



## Enhanced aqueous stability of silver oxynitrate through surface modification with alkanethiols



Yuhao Ma<sup>a</sup>, Markian Bahniuk<sup>a</sup>, Michelle Hay<sup>b</sup>, Muhammad Imran<sup>b</sup>, Carla Spina<sup>b,\*\*</sup>, Larry Unsworth<sup>a,c,\*</sup>

<sup>a</sup> Department of Biomedical Engineering, University of Alberta, Edmonton, AB, T6G 2V2, Canada

<sup>b</sup> Exciton Technologies Incorporation, Edmonton, AB, T5J 4P6, Canada

<sup>c</sup> Department of Chemical and Materials Engineering, University of Alberta, Edmonton, AB, T6G 1H9, Canada

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### ABSTRACT

Silver oxynitrate ( $\text{Ag}_7\text{NO}_{11}$ ) is an effective antimicrobial agent that has been limited in its storage and therapeutic application due to its rapid decomposition in aqueous media. In this work we investigated the effect that depositing a layer of alkane thiols at the material-aqueous interface has on inhibiting the rapid decomposition of silver oxynitrate. It was shown that thin films of dodecanethiol (DT) inhibited the decomposition of silver oxynitrate in aqueous media. DT was shown to form a self-assembled layer at the silver oxynitrate surface, yielding DT modified silver oxynitrate particles that were more resistant to decomposition in several aqueous media: water, phosphate buffer, and phosphate buffered saline. This work provides a simple and effective solution to increase the short lifetime of silver oxynitrate in aqueous environments that is crucial to both the storage and therapeutic application of these materials.

### 1. Introduction

Silver compounds have well documented broad-spectrum antimicrobial effects without exhibiting significant cytotoxicity to mammalian cells, which allows for their wide use in many medical applications as antimicrobial agents [1–8]. Studies have revealed that silver in metallic state exhibits its biocidal effect through the release of  $\text{Ag}^+$  ions [9]. The biocidal mechanisms for  $\text{Ag}^+$  was believed to be associated with its ability to block respiration and electron transfer of microbial cells by binding to free thiols on membrane proteins [10,11]. Soluble salts like  $\text{AgNO}_3$ , can be well ionized in pure water. The presence of physiological counter ions like phosphates or chlorides can cause the precipitation of silver phosphate or silver chloride, which lowers the concentration of free  $\text{Ag}^+$  and reduces the overall bactericidal activity [12]. That said, these newly formed precipitates may still present strong antimicrobial effects. For example, it was found that *Escherichia coli* treated with  $\text{AgCl}$  ( $9.3 \mu\text{M}$  concentration of  $\text{Ag}$ ) yielded no sign of bacterial growth [13]. As such,  $\text{AgCl}$  nanoparticles have been impregnated into bacterial cellulose membranes for the express purpose of imparting antimicrobial activity against both Gram-negative and Gram-positive microbes [14]. Also, it has been shown that an application of  $300 \mu\text{M}$  silver phosphate nanoparticles led to a 37.5% inhibition

of *Staphylococcus aureus* (*S. Aureus*) growth [15]. In normal medical applications safety concerns are insignificant for these silver compounds, as they are only given at very low doses. It has, however, been reported that excessive or chronic intake of metallic silver or silver sulfide can cause deposition of silver pigment in tissue to cause argyria [16].

The widespread correlation between  $\text{Ag}^+$  and the antimicrobial properties of silver meant that higher oxidation states of silver (i.e.  $\text{Ag}^{2+}$  and  $\text{Ag}^{3+}$ ) were not extensively studied for antimicrobial activity. The fact that these high oxidation state silvers are susceptible to being reduced further discouraged their study [17]. Recently, the antimicrobial activity of silver oxynitrate ( $\text{Ag}_7\text{NO}_{11}$ ) was compared to several other thiophilic silver compounds ( $\text{AgNO}_3$ ,  $\text{Ag}_2\text{SO}_4$ ,  $\text{AgO}$ ,  $\text{CuSO}_4$ ) and it was found that  $\text{Ag}_7\text{NO}_{11}$  was able to eradicate biofilm and planktonic populations at both the lowest minimal biofilm eradication concentration (MBEC) and the lowest minimal bactericidal concentration (MBC) [17]. For example, in the eradication of *S. aureus* biofilms, MBEC for  $\text{Ag}_7\text{NO}_{11}$  was less than  $100 \mu\text{M}$ , significantly lower than MBEC for  $\text{Ag}_2\text{SO}_4$  and  $\text{AgNO}_3$  at  $\sim 500 \mu\text{M}$  ( $p \leq 0.05$ ), and was much lower than MBEC for  $\text{AgO}$  and  $\text{CuSO}_4$  at  $\sim 1000 \mu\text{M}$  ( $p \leq 0.05$ ).  $\text{AgO}$  and  $\text{Ag}_2\text{O}$ , being decomposition products of  $\text{Ag}_7\text{NO}_{11}$ , required much higher MBEC to match the biocidal effect of  $\text{Ag}_7\text{NO}_{11}$ . Silver

\* Corresponding author at: Department of Chemical and Materials Engineering, University of Alberta, Edmonton, AB, T6G 1H9, Canada.

\*\* Corresponding author at: Exciton Technologies Inc., 101 College Street, Suite 300 Toronto, Ontario, M5G 1L7, Canada.

E-mail addresses: [cjspina@gmail.com](mailto:cjspina@gmail.com) (C. Spina), [larry.unsworth@ualberta.ca](mailto:larry.unsworth@ualberta.ca) (L. Unsworth).

oxynitrate was found to be the most stable species among silver oxysalts with different counterions [18]. However, when exposed to boiling water,  $\text{Ag}_7\text{NO}_{11}$  will gradually decompose into  $\text{AgO}$  [19]. We have also found in this study that 24 h of exposure to water at room temperature will decompose more than 70% of  $\text{Ag}_7\text{NO}_{11}$ . Therefore, preventing or at least inhibiting the decomposition of  $\text{Ag}_7\text{NO}_{11}$  is crucial to maintain its biocidal efficiency and efficacy in aqueous environments.

Silver is a good substrate for self-assembled monolayer (SAM) formation and can give high-quality SAM with a small tilt angle [20]. Like metallic silver, oxidized silver compounds like  $\text{Ag}_2\text{O}$  [21] and  $\text{Ag}_2\text{S}$  [22] have also been shown to be suitable substrates for modification with thiol containing SAMs. Herein, we isolated silver oxynitrate materials from the aqueous phase by forming a self-assembled layer of alkane thiols on the material surface. In addition to the ability to control the film thickness by controlling the chain length, modification by alkane thiols with varied end-group chemistries can introduce chemical moieties like  $-\text{CH}_3$ ,  $-\text{OH}$  and  $-\text{COOH}$ , which may significantly alter the surface-water interaction, wettability and, thus, aqueous stability [23]. We modified the surface of silver oxynitrate using two SAM candidates: dodecanethiol (DT) and 11-Mercapto-1-undecanol (UTOH), with different terminal groups of  $-\text{CH}_3$  and  $-\text{OH}$ . The concentrations of the DT and UTOH were varied in order to control the amount of surface adsorption. Decomposition rates of silver oxynitrate after SAM formation were studied using different media: MilliQ water, phosphate buffer (PB) and phosphate buffered saline (PBS). For the first time it was shown that the aqueous stability of silver oxynitrate could be significantly improved, with the ability to tailor its properties, using a relatively simple surface modification procedure.

## 2. Experimental

### 2.1. Material

1-Dodecanethiol (DT) and 11-Mercapto-1-undecanol (UTOH) were obtained from Sigma-Aldrich (Canada Co.) and used without further treatment. Anhydrous toluene was obtained from Sigma-Aldrich (Canada Co.). Silver oxynitrate ( $\text{Ag}_7\text{NO}_{11}$ ) was provided by Exciton Technologies Inc (Edmonton, AB, Canada). All solutions were degassed, and nitrogen was used when necessary as an atmosphere to prevent disulphide bridge formation.

### 2.2. Modification of silver oxynitrate with DT/UTOH

Silver oxynitrate ( $100 \pm 2$  mg) was dispersed into 10 ml toluene with heavy stirring, into which 5 ml of toluene with either DT or UTOH was added. The alkane thiol addition was finished within 5 min and the mixture was kept under nitrogen for 17 h at room temperature. Silver oxynitrate was settled by centrifugation, with repetitively rinsing thoroughly with toluene and centrifugation, and was then dried in a vacuum oven for 24 h to remove excess solvent. Weight measurements for DT/UTOH modified samples after drying were taken. As a control, silver oxynitrate was dispersed into toluene and collected with the same protocol used for DT/UTOH modification and was weighted after drying under vacuum. In this paper Ag is the binding element for SH and is the short form of  $\text{Ag}_7\text{NO}_{11}$ . Silver oxynitrate samples modified with DT and UTOH are denoted as Ag-DT50, Ag-DT100, Ag-DT150, Ag-UTOH50, Ag-UTOH100, Ag-UTOH150, with the number representing the microliters of DT or UTOH added during the surface modification. Unmodified silver oxynitrate is denoted as Ag-Oxysalt.

### 2.3. Characterization

An infrared spectrometer (Varian FTS7000 FTIR Imaging System) was used to characterize the surface coating layer in attenuated total reflection (ATR) mode with a resolution of  $2\text{ cm}^{-1}$ . Each sample was loaded in sufficient quantity on top of the ATR crystal to ensure total

reflection of IR beam to the detector. X-ray powder diffraction (XRD) spectra were obtained using a Bruker D8 X-ray diffractometer. The sample was mounted on a glass substrate as a pressed film, and the diffraction patterns were collected with a constant oscillation of the sample holder. Only one frame centered at  $2\theta$  of  $40^\circ$  was obtained for each decomposed sample, since characteristic diffractions of all components to be determined fall in the range of  $30\text{--}40^\circ$ . A 1500 s scanning time was used to collect spectra with adequate peak intensity. The obtained spectra were processed by EVA software and were matched with its standard powder diffraction file (PDF) database to determine each individual component, and the quantitative results were obtained using the peak integration function found in Origin software. Scanning electron microscopy (SEM) was performed using a Hitachi S-3000n instrument, and samples were observed directly without any coating.

### 2.4. Decomposition study of DT/UTOH modified silver oxynitrate

The decomposition test was performed using a variety of aqueous media. Before putting samples in aqueous media to undergo decomposition, each sample was pre-deposited onto a glass substrate to prevent self-aggregation in solution and to control the amount of surface area exposed to the various media between samples. A small amount of dichloromethane (DCM) was added to help sample dispersion. After 1 min of sonication the sample vial was put into a fume hood to allow for DCM evaporation. After DCM was evaporated, samples were found to be adhered to the vial bottom. For decomposition testing, sample films were immersed into the test buffer and were shaken at a rate of 60 rpm at room temperature. Decomposition was allowed to continue for up to 24 h. To test decomposition over a longer time scale, 14 days, samples were incubated in a temperature controlled shaker at  $37^\circ\text{C}$  and the solution pH was monitored using a pH meter. After completion of the decomposition test, samples were rinsed thoroughly with water to remove dissolved salts and dried in a vacuum oven for 24 h prior to analysis. All products derived from decomposition of silver oxynitrate were determined using XRD spectra by referring to PDF database, and the change in DT or UTOH layer after decomposition was also checked through ATR-FTIR. The extent of decomposition was determined by comparing the chosen peak in Table 2 of any single component that has been identified by us after decomposition to the most significant peak of silver oxynitrate at  $2\theta\ 31.3^\circ$ , presented in the mass percentage of residual silver oxynitrate. Calibration of chosen XRD peak of each component to mass was done before [See supporting information].

## 3. Result and discussion

### 3.1. Silver oxynitrate modification

It is well known that the chemisorption of alkane thiols occurs spontaneously at silver substrates, including silver oxide interfaces [20–22]. To this end, silver oxynitrate was dispersed in toluene containing DT or UTOH solutes, which allowed for the chemisorption of these materials. The presence of immobilized DT or UTOH was observed in FTIR spectra (Fig. 1). The most distinct peaks in the Ag-DT and Ag-UTOH spectra ( $2847$  and  $2914\text{ cm}^{-1}$ ) were attributed to the symmetric stretch ( $\nu_s$ ) and the in-plane asymmetric stretch ( $\nu_a$ ) for a methylene group, neighboring to which for Ag-DT are relative weak  $\nu_s$  and  $\nu_a$  for a methyl at  $2874$  and  $2955\text{ cm}^{-1}$ , respectively. These samples were characterized after multiple rinses and represent the characteristic methylene of end-tethered DT and UTOH. The Ag-UTOH systems had a terminal hydroxyl instead of the methyl group for DT, which yielded a broad peak between  $3100\text{--}3400\text{ cm}^{-1}$  due to the stretching of hydrogen bonds and intermolecular hydrogen bonding. Being a crystallized powder, UTOH exhibits its  $-\text{OH}$  peak at a slightly higher wavenumber and it is less broad than  $-\text{OH}$  peak for Ag-UTOH. Long chain alkane-thiol adsorption usually results in a well ordered and orientated monolayer [24] and it was reported that a near normal SAM

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