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Article

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Trojan Antibiotics: New Weapons for Fighting Against Drug Resistance

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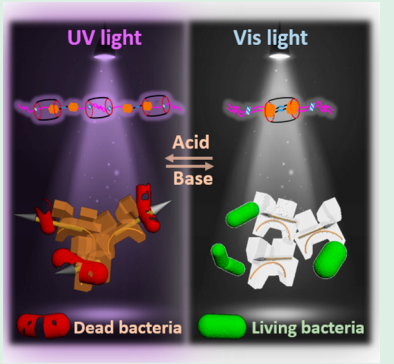
Supporting Information

ABSTRACT: Bacterial resistance has caused a global healthcare emergency due to the buildup of antibiotics in the environment. Novel approaches that enable highly efficient bactericide and auto inactivation are highly desired. Past researches mainly focused on the on−off bactericidal ability of antibiotics, which often displays unsatisfactory bactericidal efficiency. Herein, we report a Trojan antibiotic that considers the affinity of antibiotics to bacteria. A disguised host−guest supramolecule based on cucurbituril (CB[7]) and a bola-type azobenzene compound with glycosylamine heads at both ends is synthesized. This supramolecule has a surface fully decorated with sugar-like components, which are highly analogous to wall components of bacteria. This Trojan antibiotic is benign to a wide spectrum of bacteria at a weak basic pH of approximately 9.0 under daylight conditions. However, this antibiotic becomes a potent bactericide toward both Gram-negative and Gram-positive bacteria at pH 4.0 under 365 nm UV irradiation. The dual use of pH and UV light greatly enhances the efficiency of the bactericidal effect so that the 50% minimum inhibitory concentration (MIC_{50}) of the Trojan antibiotic is at least 10 times smaller than that of conventional drugs, and the removal of the UV source and reversal of pH automatically stop the antibacterial behavior, which prevents the buildup of active antimicrobial materials in the environment. We expect that the presented Trojan supramolecular strategy may open up a new paradigm in the fight against bacterial resistance.



KEYWORDS: *Trojan molecule, drug resistance, antibacterial, antibiotics, supramolecular assembly*

1. INTRODUCTION

Since the discovery of penicillin in 1928, various antibiotics have been used globally as life-saving drugs in the treatment of disease caused by bacterial infection.[1] Currently, antibiotics have expanded to many fields, such as breeding,[2] agriculture,[3] and sewage treatment.[4] The abuse of antibiotics has resulted in the emergence of drug resistance due to the accumulation of antibiotics in the environment, which triggers the mutation and evolution of bacteria.[5−7] In recent decades, numerous campaigns have been launched to counteract the increasing drug resistance of bacteria by decreasing the inappropriate use of antibiotics,[8−14] but limited progress has been achieved due to the extremely high dependence of modern society on antibiotics. Therefore, there is an urgent need for unconventional strategies to fight against bacterial resistance.

The bacterial cell wall is the first barrier that protects them from being attacked by external drugs.[15] Strong interactions between the drug and the bacterial cell wall are crucial for efficient bactericidal performance. Since the wall is generally negatively charged, molecules carrying positive charges, such as quaternary ammonium amphiphiles, are widely contained in conventional bactericidal drugs.[16−18] However, mutation of the bacteria may occur if amphiphiles that can directly kill the bacteria are built-up in the environment. To avoid the buildup of antibiotics, switchable drugs have been designed.[8,19−22] However, the research on these switchable drugs focuses only on the on−off ability of the drugs, and little attention has been paid to the interaction between the bacterial cell wall and the drugs. The low affinity of the drug to the bacterial cell wall requires a high concentration of antibiotics to achieve the desired on−off bactericidal performance. This high concentration has the risk of triggering bacterial resistance. Therefore, an ideal on−off antibiotic should have a very strong interaction with bacteria such that a small dose of the drug is sufficient for efficient antibacterial activity. To this end, we propose a Trojan supramolecular strategy to design a drug that has strong affinity to the bacterial cell wall. Because the bacterial cell wall usually composes a large amount of glycosyl groups in peptidoglycan,

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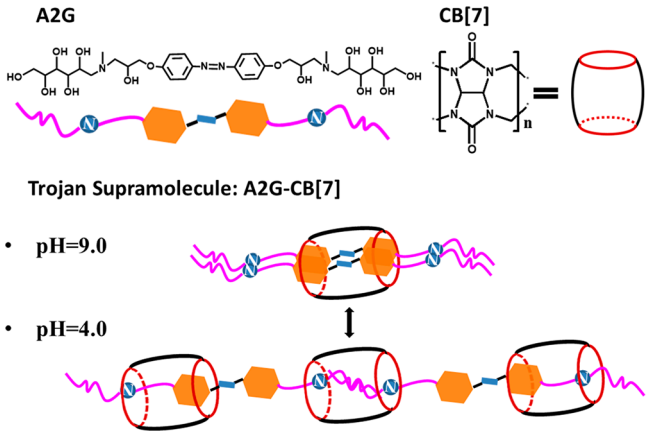
the bacteria have a strong ability to form hydrogen bonds with molecules with similar structures. In this work, we designed a bola-amphiphile bearing two glycosylamine heads to ensure strong affinity to the bacterial cell wall.[23−25] The azobenzene group is introduced between the two glycosylamine heads to act as a photoswitch.[26] Furthermore, the nitrogen atoms in the glycosylamine head work as pH switches in the bactericidal process. The combination of the pH and photoswitches significantly enhances the bactericidal efficiency. To avoid the stationary poisonousness of the Azo groups to bacteria,[11,27] the Azo moiety is threaded into the cavity of CB[7] to form a Trojan supramolecule of A2G-CB[7]. This Trojan supramolecule is harmless to bacteria under weak basic conditions of pH 9.0 but becomes drastically bactericidal at pH 4.0 and under 365 nm UV irradiation due to the protonation of the glycosylamine head and the sliding of the CB[7] from the Azo moiety. The double switches of pH and UV help to reduce the MIC_{50} value to only about one tenth of that of previously reported antibiotics. The bacteria-killing behavior stops when the UV irradiation is removed and when the pH is raised to a weak basic level. We expect this Trojan supramolecular strategy to represent a new weapon to fight against drug resistance.

2. RESULTS AND DISCUSSION

A2G is synthesized in our lab (see Supporting Information and Scheme 1). The pK_b of A2G in water is 5.1 so that the aqueous solution of A2G displays pH-dependent self-assembly behavior. The network is observed at pH 4.0, whereas spherical particles are formed at pH above neutral (Figure S1). In the following section, we show that this pH-dependent self-assembly plays a significant role in the drug's bactericidal ability. Because the A2G molecules in solution can be 100% electrical-neutral at pH above 8.9 (Figure S2), a weak basic pH 9.0 is chosen for the following pH-dependent bactericidal studies. However, the large size of glycosylamine makes the molecular packing of the Azo groups in the self-assembled structures not very tight; thus, A2G is UV active regardless of the solution pH (Figure S3). ^{1}H NMR measurements suggest the presence of 10% cis-form A2G under daylight in neutral solution (Figure S4).

Scheme 1. Supramolecular Assembly of A2G with CB[7] and the Transformation of the Supramolecule upon Varying pH



To qualify the drug's antibacterial ability, the most robust Gram-negative bacteria, *E. coli*, was treated with an aqueous solution of A2G. Figure S5 shows that more than 80% *E. coli* was killed at C_{A2G} = 10 μM regardless of the solution pH. The pH-independent bactericidal ability of A2G indicates that the toxicity is mainly a result of the presence of the azobenzene structure. Since *cis*-Azos are reported to have stronger bactericidal ability,[12] UV irradiation was applied, and the enhanced killing rate was found to be close to 100% at the same concentration of A2G. These data confirm that A2G is an excellent antibiotic. At this stage, A2G does not display satisfactory on−off antibacterial ability regulated by pH (Figure S6).

To endow the on−off bactericidal ability to the A2G molecule, we decide to create a "Trojan horse" by sheltering the poisonous azobenzene group into the cavity of CB[7] since the surface of CB[7] is full of N and C═O, which are biocompatible.[28] ^{1}H NMR measurements (Figure S7) reveal that the Azo group signals vanish upon the addition of CB[7] into the aqueous solution of A2G. Meanwhile, the signal of CB[7] occurs, indicating the formation of a host−guest complex between A2G and CB[7]. The signal of protons on the glycol groups shifted toward the upper field, indicating the breaking up of the hydrogen bonds between glycol groups. The signals of the Azo group disappear completely as the molar ratio of A2G:CB[7] is 2:1 at pH 9.0 and 2:3 at pH 4.0 (Figure S8). Similar to these results, ITC (isothermal titration calorimetry) experiments (Figure 1a, b) reveal that the binding ratio between A2G and CB[7] is 2:1 and 2:3 at pH 9.0 and pH 4.0, and the binding constant is approximately 1.0×10^3 M^{-1} and 6×10^3 M^{-1}, respectively. This means that every two A2G molecules may thread into one CB[7] where their Azo groups are fully sheltered in the cavity of CB[7] at basic pH (Scheme 1). In contrast, at acidic pH, the CB[7] molecule slides to the glycol moiety of A2G because the positive charges on N of the glycol groups may interact with CB[7].[15,29,30] With two glycol heads from two A2G molecules sharing one cavity of CB[7], the Azo group of A2G is exposed outside. This change can be further confirmed by ^{1}H NMR measurements, which clearly reveal the occurrence of Azo signals at acidic pH (Figure S9). The sliding of the CB[7] molecule along the A2G molecule is further reflected in the UV−vis spectra. Figure 1c shows that the solution color gradually changes from yellow to red as the pH decreases, while it reversibly changes from red to yellow as the pH increases. The A2G-CB[7] supramolecule remains UV active. Figure 1d shows the typical cis−trans transition of the Azo moiety observed in the A2G-CB[7] system upon 365 nm UV irradiation. The pH and UV dual responsiveness indicates that the A2G-CB[7] system could be used as a Trojan supramolecule for antibacterial applications.

Next, we examined the antibacterial performance of the pH and UV dual-responsive Trojan supramolecule. Figure 2 reveals that as basic A2G-CB[7] solution is added to the system of *E. coli* with OD_{600} = 1, its colony increases with time at the same rate as the control, confirming that the Trojan supramolecule is benign to *E. coli* under weak basic conditions. However, in acidic pH 4.0, a strong antibacterial activity was observed, and the MIC_{50} value was approximately 5 μM. UV irradiation can further reduce the MIC_{50} value from 5 μM to <1 μM. UV irradiation alone only exhibits slight bactericidal ability, whereas the combination of acidic pH and UV irradiation generates the highest bactericidal performance. To further demonstrate the effectiveness of this bactericidal drug,

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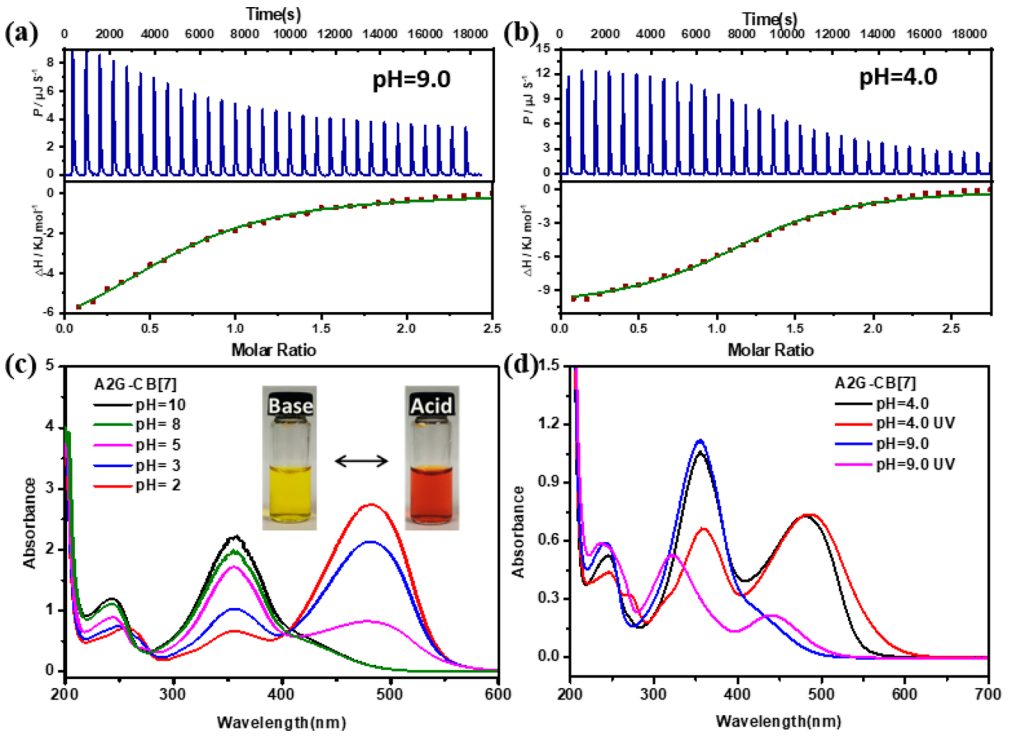

Figure 1. (a,b) Isothermal titration calorimetry (ITC) results for the A2G-CB[7] system at (a) pH 4.0 and (b) pH 9.0. (c,d) UV−vis spectra of A2G-CB[7] (0.5 mM) (c) mediated by pH; (d) pH = 4.0 and 9.0 under UV (λ = 365 nm) irradiation.

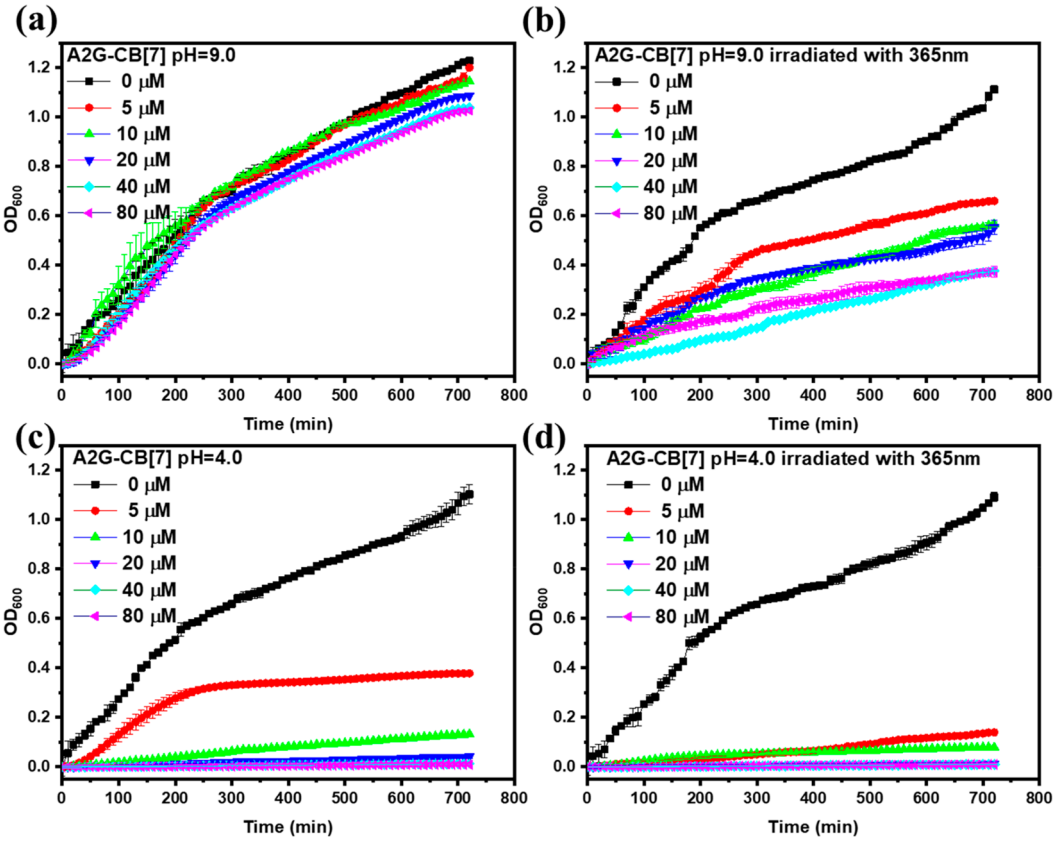

Figure 2. Bacterial growth curves of *E. coli* at increasing concentrations of A2G-CB[7] at pH = 9.0 (a) with and (b) without 365 nm UV irradiation and at pH = 4.0 (c) with and (d) without 365 nm UV irradiation. Error bars show standard deviation calculated from measurements in triplicate. The concentration of *E. coli* is OD_{600} = 1.

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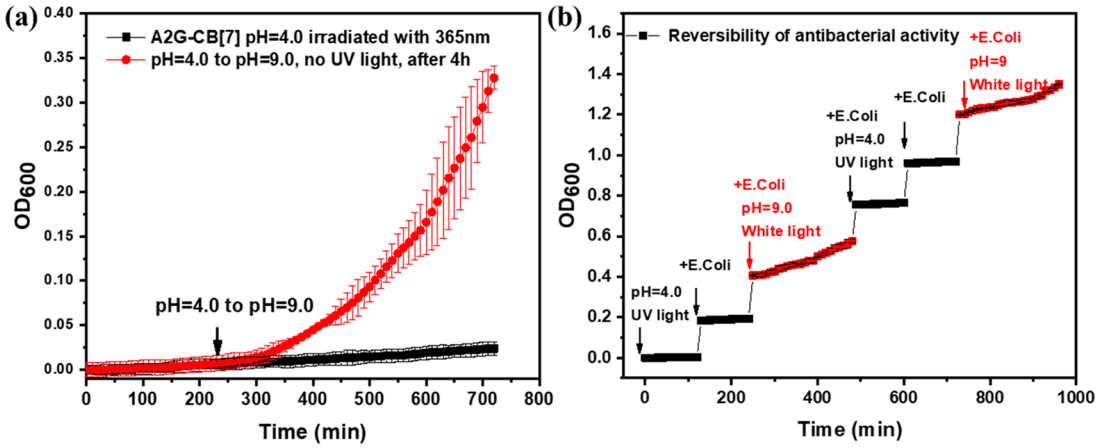

Figure 3. (a) Bacterial growth curves of *E. coli* under different pH. Black line: 10 μm A2G-CB[7] at pH 4.0 under 365 nm UV irradiation. Red line: 10 μm A2G-CB[7] at pH 9.0 without 365 nm UV irradiation. (b) Bacterial growth curves of *E. coli* treated with 10 μm A2G-CB[7] at pH 4.0 under 365 nm UV light, and then additional *E. coli* was added for cultivation. After 2 h, the pH was turned alkaline, and *E. coli* was added again. This process was repeated twice. Error bars show standard deviations calculated from measurements in triplicate. The original concentration of *E. coli* is OD_{600} = 1, and the concentration of *E. coli* in each addition is OD_{600} = 0.2.

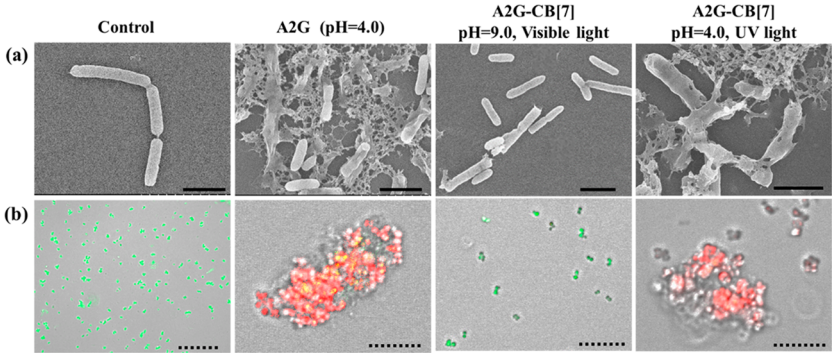

Figure 4. (a,b) SEM and CLSM images of *E. coli* before and after incubation with A2G and A2G-CB[7] for 15 min. Upper row: SEM images. Scale bars: 10 μm. Lower row: CLSM images. Scale bars: 50 μm. The concentration of *E. coli* is OD_{600} = 1.

we performed colony-forming unit (CFU) reduction of A2G-CB[7] with both acidic pH and UV irradiation. As shown in Figure S10, the same antibacterial performance of this dual-responsive Trojan supramolecule could be detected, and the MIC_{50} value of A2G-CB[7] with UV irradiation in acidic pH 4.0 can drop as low as 0.1 μM. This MIC_{50} value is extremely low for an on−off bactericidal drug. To the best of our knowledge, literature reports of similar MIC_{50} level were made on a low *E. coli* colony density of OD_{600} = 0.1.[9,31−35]

One of the main reasons for drug resistance is the accumulation of drugs in nature, so that the surviving bacteria can mutate to resist them.[36,37] To test whether the Trojan antibiotics can be switched into a benign state *in situ*, the pH is switched to basic conditions, and the UV light is removed. Figure 3a shows that rebound of the bacterial population occurs immediately, verifying the loss of bactericidal ability. This means that the antibiotic activity can be completely stopped by switching pH and UV light after each bactericidal treatment, thus optimally reducing the possibility for bacteria to adapt to the accumulated drugs. Figure 3b shows this switching effect more clearly. As a new colony of *E. coli* was added to a system treated with Trojan antibiotics at pH 4.0 and UV irradiation, no growth of these newly added *E. coli* was observed, and their growth occurred immediately after the system was switched to pH 9.0 and natural light. This scenario can occur repeatedly, suggesting that this Trojan antibiotic indeed works stably in on−off bacteria-killing behavior.

To further verify the bactericidal ability of the Trojan supramolecule, confocal laser scanning microscopy (CLSM) and scanning electron microscopy (SEM) measurements (Figure 4) were performed to study the variation of the microstructure of the bacteria. Two fluorescent nucleic acid staining agents, SYTO9 and propidium iodide (PI), were employed to facilitate CLSM observations.[38] SYTO9 penetrates both live and dead bacteria, while PI penetrates dead bacteria with damaged membranes and quenches SYTO9 fluorescence. Figure 4 shows that green fluorescence of SYTO9 is observed for *E. coli* cultivated with the Trojan supramolecule at pH 9.0, suggesting that the Trojan supramolecule does not harm the bacteria at pH 9.0 under natural light, whereas it breaks the wall of the *E. coli* at pH 4.0 under 365 nm UV irradiation, which is confirmed by the occurrence of red fluorescence. In SEM images, *E. coli* was attracted to the network structure formed by A2G or A2G-CB[7] in acid (Figure S11), and their walls were broken, leading to collapsed structures and merging of their inner contents. It is possible that the concentrated positive charges interact strongly with the negatively charged surface of bacteria, so that the A2G and A2G-CB[7] in an acid state have a strong affinity to the bacterial cell wall, which facilitates the unprotected Azo moiety penetrating the bacterial cell wall. However, A2G-CB[7] in the

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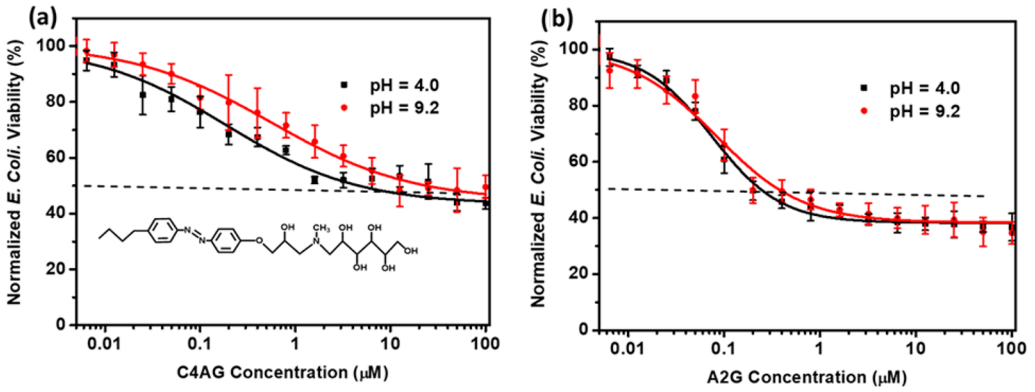

Figure 5. *E. coli* viability after incubation with different concentration of C4AG (a) and A2G (b). The *E. coli* solution was prepared in base (pH = 9.0) and acid (pH = 4.0) conditions, and overnight cultures of *E. coli* were diluted to an optical density at 600 nm (OD_{600}) of 2. The molecular structure of C4AG is given as the inset in (a).

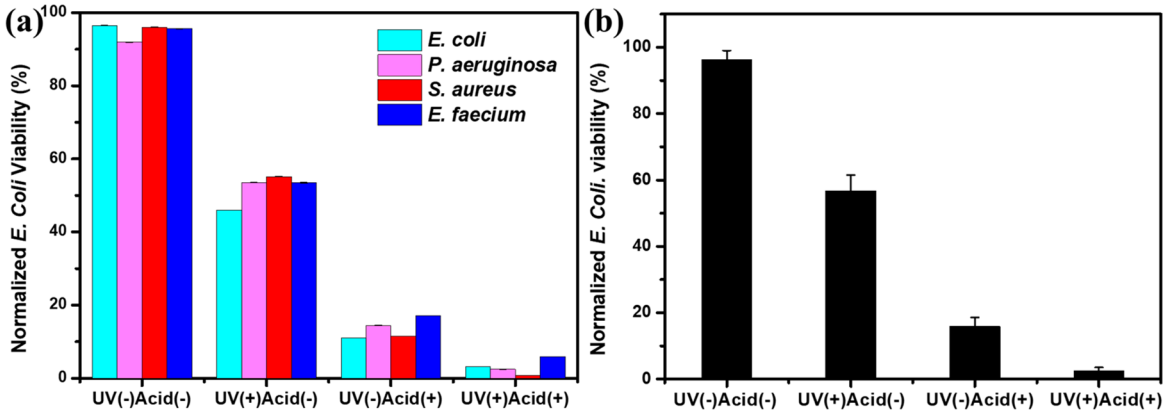

Figure 6. (a) Normalized *E. coli* viability in the presence of A2G-CB[7] at 10 μM with (+) and without (−) acid and UV (λ = 365 nm) irradiation: for *E. coli* ATCC8099; *P. aeruginosa* JCM5803; *S. aureus* ATCC25923; *E. faecium* ATCC35663. Standard deviations were calculated from triplicate experiments. The concentration of each bacteria is OD_{600} = 1. (b) Normalized *E. coli* viability in model polluted water in the presence of 10 uM A2G-CB[7].

basic state tends to form a spherical structure (Figure S11) without charges, which has no strong interaction with the *E. coli* cell wall.

The bola-type structure of the Trojan supramolecule is crucial for the high efficiency of its bactericidal effects. As A2G is replaced by C4AG (inset in Figure 5a),[39,40] which has one sugar-glycol head, the bactericidal ability is significantly reduced. In Figure 5, we show that for the same bacteria colony (OD_{600} = 2) and the same drug concentrations C4AG (10 μM) is only able to kill 25% of the bacteria (Figure 5a), whereas A2G kills 64% of the bacteria (Figure 5b). This indicates that the bola-type head has a synergistic behavior in promoting the antibacterial ability. Obviously, glycosylamine has strong affinity to the bacterial cell wall, and it is easy to form a transmembrane structure[41] to break the bacterial cell wall.

The Trojan supramolecule displays wide spectrum bactericidal ability. Figure 6a shows that both Gram-negative and Gram-positive bacteria died as the Trojan antibiotics were activated under acidic pH and 365 nm UV light. The growth of *E. coli* (Gram-negative bacteria), *P. aeruginosa* (Gram-negative bacteria), *S. aureus* (Gram-positive bacteria), and *E. faecium* (Gram-positive bacteria) can be partly inhibited if only the single switch of UV [UV(+)Acid(−)] or pH [UV(−)Acid(+)] was on, whereas a most efficient inhibition can be achieved as both switches were on [UV(+)Acid(+)], confirming that both the positive charges and the UV irradiation are beneficial for the excellent switching behavior of the Trojan supramolecule. It is noteworthy that the pH/UV dual-activated antibacterial effect of A2G-CB[7] remains in polluted water. We built an artificial polluted water model according to the literature method.[42] It was found that the A2G-CB[7] supramolecule can inhibit ∼97.6% *E. coli* in acidic polluted water after receiving 365 nm UV irradiation (Figure 6b). This inhibition rate is significantly higher than those receiving only one treatment (∼84.2% in acidic polluted water and ∼43.3% under UV irradiation) or without any treatment (∼3.8% in neutral polluted water and without UV irradiation). Therefore, the A2G-CB[7] was feasible for potential antibacterial application in real samples.

3. CONCLUSIONS

In summary, we have shown a proof of concept for the use of Trojan antibiotics with dual pH and light switches to fight against drug resistance. This Trojan antibiotic is constructed via host−guest chemistry between a bola-amphiphile containing glycosylamines and an Azo spacer group. Upon complexation with CB[7], the surface of the sugar is fully covered with CB[7], which is very close to the wall components of most bacteria. In this way, the Trojan antibiotic is benign to bacteria,

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while it immediately transforms into a bactericidal state when both the pH and UV switches are turned on. This dual switch significantly enhances the bactericidal efficiency, and an extremely low MIC_{50} value of 0.1 μM is acquired. This low MIC_{50} value, together with the efficient on−off switches, is expected to avoid the accumulation of antibiotics in the environment and to reduce the chance for bacteria to mutate. We expect the present strategy to open a new paradigm for the design of new generations of antibiotics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsabm.8b00648.

Experimental section and the supplemental figures (PDF)

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Author Contributions

⊥Xuejiao Wang and Yuxin Liu contributed equally. The manuscript was written through contributions by all the authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CB[7], cucurbituril [7]
Azo, azobenzene
A2G, Azo molecule bearing two glycosylamines

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