ACS Macro Letters

pubs.acs.org/macroletters Letter

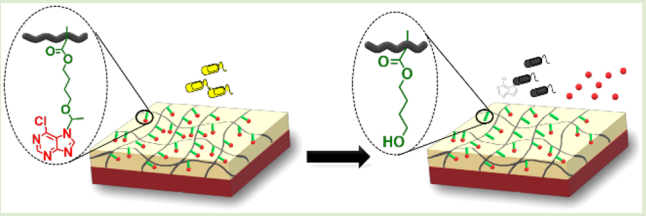
# Polymers with Hemiaminal Ether Linkages for pH-Responsive Antibacterial Materials

Piangtawan Phoungtawee, Farzad Seidi, Alongkot Treetong, Choochart Warin, Annop Klamchuen, and Daniel Crespy*

Cite This: ACS Macro Lett. 2021, 10, 365−369 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** Antibacterial materials containing biocides suffer from the fact that biocides are usually quickly released and hence display a limited antibacterial ability over a long period of time. To overcome this problem, the antibacterial agent 6-chloropurine is conjugated to a monomer via a hemiaminal ether linkage. The functional monomer is then reacted with a urethane acrylate by photopolymerization to yield thin polymer coatings. The release of the antibacterial agent from the coatings is sustained due to the slow kinetics of the hydrolysis of the hemiaminal ether linkage. Antibacterial performance is achieved against *S. aureus* and *E. coli* bacteria. This simple strategy can be applied for the rapid preparation of antibacterial coatings on various substrates and other applications such as antifouling or anticorrosion coatings.






Bacteria attachment and biofilm formation occur due to accumulation and growth of microbial communities.[1,2] Bacterial biofilms on solid surfaces can cause serious detrimental effects in the food industry, water supply,[3] and in healthcare environments such as hospitals and clinics.[4] A method for reducing biofilm growth is to coat surfaces with functional antibacterial materials. Bacteria-resistant coatings can be fabricated with polymers that can repel bacterial attachment.[5] Another strategy relies on coatings formed by materials that are themselves biocides (contact-killing) or that contain biocides (release-killing).[6−8] Purine and purine nucleoside derivatives display strong antiviral, antifungal, and antibacterial activities.[9−11] 6-Chloropurine analogues are known to inhibit bacterial RNA polymerases by site-directed alkylation.[12] To the best of our knowledge, purines have not yet been embedded by physical or chemical entrapment in coatings.

One major challenge for antibacterial materials containing biocides is that biocides are usually quickly released, thereby limiting the durability of the antibacterial performance.[13] One approach to overcome this issue is to program the materials to release biocides in preferential conditions, for example, upon a change in pH value.[14−18] Indeed, the environment of biofilms is acidic due to the production of acids by the bacteria.[19,20] Multilayers containing weak polyelectrolytes can be used to fabricate pH-responsive coatings.[21−33] The multilayers were assembled by sequential deposition of oppositely charged polyelectrolytes,[21−25] polyelectrolytes and a hydrogel,[26] polyelectrolytes and micelles,[27−30] or polyelectrolytes and nanocapsules.[31−33] The release of antibacterial agents occurred by swelling or shrinking of the multilayers due to protonation or deprotonation of the ionic groups. By nature, polyelectrolyte multilayer coatings can be disintegrated upon pH variation. Moreover, the layer-by-layer method is usually time demanding.

One approach for the rapid preparation of antibacterial coatings in one step is to program the pH-responsive behavior in the polymer by incorporating monomers that are biocides functionalized with acid-labile linkages.[34] Antibacterial agents were also conjugated to polymers via acid-labile bonds. The antibacterial peptide melittin was reacted with poly(acrylic acid) brushes to form $\beta$-carboxylic acid amide groups.[35] The new bond was quickly hydrolyzed, inducing a release of ∼50% melittin in 24 h. Similarly, the antibacterial agent gentamicin, which was conjugated to alginate dialdehyde to form a Schiff base, was released faster at pH 5.8 than at pH 7.4.[36] In acidic conditions, ∼50% of the maximum cumulated amount was released after ∼72 h. Dicholorophen, an anticestodal agent, was modified and polymerized to yield a polymer with thiopropionate linkages in its main chain.[37] The drug could be released in acidic conditions, yielding to fragmentation of the polymer and loss of its mechanical integrity. Streptomycin was conjugated to a polymer via an imine bond and ∼65% was released after 30 h at pH 6.0.[38] A dialkene acetal monomer containing an antimicrobial aldehyde was reacted with monomers containing a thiol group to form a polymer

**Received:** January 6, 2021
**Accepted:** February 9, 2021




https://dx.doi.org/10.1021/acsmacrolett.1c00009
ACS Macro Lett. 2021, 10, 365−369

network by thiol−ene photopolymerization.[39] The acid-cleavable acetal bond was degraded to yield the aldehydes within 48 h in acidic conditions. In these cases, the release of the antibacterial agent was rapid.

Herein, we aim at designing a coating that is durable (not disintegrating) and that provides durable antibacterial properties. We prepared pH-responsive antibacterial coatings from polymers connected to the potent antibacterial agent 6-chloropurine via a hemiaminal ether linkage. A UV-curable resin was selected as the coating's matrix because it can be applied on various surfaces and surface geometries. Although very scarcely investigated,[40,41] the hemiaminal ether group linked to polymers is very interesting because it allows for long and sustained release of molecules in mild acidic conditions. We hypothesized that the UV-curable pH-responsive antibacterial coatings could allow for a sustained release of an antibacterial agent and provide antibacterial activity against Gram-positive *S. aureus* and Gram-negative *E. coli* bacteria.

The purpose of this study is to prepare a UV-curable coating that prevents attachment of bacteria on coatings, which can lead to the formation of a biofilm. To avoid leaching of antibacterial agents from the coating, they were connected to a polymer via a labile linkage. This linkage was selected to be a pH-responsive hemiaminal ether group. Indeed, this group was found to be cleaved very slowly under mild acidic conditions.[40] 6-Chloropurine was conjugated to the synthesized 4-(vinyloxy)butyl methacrylate (VBMA) to yield 4-(1-(6-chloro-7*H*-purin-7-yl)ethoxy)butyl methacrylate (CPBMA) as a polymerizable pH-responsive antibacterial monomer (Figure 1a). The nucleophilic addition of purine to the vinyl ether group of VBMA was catalyzed by trifluoroacetic acid. To prevent the degradation of the monomer, a small amount of triethylamine was added to the eluent during column chromatography purification because the weak acidity of the silica gel induced the cleavage of hemiaminal linkages in CPBMA. The successful synthesis of CPBMA was confirmed by $^1$H NMR spectroscopy and UV−vis spectroscopy (Figures S1a and S2). To verify that the CPBMA could be hydrolytically cleaved to yield 6-chloropurine, the reaction was monitored by $^1$H NMR spectroscopy in neutral and acidic conditions. The acidic hydrolysis of CPBMA was monitored by $^1$H NMR spectroscopy of CPBMA dissolved in a $D_2O$/DCl/DMSO-$d_6$ mixture (see Figure S3). The integral of the signal associated with the aldehyde proton of acetaldehyde at 9.66 ppm during degradation ($I_a$) was compared with the integral of the signal associated with the proton associated with the pyridine ring in 6-chloropurine at 8.91 ppm ($I_b$). A total of 99% of the 6-chloropurine was released in acidic conditions after 15 h, whereas no cleavage of the CPBMA monomer was observed in neutral conditions (Figure 1b). The copolymer of urethane acrylate and CPBMA P(UA-*co*-CPBMA) coatings were obtained by photopolymerization of a urethane/silicone-acrylate and CPBMA (6.56 wt %). Photopolymerization is a convenient process for preparing coatings based on polymerized urethane acrylate on various surfaces.[42,43] The decrease of the intensity of the signal at 1635 cm$^{-1}$ for C═C bonds confirmed the polymerization of the monomers by UV photopolymerization (Figure S4). Raman spectra of noncured and cured polyurethane acrylate (PUA, Figure S5) and P(UA-*co*-CPBMA) (Figure 2a) displayed characteristic bands associated with the carbonyl group of the urethane bond (1730 cm$^{-1}$), Si−C (1094 cm$^{-1}$), and Si−O−Si (500 cm$^{-1}$). The polymerization was associated with a reduction in the intensity of the signal at 1635 cm$^{-1}$ for C═C bonds after curing. The elemental composition of the coatings was measured by SEM-EDS (Figure S6). Chlorine could be detected in the P(UA-*co*-CPBMA) (Cl/C = 0.4%), but not in the PUA coatings (Cl/C = 0%), hence, confirming the presence of CPBMA after curing. The surface composition of the coatings was analyzed by X-ray photoelectron spectroscopy (XPS). The C 1s core-level spectrum of the PUA coating (Figure 2b) could be deconvoluted in three components with binding energies at 284.6, 285.2, and 288.9 eV, corresponding to C—C, C—O, and C═O bonds, respectively. For the P(UA-*co*-CPBMA) coating (Figure 2c), an additional component at 287.9 eV was observed and assigned to the

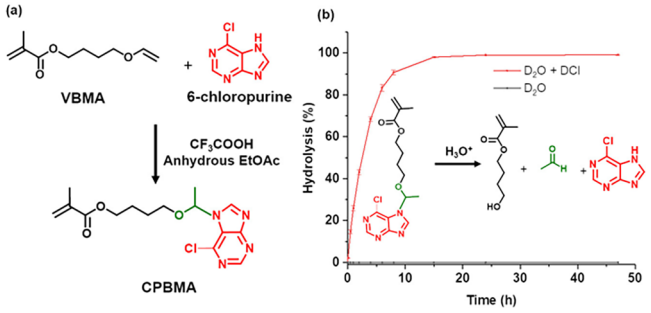



**Figure 1.** (a) Synthetic route for the polymerizable functional monomer (CPBMA) containing 6-chloropurine and a hemiaminal ether linkage. (b) The degradation of the hemiaminal ether group in the CPBMA was determined by $^1$H NMR spectroscopy in acidic and neutral conditions.

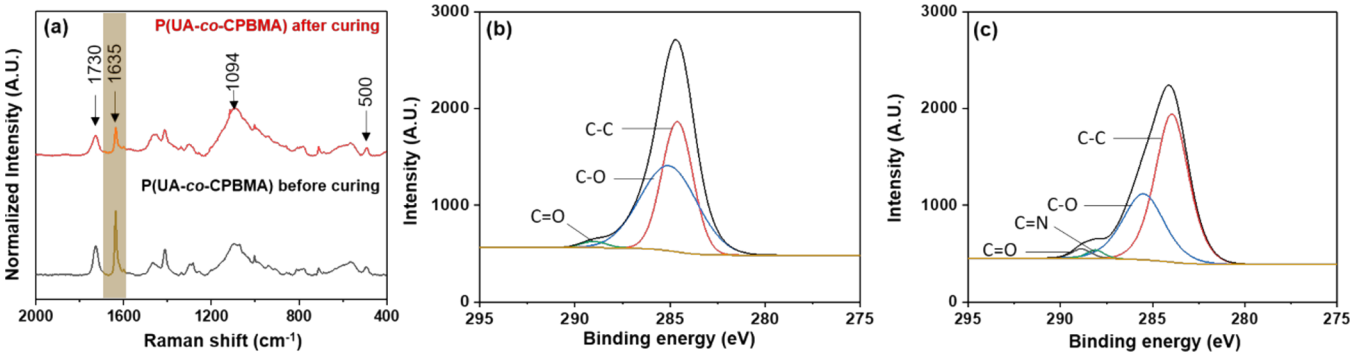



**Figure 2.** (a) Normalized Raman spectra (relative to the height of the Si−O signal at 500 cm$^{-1}$) of the P(UA-*co*-CPBMA) coatings on glass slides before and after curing. High-resolution XPS spectra of the C 1s region for (b) PUA and (c) P(UA-*co*-CPBMA) coatings.


https://dx.doi.org/10.1021/acsmacrolett.1c00009
ACS Macro Lett. 2021, 10, 365−369

C═N bond in 6-chloropurine, hence, confirming the presence of the drug in the coating. P(UA-*co*-CPBMA) showed a slightly different thermal stability than PUA. The thermal degradation (≥10%) of P(UA-*co*-CPBMA) and PUA started at 300 and 320 °C, respectively (see Figure S7). While the TGA thermogram of the PUA coating showed a degradation in a single step (320−485 °C), weight loss for P(UA- *co*-CPBMA) occurred in two stages: at 300−450 °C (weight loss ∼ 59 wt %) and 450−500 °C (weight loss ∼ 9 wt %). The first stage corresponded to the thermal decomposition of urethane segments and the second step arose from decomposition of the purine moiety. Indeed, nitrogen-rich purine moieties provide intermolecular interactions, such as hydrogen bonding and $\pi-\pi$ stacking.[44] The adhesion of PUA and P(UA- *co*-CPBMA) coatings on cold rolled steel was compared using the pull-off adhesion test. The adhesion strength of PUA and P(UA-*co*-CPBMA) coatings was 3.80 ± 0.18 and 3.03 ± 0.15 MPa, respectively. The mechanical properties of the coatings were further investigated by quantitative AFM imaging (Figure S8a−d). The Young's modulus of the P(UA- *co*-CPBMA) coating (1.03 ± 0.07 GPa) was the same as for the PUA coating (1.04 ± 0.01 GPa). These values are close to Young's moduli of cured urethane-acrylate resins measured by nanoindentation (0.5−3.1 GPa).[45] Therefore, the presence of 6-chloropurine moieties in the coating did not significantly influence the mechanical properties of the coating.

Release kinetics of 6-chloropurine were performed by immersing coated samples in buffer solutions at pH 3.5 or 7.4 (Figure 3). We confirmed first that the PUA matrix was not degraded in acidic conditions by investigating the liquid used for extracting PUA by $^1$H NMR spectroscopy and by analyzing the surface of the coatings after immersion in acidic media. No chemicals could be detected in the release media while the surface of the PUA coatings remained smooth, indicating that PUA is stable in acidic conditions (Figures S9 and S10). The amount of 6-chloropurine was then detected by UV−vis spectroscopy. 6-Chloropurine was also physically entrapped, that is, not covalently bonded to the polymer, in PUA as control samples. After 1 day, >90% entrapped 6-chloropurine was released at both pH values. Burst release hence occurred, and there was no major distinction between release in acidic and neutral media, meaning that the release was not pH-selective. On the contrary, the release of 6-chloropurine from P(UA-*co*-CPBMA) was sustained and very slow. Indeed, only 9% of 6-chloropurine was released after 58 days at pH 7.4. At pH 3.5, 7% of 6-chloropurine was released after 20 days against 5% at pH 7.4. After 20 days, the pH was dropped from 3.5 to 1.0 to accelerate the release and observe if more 6-chloropurine could be released. As expected, the release rate increased and 26% of the drug could be detected after 58 days (20 days at pH 3.5 and 38 days at pH 1.0). Therefore, the release of 6-chloropurine was strongly delayed over time when it was conjugated to the polymer and displayed an acid-sensitive behavior. Compared with results from the literature,[35,36] the antibacterial agent was released slower from P(UA-*co*-CPBMA) coatings and faster from PUA/6-chloropurine coatings.

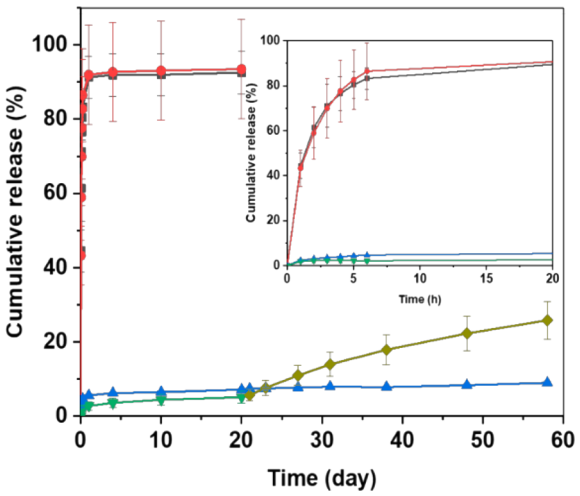



**Figure 3.** Release profile of 6-chloropurine from PUA at pH 7.4 (black line), PUA at pH 3.5 (red line), P(UA-*co*-CPBMA) at pH 7.4 (blue line), P(UA-*co*-CPBMA) at pH 3.5 (green line), and P(UA-*co*-CPBMA) at pH 1.0 (olive-green line). The released amounts were determined by UV-spectroscopy measurements of the release media.

The bactericidal activity of the P(UA-*co*-CPBMA) coating against *E. coli* and *S. aureus* bacteria was investigated (Figure 4). The P(UA-*co*-CPBMA) coating exhibited a reduction of 99.94% and 99.99% in the colony count of *E. coli* and *S. aureus* bacteria, respectively (Figure 4). The release of the antibacterial agent proceeded upon acidification of the medium, which was reported to occur in an infected wound (pH 5.5).[46,47] The lower pH value is caused by hypoxia and the production of lactic acid by bacteria. Because rapid release could be obtained by physical entrapment of 6-chloropurine in PUA coatings (see Figure 3), we also prepared P(UA-*co*-CPBMA) with ∼0.5 wt % entrapped 6-chloropurine so that the coatings contained both conjugated (covalently linked, 82%) and physically entrapped 6-chloropurine (18%). P(UA- *co*-CPBMA)/6-chloropurine displayed a reduction of 99.93% and 99.99% in the colony count of *E. coli* and *S. aureus* bacteria, showing that P(UA-*co*-CPBMA)/6-chloropurine and P(UA-*co*-CPBMA) coatings displayed a similar antibacterial activity. Acetaldehyde is a byproduct of the acidic hydrolysis of hemiaminal ether linkages. A total of 100 ppm of acetaldehyde was reported to inhibit the growth of *S. aureus*,[48] while 1000 ppm of acetaldehyde inhibited *E. coli* bacteria growth.[49] The release experiments showed that a maximum of ∼7% chloropurine was released from the P(UA-*co*-CPBMA) coating

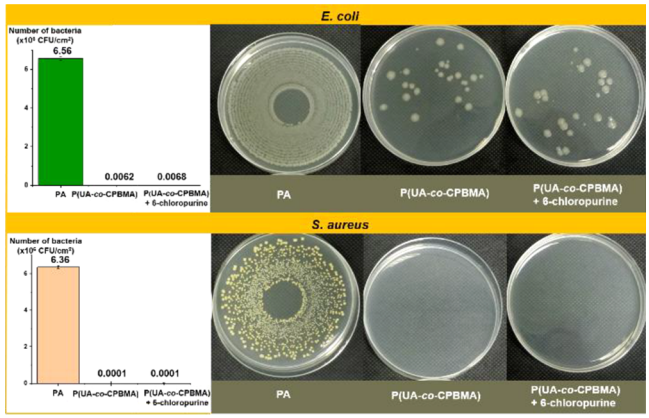



**Figure 4.** Numbers of *E. coli* and *S. aureus* bacteria determined by the plate count method and photographs of the colony after incubating bacteria present on uncoated samples (polyamide substrate) and P(UA-*co*-CPBMA) coatings.


https://dx.doi.org/10.1021/acsmacrolett.1c00009
ACS Macro Lett. 2021, 10, 365−369

after 20 days at pH 3.5. This would correspond to a concentration of ∼50 ppm acetaldehyde in the dispersion of bacteria. Thus, acetaldehyde shall hence not significantly contribute to the antibacterial activity of the coatings.

In summary, pH-responsive antibacterial coatings were prepared by UV polymerization. First, the antibacterial agent 6-chloropurine was functionalized to yield 4-(1-(6-chloro-7*H*-purin-7-yl)ethoxy)butyl methacrylate (CPBMA). The polymerizable derivative of the drug contained a hemiaminal ether linkage so that the drug could be slowly released in mild acidic conditions. CPBMA was then copolymerized with a commercial UV-curable resin to obtain pH-responsive antibacterial coatings. The coatings released the antibacterial agent in a very sustainable way over extended periods of time and provided antibacterial activity. This simple strategy could be applied for the rapid preparation of antibacterial coatings on glass, plastics, or metallic substrates. Applications for these coatings include waterproofing, sealants, antifouling, and anticorrosion coatings.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.1c00009.

Procedures for the synthesis of monomers, coating preparation, procedures for the release study of 6-chloropurine, procedures for antibacterial activity, NMR spectra, FT-IR spectra, Raman spectra, EDS spectra, TGA thermograms, and Young's Modulus histograms (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

**Daniel Crespy** − *Department of Materials Science and Engineering, School of Molecular Science and Engineering, Vidyasirimedhi Institute of Science and Technology (VISTEC), Rayong 21210, Thailand;* orcid.org/0000-0002-6023-703X; Email: daniel.crespy@vistec.ac.th

### Authors

**Piangtawan Phoungtawee** − *Department of Materials Science and Engineering, School of Molecular Science and Engineering, Vidyasirimedhi Institute of Science and Technology (VISTEC), Rayong 21210, Thailand*

**Farzad Seidi** − *Department of Materials Science and Engineering, School of Molecular Science and Engineering, Vidyasirimedhi Institute of Science and Technology (VISTEC), Rayong 21210, Thailand;* orcid.org/0000-0001-5510-9554

**Alongkot Treetong** − *National Nanotechnology Center (NANOTEC), National Science and Technology Development Agency (NSTDA), Khlong Luang, Pathum Thani 12120, Thailand*

**Choochart Warin** − *National Nanotechnology Center (NANOTEC), National Science and Technology Development Agency (NSTDA), Khlong Luang, Pathum Thani 12120, Thailand*

**Annop Klamchuen** − *National Nanotechnology Center (NANOTEC), National Science and Technology Development Agency (NSTDA), Khlong Luang, Pathum Thani 12120, Thailand;* orcid.org/0000-0002-0477-4893

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmacrolett.1c00009



### Funding

Financial support provided by the Vidyasirimedhi Institute of Science and Technology (VISTEC).

### Notes

The authors declare no competing financial interest.


## ■ ACKNOWLEDGMENTS

The authors are thankful for the financial support provided by the Vidyasirimedhi Institute of Science and Technology (VISTEC), the National Research Council of Thailand (NRCT5-RSA63025), and Allnex (Thailand) Ltd. for providing the UV-curable resins.

## ■ REFERENCES


(1) Costerton, J. W.; Stewart, P. S.; Greenberg, E. P. Bacterial Biofilms: A Common Cause of Persistent Infections. *Science* **1999**, *284* (5418), 1318.

(2) Flemming, H.-C.; Wingender, J. The Biofilm Matrix. *Nat. Rev. Microbiol.* **2010**, *8* (9), 623−633.

(3) Garrett, T. R.; Bhakoo, M.; Zhang, Z. Bacterial Adhesion and Biofilms on Surfaces. *Prog. Nat. Sci.* **2008**, *18* (9), 1049−1056.

(4) Feng, G.; Cheng, Y.; Wang, S.-Y.; Borca-Tasciuc, D. A.; Worobo, R. W.; Moraru, C. I. Bacterial Attachment and Biofilm Formation on Surfaces Are Reduced by Small-diameter Nanoscale Pores: How Small Is Small Enough? *npj Biofilms Microbiomes* **2015**, *1* (1), 15022.

(5) Wei, T.; Yu, Q.; Chen, H. Responsive and Synergistic Antibacterial Coatings: Fighting Against Bacteria in A Smart and Effective Way. *Adv. Healthcare Mater.* **2019**, *8* (3), 1801381.

(6) Kaur, R.; Liu, S. Antibacterial Surface Design − Contact Kill. *Prog. Surf. Sci.* **2016**, *91* (3), 136−153.

(7) Li, X.; Wu, B.; Chen, H.; Nan, K.; Jin, Y.; Sun, L.; Wang, B. Recent Developments in Smart Antibacterial Surfaces to Inhibit Biofilm Formation and Bacterial Infections. *J. Mater. Chem. B* **2018**, *6* (26), 4274−4292.

(8) Hetrick, E. M.; Schoenfisch, M. H. Reducing Implant-Related Infections: Active Release Strategies. *Chem. Soc. Rev.* **2006**, *35* (9), 780−789.

(9) Narayana, K.; Rao, D.; Madhava, G.; Venkateswarlu, N.; Vijaya, T.; Raju, C. Sulfonamide and Carbamate Derivatives of 6-Chloropurine: Synthesis, Characterization and Antimicrobial activity Evaluation. *Org. Commun.* **2016**, *9*, 42−53.

(10) Schwarz, S.; Siewert, B.; Csuk, R.; Rauter, A. P. New Antitumor 6-Chloropurine Nucleosides Inducing Apoptosis and G2/M Cell Cycle Arrest. *Eur. J. Med. Chem.* **2015**, *90*, 595−602.

(11) Subramanyam, C.; Rao, D. S.; Raju, C. N.; Adam, S.; Murthy, S. D. S. New N-Linked Phosphonamidate Derivatives of 6-Chloropurine: Synthesis and Evaluation of Antimicrobial and Antioxidant Activities. *Phosphorus, Sulfur Silicon Relat. Elem.* **2014**, *189* (10), 1572−1585.

(12) Ruddon, R. W.; Rainey, C. H.; Zedeck, M. S. Inhibition of RNA Polymerase and Formyltetrahydrofolate Synthetase Activity By 6-Chloro-8-Aza-9-Cyclopentylpurine. Structure-Activity Relationships. *FEBS Lett.* **1970**, *7* (2), 119−124.

(13) Zhang, Q.; Liu, H.; Zhan, X.; Chen, F.; Yan, J.; Tang, H. Microstructure and Antibacterial Performance of Functionalized Polyurethane Based on Polysiloxane Tethered Cationic Biocides. *RSC Adv.* **2015**, *5* (95), 77508−77517.

(14) Yan, S.; Shi, H.; Song, L.; Wang, X.; Liu, L.; Luan, S.; Yang, Y.; Yin, J. Nonleaching Bacteria-Responsive Antibacterial Surface Based on A Unique Hierarchical Architecture. *ACS Appl. Mater. Interfaces* **2016**, *8* (37), 24471−24481.

(15) Liu, P.; Xu, G.; Pranantyo, D.; Xu, L. Q.; Neoh, K.-G.; Kang, E.-T. pH-Sensitive Zwitterionic Polymer as An Antimicrobial Agent

with Effective Bacterial Targeting. *ACS Biomater. Sci. Eng.* **2018**, *4* (1), 40−46.
(16) Deirram, N.; Zhang, C.; Kermaniyan, S. S.; Johnston, A. P. R.; Such, G. K. pH-Responsive Polymer Nanoparticles for Drug Delivery. *Macromol. Rapid Commun.* **2019**, *40* (10), 1800917.
(17) Jobdeedamrong, A.; Theerasilp, M.; Wongsuwan, N.; Nasongkla, N.; Crespy, D. Inflammation-Responsive Nanocaspules for The Dual-Release of Antibacterial Drugs. *Chem. Commun.* **2020**, *56*, 12725−12728.
(18) Pavlukhina, S.; Lu, Y.; Patimetha, A.; Libera, M.; Sukhishvili, S. Polymer Multilayers with pH-Triggered Release of Antibacterial Agents. *Biomacromolecules* **2010**, *11* (12), 3448−3456.
(19) Hidalgo, G.; Burns, A.; Herz, E.; Hay, A.; Houston, P.; Wiesner, U.; Lion, L. Functional Tomographic Fluorescence Imaging of pH Microenvironments in Microbial Biofilms by Use of Silica Nanoparticle Sensors. *Appl. Environ. Microbiol.* **2009**, *75*, 7426−35.
(20) Vroom, J. M.; De Grauw, K. J.; Gerritsen, H. C.; Bradshaw, D. J.; Marsh, P. D.; Watson, G. K.; Birmingham, J. J.; Allison, C. Depth Penetration and Detection of pH Gradients in Biofilms by Two-Photon Excitation Microscopy. *Appl. Environ. Microbiol.* **1999**, *65*, 3502−11.
(21) Kumorek, M.; Minisy, I. M.; Krunclová, T.; Voršiláková, M.; Venclíková, K.; Chánová, E. M.; Janoušková, O.; Kubies, D. pH-Responsive and Antibacterial Properties of Self-Assembled MultiLayer Films Based on Chitosan and Tannic Acid. *Mater. Sci. Eng., C* **2020**, *109*, 110493.
(22) Lee, H.-S.; Dastgheyb, S. S.; Hickok, N. J.; Eckmann, D. M.; Composto, R. J. Targeted Release of Tobramycin from A pH-Responsive Grafted Bilayer Challenged with *S. aureus*. *Biomacromolecules* **2015**, *16* (2), 650−659.
(23) Nalam, P. C.; Lee, H.-S.; Bhatt, N.; Carpick, R. W.; Eckmann, D. M.; Composto, R. J. Nanomechanics of pH-Responsive, Drug-Loaded, Bilayered Polymer Grafts. *ACS Appl. Mater. Interfaces* **2017**, *9* (15), 12936−12948.
(24) Xu, G.; Neoh, K. G.; Kang, E.-T.; Teo, S. L.-M. Switchable Antimicrobial and Antifouling Coatings from Tannic Acid-Scaffolded Binary Polymer Brushes. *ACS Sustainable Chem. Eng.* **2020**, *8* (6), 2586−2595.
(25) Zhuk, I.; Jariwala, F.; Attygalle, A. B.; Wu, Y.; Libera, M. R.; Sukhishvili, S. A. Self-Defensive Layer-by-Layer Films with Bacteria-Triggered Antibiotic Release. *ACS Nano* **2014**, *8* (8), 7733−7745.
(26) Lu, Y.; Wu, Y.; Liang, J.; Libera, M. R.; Sukhishvili, S. A. Self-Defensive Antibacterial Layer-by-Layer Hydrogel Coatings with pH-Triggered Hydrophobicity. *Biomaterials* **2015**, *45*, 64−71.
(27) Zhou, W.; Jia, Z.; Xiong, P.; Yan, J.; Li, M.; Cheng, Y.; Zheng, Y. Novel pH-Responsive Tobramycin-Embedded Micelles in Nanostructured Multilayer-Coatings of Chitosan/Heparin with Efficient and Sustained Antibacterial Properties. *Mater. Sci. Eng., C* **2018**, *90*, 693−705.
(28) Wang, B.; Liu, H.; Wang, Z.; Shi, S.; Nan, K.; Xu, Q.; Ye, Z.; Chen, H. A Self-Defensive Antibacterial Coating Acting Through The Bacteria-Triggered Release of A Hydrophobic Antibiotic from Layer-by-Layer Films. *J. Mater. Chem. B* **2017**, *5* (7), 1498−1506.
(29) Onat, B.; Bütün, V.; Banerjee, S.; Erel-Goktepe, I. Bacterial Anti-Adhesive and pH-Induced Antibacterial Agent Releasing Ultra-Thin Films of Zwitterionic Copolymer Micelles. *Acta Biomater.* **2016**, *40*, 293−309.
(30) Ulusan, S.; Bütün, V.; Banerjee, S.; Erel-Goktepe, I. Biologically Functional Ultrathin Films Made of Zwitterionic Block Copolymer Micelles. *Langmuir* **2019**, *35* (5), 1156−1171.
(31) Cai, H.; Wang, P.; Zhang, D. pH-Responsive Linkages-Enabled Layer-by-Layer Assembled Antibacterial and Antiadhesive Multilayer Films with Polyelectrolyte Nanocapsules as Biocide Delivery Vehicles. *J. Drug Delivery Sci. Technol.* **2019**, *54*, 101251.
(32) Hao, X.; Wang, W.; Yang, Z.; Yue, L.; Sun, H.; Wang, H.; Guo, Z.; Cheng, F.; Chen, S. pH Responsive Antifouling and Antibacterial Multilayer Films with Self-Healing Performance. *Chem. Eng. J.* **2019**, *356*, 130−141.
(33) Hao, X.; Chen, S.; Qin, D.; Zhang, M.; Li, W.; Fan, J.; Wang, C.; Dong, M.; Zhang, J.; Cheng, F.; Guo, Z. Antifouling and Antibacterial Behaviors of Capsaicin-Based pH Responsive Smart Coatings in Marine Environments. *Mater. Sci. Eng., C* **2020**, *108*, 110361.
(34) Seidi, F.; Jenjob, R.; Crespy, D. Designing Smart Polymer Conjugates for Controlled Release of Payloads. *Chem. Rev.* **2018**, *118* (7), 3965−4036.
(35) Zhang, J.; Zhu, W.; Xin, B.; Lin, S.; Jin, L.; Wang, H. Development of An Antibacterial Surface with A Self-Defensive and pH-Responsive Function. *Biomater. Sci.* **2019**, *7* (9), 3795−3800.
(36) Tao, B.; Deng, Y.; Song, L.; Ma, W.; Qian, Y.; Lin, C.; Yuan, Z.; Lu, L.; Chen, M.; Yang, X.; Cai, K. BMP2-Loaded Titania Nanotubes Coating with pH-Responsive Multilayers for Bacterial Infections Inhibition and Osteogenic Activity Improvement. *Colloids Surf., B* **2019**, *177*, 242−252.
(37) Klahan, B.; Seidi, F.; Crespy, D. Oligo(thioether-ester)s Blocks in Polyurethanes for Slowly Releasing Active Payloads. *Macromol. Chem. Phys.* **2018**, *219* (23), 1800392.
(38) Ye, M.; Zhao, Y.; Wang, Y.; Yodsanit, N.; Xie, R.; Gong, S. pH-Responsive Polymer−Drug Conjugate: An Effective Strategy to Combat the Antimicrobial Resistance. *Adv. Funct. Mater.* **2020**, *30*, 2002655.
(39) Amato, D. N.; Amato, D. V.; Adewunmi, Y.; Mavrodi, O. V.; Parsons, K. H.; Swilley, S. N.; Braasch, D. A.; Walker, W. D.; Mavrodi, D. V.; Patton, D. L. Using Aldehyde Synergism to Direct The Design of Degradable Pro-Antimicrobial Networks. *ACS Appl. Bio Mater.* **2018**, *1* (6), 1983−1991.
(40) Seidi, F.; Druet, V.; Huynh, N.; Phakkeeree, T.; Crespy, D. Hemiaminal Ether Linkages Provide A Selective Release of Payloads from Polymer Conjugates. *Chem. Commun.* **2018**, *54* (97), 13730−13733.
(41) Dararatana, N.; Seidi, F.; Crespy, D. Acid-Cleavable Polymers for Simultaneous Fast and Slow Release of Functional Molecules. *Polym. Chem.* **2020**, *11*, 4723−4728.
(42) Jančovičová, V.; Mikula, M.; Havlínová, B.; Jakubíková, Z. Influence of UV-Curing Conditions on Polymerization Kinetics and Gloss of Urethane Acrylate Coatings. *Prog. Org. Coat.* **2013**, *76* (2), 432−438.
(43) Bakhshandeh, E.; Bastani, S.; Saeb, M. R.; Croutxé-Barghorn, C.; Allonas, X. High-Performance Water-based UV-Curable Soft Systems with Variable Chain Architecture for Advanced Coating Applications. 2019. *Prog. Org. Coat.* **2019**, *130*, 99−113.
(44) Hu, J.; Wang, Z.; Lu, Z.; Chen, C.; Shi, M.; Wang, J.; Zhao, E.; Zeng, K.; Yang, G. Bio-Based Adenine-Containing High Performance Polyimide. *Polymer* **2017**, *119*, 59−65.
(45) Choi, H.; Kwon, S.; Jung, Y.-G.; Cho, Y. T. Comparison of Durability for PUA Type Resin Using Wear and Nano-indentation Test. *Korean Society of Manufacturing Process Engineers* **2018**, *17*, 8−15.
(46) Jones, E.; Cochrane, C.; Percival, S. The Effect of pH on the Extracellular Matrix and Biofilms. *Adv. Wound Care* **2015**, *4*, 431−439.
(47) Schneider, L. A.; Korber, A.; Grabbe, S.; Dissemond, J. Influence of pH on Wound-Healing: A New Perspective for Wound-Therapy? *Arch. Dermatol. Res.* **2007**, *298* (9), 413−420.
(48) Kulshrestha, D. C.; Marth, E. H. Inhibition of Bacteria by Some Volatile and Non-Volatile Compounds Associated with Milk: III. *Staphylococcus Aureus*. *J. Milk Food Technol.* **1974**, *37* (11), 545−550.
(49) Kulshrestha, D. C.; Marth, E. H. Inhibition of Bacteria by Some Volatile and Non-Volatile Compounds Associated with Milk: III. Escherichia coli. *J. Milk Food Technol.* **1974**, *37* (11), 510−516.


https://dx.doi.org/10.1021/acsmacrolett.1c00009
*ACS Macro Lett.* 2021, 10, 365−369