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Synthesis and antimicrobial applications of 5,5′-ethylenebis[5-methyl-3-(3-triethoxysilylpropyl)hydantoin]

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Abstract

A novel, durable, long lasting, *N*-halamine siloxane monomer precursor, 5,5′-ethylenebis[5-methyl-3-(3-triethoxysilylpropyl)hydantoin] has been prepared and characterized by ^{1}H-NMR and FTIR for the purpose of functionalizing the surfaces of various materials. In this work, the precursor *N*-halamine moiety was attached by siloxane covalent bonding to surfaces of cotton fibers. Simulated laundering tests indicated that the chlorinated *N*-halamine structure could survive many repeated home launderings. The materials were rendered biocidal after exposure to oxidative halogen solutions, i.e. dilute household bleach. Once chlorinated, these materials were biocidal against *Staphylococcus aureus* and *Escherichia coli*. Upon loss of the halogen from either long-term use or consumption by the microbes on the surfaces, they could be simply recharged by further exposure to dilute bleach to regain biocidal activity.

Keywords: Biocides; Bioactivity; *N*-halamine; Siloxane

1. Introduction

Recently there has been a growing concern about how to reduce or eliminate infections completely, especially those caused by antibiotic-resistant, Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococci* (VRE). These bacteria have been shown to have long survival times on commonly used hospital fabrics, such as hospital privacy drapes, scrub suits, and lab coats [1,2]. The survival and transfer of microorganisms between patients and health care workers have been documented [3–6]. The medical gowns and uniforms used currently have been proven to provide ineffective barriers for health care workers in numerous studies [7–11]. This demonstrates a great need for antimicrobial textiles and polymers that are able to protect against all major pathogens [12–14]. *N*-halamine compounds could provide such protection since they have shown excellent biocidal functions against a wide range of microorganisms such as fungi, bacteria, viruses, and yeasts [15–17]. In addition, *N*-halamines have demonstrated the capability of rapid and total inactivation of various microorganisms without causing the microorganisms to develop resistance to them [18]. The stability of *N*-halamines is directly related to their structures, which is evidenced by their dissociation constants in solution [19]. Furthermore, *N*-halamine structures are capable of killing microorganisms directly without the release of free chlorine into the system [20]. *N*-halamines can be composed of amine, amide, and imide halamine bonds, the dissociation constants for which are presented in Table 1 [19]. It is thought that those structures containing amide halamine bonds are of the most practical use since they exhibit a moderate rate of transfer of active chlorine from the *N*-halamine structures in aqueous solution to cells of organisms and provide reasonably rapid biocidal activity. The equilibrium of dissociation of a halamine

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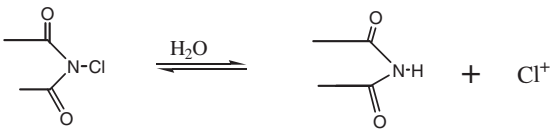
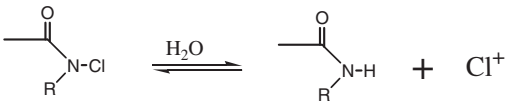
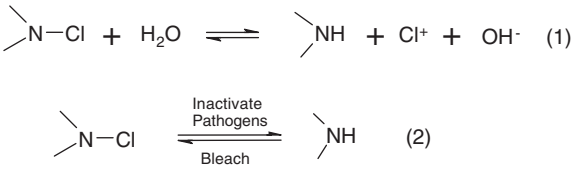
Table 1
Stability of *N*-halamine structures [19]

Dissociation reaction	Dissociation constant for example
Imide structure 	1.6×10^{-12}–8.5×10^{-4} trichlorocyanuric acid 2.54×10^{-4} 1,3-dichloro-5,5-dimethylhydantoin
Amide structure 	2.6×10^{-8} 1,3-dichloro-2,2,5,5-tetramethylimidazolidin-4-one 2.3×10^{-9} 3-chloro-4,4-dimethyl-2-oxazolidinone
Amine structure 	$<10^{-12}$ 1-chloro-2,2,5,5-tetramethylimidazolidin-4-one

in aqueous solution can best be understood from Eqs. (1) and (2).



The amine halamine bonds are the most stable, but offer a slower kill rate than do the amide halamines, and although the imide halamine offers a very rapid kill rate, it is the least stable structure and can rapidly lose active chlorine. Thus, the amide function seems to be a reasonable compromise between stability and biocidal efficacy. With this in mind, the precursor 5,5′-ethylenebis[5-methyl-3-(3-triethoxysilylpropyl)hydantoin] was designed so that once chlorinated, it would provide an effective biocide which would be capable of having two or more siloxyl bonds to surfaces. This could enable a textile coated with it to withstand numerous home laundering cycles, providing a durable and effective broad-spectrum biocidal textile. Examples of surfaces and materials which can be rendered biocidal with the *N*-halamine siloxanes include cellulose, synthetic fibers, ceramics, plastics, polyurethanes, and metals [17]. In the case of cellulose, the binding to the surface is almost certainly covalent in nature due to a condensation reaction of the OH groups on the siloxane with those on the cellulose. Upon loss of the halogen from either long-term use or consumption by the microbes on the surfaces, surfaces such as for textiles can be simply recharged by further exposure to dilute bleach and thus regain their biocidal activity [21–23]. The limiting factor of the biocidal efficacy ultimately is how readily the *N*-halamine, and/or the precursor, can be washed off the surfaces of the materials due to hydrolysis of the formed silyl ether linkages. Prior work on a lower molecular-weight monomer 3-triethoxysilylpropyl-5,5-dimethylhydantoin has shown excellent biocidal efficacy on textiles, but a tendency to hydrolyze off the fabrics after extended machine washings [22]. Therefore, it seemed reasonable that increasing the molecular weight, hydrophobicity, and the number of chemical bonds to the surface would provide for an effective and durable antimicrobial coating for various materials.

2. Experimental

2.1. Materials

All chemicals were purchased from the Aldrich Chemical Company, Milwaukee, WI and used as they were received without further purification unless otherwise noted. The fabric used was (Style 400 Bleached 100% Cotton print Cloth, Testfabics, Inc., West Pittston, PA). The household bleach was Clorox® brand (Clorox, Inc., Oakland, CA). The bacteria used were *S. aureus* ATCC 6538 and *Escherichia coli* O157:H7 ATCC 43895 (American Type Culture Collection, Rockville, MD). The Trypticase soy agar employed was from (Difco Laboratories, Detroit, MI).

2.2. Instruments

The NMR spectra were obtained using a Bruker 400 MHz spectrometer; the IR data were obtained with a Shimadzu IR Prestige-21 FTIR. Tensile strengths were measured with a model 1122 Instron Universal Materials Testing Machine. The reactor used was a Parr 4841 high-pressure reactor.

2.3. Preparation of 5,5′-(1,2-ethanediyl)bis[5-methylhydantoin] Scheme 1

Preparation of 5,5′-(1,2-ethanediyl)bis[5-methylhydantoin] was carried out, for example in one experiment, by adding 5.71 g (0.05 mol) of 97% acetonylacetone to a 250 mL stainless steal vessel, along with 13.02 g (0.20 mol) of 97% potassium cyanide and 38.44 g (0.40 mol) of 98% ammonium carbonate in 200 mL of a 1:1 (v/v) mixture of ethanol and water as solvent. This mixture was then sealed and heated to 85 °C with constant stirring for 72 h. The reactor vessel was then allowed to cool to room temperature, and the reaction mixture was poured into a 500 mL beaker containing 300 mL of water. The precipitate formed was then vacuum filtered from the mother liquor which was then neutralized to a pH ≈ 7 by drop wise addition of a 6 N HCl acid solution over a period of