 (d, J = 5, 2H), 3.37 (s, 3H), 2.48 (t, J = 8, 2H), 1.55–1.50 (m, 2H), 1.34–1.25 (m, 6H), 0.87 δ (t, J = 7, 3H). ^{13}C-NMR ($CDCl_3$): 154.3, 154.2, 130.7, 121.3, 107.5, 102.9, 73.4, 61.5, 58.7, 31.7, 29.2, 29.1, 22.6, 14.1 δ. ANAL. Calcd for $C_{15}H_{24}O_3$: C, 71.39%; H, 9.59%. Found: C, 71.68%; H, 9.31%.

3b

FTIR: 3346, 2961, 2922, 2858, 1622, 1519, 1459, 1376, 1301, 1225, 1166, 1118, 968 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 6.92 (d, J = 9, 1H), 6.36 (d, J = 2, 1H), 6.32 (d, J = 6, 1H), 5.37 (bs, 1OH), 3.78 (t, J = 6, 2H), 3.66 (t, J = 5, 2H), 3.63–3.59 (m, 4H), 3.42 (s, 3H), 2.50 (t, J = 6, 2H), 1.55–1.51 δ (m, 2H). ^{13}C-NMR ($CDCl_3$): 154.6, 154.4, 130.6, 120.9, 107.4, 102.8, 72.2, 71.9, 69.9, 61.8, 58.9, 31.7, 30.0, 29.2, 29.1, 22.6, 14.1 δ. ANAL. Calcd for $C_{17}H_{28}O_4$: C, 68.89%; H, 9.52%. Found: C, 68.73%; H, 9.44%.

3c

FTIR: 3345, 2950, 2913, 2851, 1626, 1601, 1519, 1459, 1380, 1348, 1301, 1217, 976 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 6.91 (d, J = 9, 1H), 6.41 (d, J = 2, 1H), 6.33 (d, J = 6, 1H), 3.77–3.73 (m, 2H), 3.70–3.56 (m, 10H), 3.38 (s, 3H), 2.50 (t, J = 6, 2H), 1.55–1.49 (m, 2H), 1.33–1.27

(m, 6H), 0.87 δ (t, J = 6, 3H). ^{13}C-NMR ($CDCl_3$): 155.0, 154.7, 130.5, 120.7, 106.9, 102.6, 72.4, 71.7, 70.5, 70.3, 70.2, 61.6, 58.9, 31.8, 30.0, 29.3, 29.2, 22.6, 14.1 δ. ANAL. Calcd for $C_{19}H_{32}O_5$: C, 67.03%; H, 9.47%. Found: C, 66.85%; H, 9.27%.

3d

FTIR: 3342, 2930, 2858, 1618, 1606, 1523, 1459, 1344, 1301, 1253, 1198, 1094, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 6.91 (d, J = 9, 1H), 6.41 (d, J = 2, 1H), 6.33 (d, J = 6, 1H), 3.75 (t, J = 6, 2H), 3.68–3.55 (m, 14H), 3.37 (s, 3H), 2.50 (t, J = 9, 2H), 1.55–1.52 (m, 2H), 1.33–1.24 (m, 6H), 0.87 δ (t, J = 6, 3H). ^{13}C-NMR ($CDCl_3$): 155.0, 154.7, 130.5, 120.7, 106.9, 102.7, 72.4, 71.8, 70.5 (overlapping peak), 70.4, 70.3, 70.1, 61.7, 58.8, 31.8, 30.1, 29.3, 29.2, 22.6, 14.1 δ. ANAL. Calcd for $C_{21}H_{36}O_6$: C, 65.60%; H, 9.44%. Found: C, 65.86%; H, 9.38%.

3e

PEG molecular weight ~ 750. FTIR: 3347, 2957, 2926, 2851, 1620, 1604, 1452, 1345, 1315, 1259, 987 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 6.84 (s, 1H), 6.28 (d, J = 6, 1H), 6.19 (d, J = 6, 1H), 4.10 (t, J = 4, 2H), 3.76–3.50 (m, 64H), 2.55 (t, J = 6, 2H), 1.64–1.60 (m, 2H), 1.33–1.29 (m, 6H), 0.96 δ (t, J = 6, 3H). ^{13}C-NMR ($CDCl_3$): 157.6, 157.3, 130.2, 118.2, 106.5, 101.1, 73.1, 73.0, 70.7 (overlapping peaks), 70.6 (overlapping peaks), 70.5 (overlapping peaks), 53.9, 32.7, 32.5, 32.0, 29.5, 25.5, 25.4, 13.9 δ.

CONCLUSIONS

A series of novel nonionic amphiphilic phenolic molecules were prepared and evaluated for their antimicrobial activity in solution with a standard technique, which reports biocidal activity as MIC. The functional phenols were also evaluated for surface antimicrobial activity in polymer blends with a urethane hydrogel through the use of a new testing protocol developed in our laboratory. Although solution MICs were found to be unremarkable for the phenolic series, high surface antimicrobial activity could be obtained and was expressed as a log kill reduction in colony-forming units starting from an initial bacterial concentration of 10^7 CFU. The structural features of the phenolic biocide were found to contribute significantly to the observed antimicrobial activity. Moreover, the highest activity was observed in samples containing the phenolic compound with the shortest ethylene oxide polar structural feature and, therefore, the highest mobility in the polar urethane resin. Coatings having these characteristics are potentially useful in the food storage and medical industries.

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