Formation of Water-Soluble Pincer Silver(I)−Carbene Complexes: A Novel Antimicrobial Agent

Abdulkareem Melaiye,[†] Richard S. Simons,[†] Amy Milsted,[‡] Francesco Pingitore,[†] Chrys Wesdemiotis,[†] Claire A. Tessier,[†] and Wiley J. Youngs*[,†]

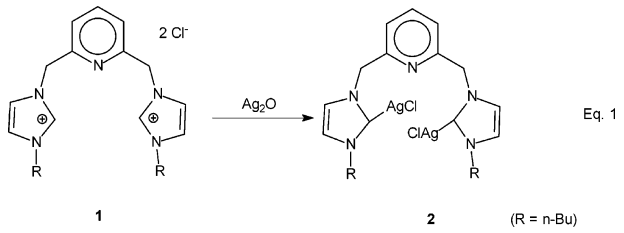
Departments of Chemistry and Biology, University of Akron, Akron, Ohio 44325

Received May 29, 2003

Silver(I)−2,6-bis(ethanolimidazolemethyl)pyridine hydroxide (**4a**) and silver(I)−2,6-bis(propanolimidazolemethyl)pyridine hydroxide (**4b**) are water-soluble silver(I)−carbene complexes that were synthesized in high yield by reacting silver(I) oxide with N-substituted pincer ligands **3** (**a** = 2,6-bis(ethanolimidazoliummethyl)pyridine diiodide, **b** = 2,6-bis(propanolimidazoliummethylpyridine)pyridine dibromide). The X-ray crystal structure of **4a** is a one-dimensional linear polymer, whereas the mass spectroscopy confirms a monomer in the gas phase. A change in the anion of **4a** from a hydroxide to a hexafluorophosphate formed a silver(I)−carbene complex **4c** that is dimeric in structure and insoluble in water. The bactericidal activities of the water-soluble silver(I)−carbene complexes were found to be improved over that of silver nitrate.

Introduction

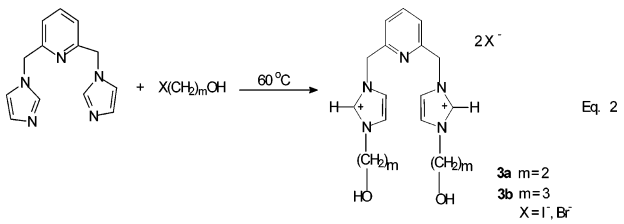
Silver has been recognized as an antimicrobial agent for burn wounds for decades.[1] The most widely used reagents have been silver nitrate and silver sulfonamides. In particular, silver sulfadiazine has been used in the treatment of burn wounds.[2] It has been assumed that the slow release of silver at the area of the superficial wound is responsible for the prevention of infection as well as aiding in the process of healing. It has also been recognized that the usefulness of silver sulfonamides has some limitations. In particular, sulfonamide-resistant organisms have been reported, limiting the clinical usefulness of silver sulfadiazine.[3] Although there have been considerable advances in wound management, infections are well-documented to be the leading cause of diseases in injured patients.[4] The pioneer work on metal *N*-heterocyclic carbenes by Ofele[5] and Wanzlick[6] in the 1960s and the isolation of free stable crystalline *N*-heterocyclic carbene by Ardunego in the early 1990s[7] have generated a wide interest in carbene chemistry in the past decade. Carbenes are known to be strong Lewis bases and excellent nucleophiles that bind metals better than phosphines.[8−10] Carbenes have been proposed to bind almost all metals across the spectrum of the periodic table with better stability than phosphines.[10,11] There are relatively few publications on silver−carbene complexes and there applications, aside being used as metal transferring agents. We have reported silver(I) *n*-pincer-type heterocyclic biscarbene complexes,[12−14] the most recent being the synthesis of bis(silver(I)−carbene) complex **2** of the pincer ligand 2,6-bis(*n*-butylmethylimidazoliummethyl)pyridine **1** (R = Bu)[15] (eq 1). It was envisioned that R could be tailored to provide solubility of **2** in aqueous media and aqueous solutions of **2** would have use as antimicrobial agents.



We report herein the synthesis of **3** (R = CH_2CH_2-OH, $CH_2CH_2CH_2OH$) and the water-soluble silver complexes **4a** and **4b**. To our knowledge, silver−carbene complexes have not been previously evaluated as antimicrobial agents. We report herein that **4a** and **4b** are useful antimicrobial agents.

Results and Discussion

Pincer ligands **3a** and **3b** are easily prepared by the reaction of 2,6-bis(imidazolemethyl)pyridine[16] with 2-iodoethanol or 3-bromopropanol respectively (eq 2). The



IR spectra show the O−H stretching vibration at 3325 cm^{-1}. The FAB-MS spectra obtained from **3** in nitrobenzyl matrixes showed [**3a**][I]$^+$ ($C_{17}H_{23}N_5O_2I$) at *m*/*z* 456 and [**3b**][I]$^+$ ($C_{19}H_{27}N_5O_2Br$) at *m*/*z* 436.

Pincer ligands **3a** and **3b** readily react with Ag_2O in aqueous methanol or in water to form the silver−bis(carbene) pincer complex **4a** and **4b** in high yield (eq 3).

The formation of **4a** and **4b** is confirmed by the loss of the imidazolium proton at 9.13 ppm for **4a** and 9.36 ppm for **4b** in the ^1H NMR spectra and the appearance

* To whom correspondence should be addressed. Fax: 330-972-7370. E-mail: youngs@uakron.edu.
† Department of Chemistry.
‡ Department of Biology.

10.1021/jm030262m CCC: $27.50
Published on Web 01/14/2004

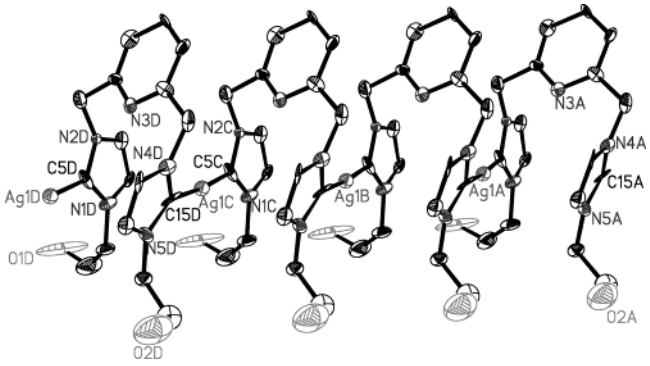
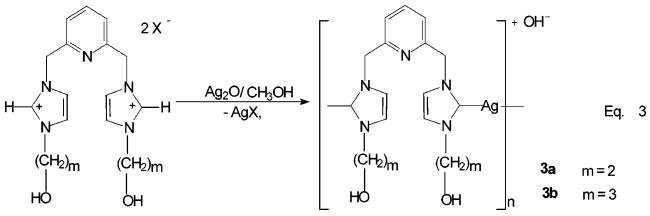


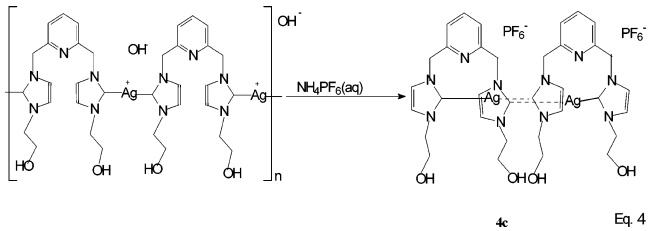
Figure 1. Thermal ellipsoid plot of **4a** with the thermal ellipsoid drawn at 50% probability level. Hydrogen atoms attached to carbon have been omitted for clarity.



of a resonance at 181 ppm in the ^{13}C NMR spectra. Further evidence for the formation and structure of **4a** is provided by X-ray crystallography.

Colorless crystals of **4a** were obtained by slow evaporation of a mixture of methanol and acetonitrile solution. Interestingly, the iodide ions of **3a** are completely replaced by hydroxide ions in **4a**. In the solid state, **4a** exists as a one-dimensional linear polymer (Figure 1). The geometry at the silver atoms is nearly linear with a C5−Ag1−C15 bond angle of 174.7(4)° and Ag1−C5 and Ag1−C15 bond distances of 2.108(11) and 2.060-(13) Å, respectively. Mass spectroscopy suggested that in solution and in the gas phase **4a** exists as a monomer, whereas X-ray crystallography shows that **4a** is polymeric.

The anion exchange reaction of **4a** with aqueous ammonium hexafluorophosphate results in the formation of **4c** (eq 4). In the solid state, **4c** exists as a dimer



(Figure 2). Table 1 gives a summary of the crystal data of **4a** and **4c**. The geometry of the silver atoms is nearly linear, with the following bond angles and lengths: C32−Ag1−C5, 175.7(4)°; C22−Ag2−C17, 174.6(3)°; Ag1−C32, 2.070(9) Å; Ag1−C5, 2.091(9) Å; Ag2−C22, 2.064-(9) Å; Ag2−C17, 2.074(8) Å. The nature of the anions is significant to the structural changes of **4a** versus **4c**, and the choice of anion has a pronounced effect on the solubility of **4**. For example, **4a** is soluble in aqueous media, whereas **4c** is not.

The usefulness of **4a** and **4b** as antimicrobial agents was evaluated. The test organisms (*Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa*)

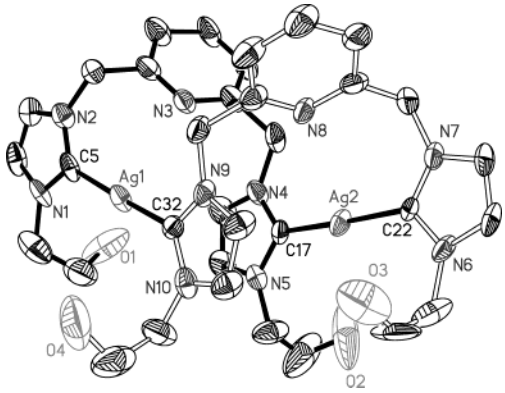


Figure 2. Thermal ellipsoid plot for **4c**, with the thermal ellipsoid draw at 50% probability level. Hydrogen atoms attached to carbon are omitted for clarity.

Table 1. Sensitivity Test of the Silver Compounds in Inhibiting Bacterial Growth

tested compds (w/v)	Ag (μg/mL)[b]	diameter of the zone of inhibition[a]		
		E. coli	S. aureus	P. aeruginosa
$AgNO_3$ (0.5%)	3176	11.38	10.88	11.00
4a (1.31%)	3130	11.50	11.00	12.00
4b (1.42%)	3195	11.58	10.67	10.25
4a (0.50%)	1195	10.13	10.00	11.13
4b (0.50%)	1125	10.00	9.00	12.00
3a (0.50%)		6.00	6.00	6.00
3b (0.50%)		6.00	6.00	6.00

[a] The diameter of the zone of inhibition is in mm, with filter paper disk diameter of 6 mm. [b] The amount of silver (μg) per mL for each silver compound was calculated as (molecular mass of Ag/formula wt of compound) x wt %.

were laboratory strains used to test a range of concentrations of the silver compounds for both the growth inhibition and minimum inhibitory concentration (MIC) determination. In both antimicrobial test methods, silver nitrate was the reference standard used, whereas the pincer ligands served as control.

A modified Kirby−Bauer method was used to obtain the sensitivity data as presented in Table 2. A constant number (volume) of bacteria were spread on the surface of a nutrient agar plate to obtain the lawn of organisms. A filter paper disk (6 mm diameter) was soaked with 20 μL of a solution of the silver compounds at a known concentration and placed on the lawn of organisms. The antimicrobial activity of the silver compounds was determined after an overnight incubation by measuring the diameter of the clear zone of growth inhibition of the organism around the filter disk.

Our testing by the modified Kirby−Bauer method confirmed **4a** and **4b** have antimicrobial properties at a level comparable to silver nitrate, as shown in Table 2, while the pincer ligands themselves have no activity. A limitation of the Kirby−Bauer method was observed, when an approximately 2-fold increase in the concentration of the test silver solutions showed no significant change in the measured zone of inhibition. Lajos et al. reported a similar trend for the same set of organisms when a range of silver nitrate concentration was tested.[17]

Table 2. MIC Result of the Silver Compounds (Less Silver Chloride)[a]

test compds	Ag (mg/mL)	E. coli		P. aeruginosa		S. aureus	
		day 1	day 2	day 1	day 2	day 1	day 2
3a	1186	−	−	−	−	−	−
1 DF		−	+	−	−	−	+
2 DF		−	+	−	+	+	
3 DF		+		+		+	
4 DF		+		+		+	
3b	1125	−	−	−	−	−	−
1 DF		−	+	−	+	−	+
2 DF		−	+	−	+	−	
3 DF		+		+		+	
4 DF		+		+		+	
$AgNO_3$	3176	−	+	−	+	+	
1 DF		+		+		+	
2 DF		+		+		+	
3 DF		+		+		+	
4 DF		+		+		+	

[a] 0.5% w/v each of the silver compounds was used. DF is the dilution factor (1 mL). 20 μL per day of freshly grown organism was added to each culture. + = growth, − = no growth.

The diffusibility of the silver solution might have been limited by the formation of secondary silver compounds (especially silver chloride) in the test media.

The MIC is a standard microbiological technique used to evaluate the bacteriostatic activity of antimicrobial agents. In this case, the MIC was based on the total amount of silver available and not a measure of the concentration of silver ions.[18] Upon dissolving the silver complexes in the culture medium (LB broth), a precipitate of AgCl was observed in all samples. A dilution series of the supernatant portion of the silver complex solutions were prepared in LB broth, with the addition of constant volume of freshly grown organism (20 μL) per day. The MIC was obtained by visual inspection of the turbidity of the solution, as reported in Table 3 (see Supporting Information). Compounds **4a** and **4b** showed better bacteriostatic activity than silver nitrate, even at much lower concentration (Table 3). This can be attributed to the availability of more silver in the supernatant solutions of **4a** and **4b** than silver nitrate. Thus, **4a** and **4b** react more slowly with the chloride ions than silver nitrate in the growth medium. The contribution of the pincer ligands is significant toward reducing the formation of silver chloride in the LB broth solution compared to silver nitrate. Thus, **4a** and **4b** appear more stable than silver nitrate in the LB broth solution containing 0.1% chloride ions, a value that is close to the physiological amount of sodium chloride (0.15 M).

This is an excellent property of both **4a** and **4b** when considering silver compounds for in vivo application. It is important to state that, although equal weights of silver compounds were used, the theoretical amount of silver ions released by **4a** and **4b** is about 2.7 times lower than that from the quantity of silver nitrate used.

When the MIC test was repeated in the presence of insoluble silver chloride, the activity of the silver compounds was enhanced, with silver nitrate performing better, as shown in Table 4 (see Supporting Information). It has been previously reported that the presence of chloride contributes to the toxicity of silver to sensitive strains of organisms.[19]

The amount of silver and the rate of release are known to be factors that contribute to the antimicrobial activity of silver compounds.[20] The MIC of **4a** and **4b** was observed to be better than that of silver nitrate using about the same amount of silver for each of the test compounds, as shown in Table 5 (see Supporting Information). The minimum lethal concentration was determined to evaluate the bacteriocidal properties of **4a** and **4b**. The clear (no growth) portion of the culture media with the lowest Ag compound concentration was used, by streaking 0.01 mL of the solution on agar plate using a sterilized loop followed by incubation at 37 °C for 24−48 h. The colonies were visually counted, with the end point of the minimum bacteriocidal concentration (MBC) as no growth on the agar plate. Our test compounds showed an improved bacteriocidal effect compared to silver nitrate up to day 7 of incubation and MBC test, with no growth observed after the day 10 of incubation and testing for the silver compounds. This is interesting considering the fact that freshly grown organisms were added per day to the culture media containing the silver compounds throughout the incubation period. The bacteriocidal and bacteriostatic properties of **4a** and **4b** are attributed to its slow decomposition of the Ag−C donor (carbene) ligand bond over time to silver metal, silver ion, and AgCl and to their solubility in water. We observed a slow decomposition of **4a** and **4b** in aqueous solution after 24 h of standing in light and formation of silver mirror after 18 days on standing and exposure to light.

Conclusion

In conclusion, the alkanol *N*-functionalized silver−carbene complexes **4a** and **4b** are soluble in aqueous media. The choice of anion has a pronounced effect on the solubility of **4** and its structure in the crystal forms. It has proved to be a useful antimicrobial agent, and its solubility in water makes it an excellent silver compound for in vivo applications. The solubility and stability of silver complexes in chloride solution are key factors that limit the use of silver complexes for in vivo application. The use of Ag−C donor (carbene) compounds has demonstrated its potential as a therapeutic agent.

Experimental Section

Acetone, methanol, acetonitrile, silver(I) oxide, silver nitrate, ammonium hexafluorophosphate, 3-bromopropanol, and 2-iodoethanol were purchased from ACROS. LB Broth Miller (DIFCO) and Bacto-agar (DIFCO) where all used without further purification. Infrared spectra were recorded on Nicolet Nexus 870 FT-IR spectrometer. The ^{1}H and ^{13}C NMR data were recorded on a Varian Gemini 300 MHz instrument, and the spectra obtained were referenced to the deuterated solvents. Mass spectroscopy data were recorded on a VG AutoSpec EBQ mass spectrometer equipped with EI, CI, and FAB ion sources.

Synthesis of 2,6-Bis(ethanolimidazoliummethyl)pyridine Diiodide (3a). A neat solution of 2,6-bis(imidazolmethyl)pyridine (0.24 g, 1.0 mmol) and 2-iodoethanol (0.67 g, 4.0 mmol) was stirred at 60 °C for 8 h. After cooling to ambient temperature, acetone (60 mL) was added and stirring was continued for 2 days. Filtration yielded **3a** as a white precipitate. Yield: 0.55 g, 0.95 mmol, 95%. Mp: 134−136 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.75 (t, 4 H, CH_2CH$_2$OH), 4.28 (t, 4 H, CH$_2$CH_2OH), 5.19 (s, 2 H, CH$_2$CH$_2$OH), 5.57 (s, 4 H, CH$_2$), 7.47 (d, 2 H, J = 7.8 Hz, m-pyr), 7.69 (s, 2 H, NC(H)CH), 7.77 (s, 2 H, NC(H)CH), 7.96 (t, 1 H, J = 7.8 Hz, p-pyr), 9.18 (s, 2 H, NC(H)N). ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.7, 52.6, 59.2,

122.1, 122.6, 123.0, 136.9, 138.9, 153.6. FAB-MS *m*/*z*: 328 [M^+], 456 [$M - I^+$]. FT IR (Nujol, cm^{-1}): 3356 (vs), 3091, 1601, 1565, 1437, 1344, 1059, 762, 656.

Synthesis of Silver(I)−2,6-Bis(ethanolimidazolemethyl)pyridine Hydroxide (4a). A methanol (70 mL) solution of **3a** (0.33 g, 1.0 mmol) and Ag_2O (0.23 g, 1.0 mmol) was stirred at ambient temperature for 2 h. The solution was filtered through Celite, and the volatile components were removed under reduced pressure, yielding **4a** as a tan solid. Yield: 0.4 g, 0.8 mmol, 84%. Mp: 163−165 °C (dec). Anal. Calcd for $C_{17}H_{21}AgO_2N_5$: Ag, 23.79; C, 44.93; H, 5.07; N, 15.42. Found: Ag, 23.66; C, 44.49; H, 4.71; N, 14.48. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (t, 4 H, CH_2CH$_2$OH), 4.04 (t, 4 H, CH$_2$CH_2OH), 5.13, (s, 2 H, CH$_2$CH$_2$OH), 5.14 (s, 4 H, CH$_2$), 7.07 (d, 2 H, J = 7.8 Hz, m-pyr), 7.23 (s, 2 H, NC(H)CH), 7.26 (s, 2 H, NC(H)CH), 7.65 (t, 1 H, J = 7.8 Hz, p-pyr). ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.0, 55.6, 61.5, 121.9, 122.1, 122.9, 139.5, 156.1, 181.1. FT IR (Nujol, cm^{-1}): 3227, 3152, 2935, 1621, 1450, 1418, 1340, 1235, 1075, 762, 657. FAB-MS *m*/*z*: 328 [M^+], 454 [M^+].

Synthesis of 2,6-Bis(propanolimidazoliummethyl)pyridine Dibromide (3b). The synthesis procedure was same as for **3a**, with 2,6-bis(imidazolmethyl)pyridine (0.24 g, 1.0 mmol) and 3-bromopropanol (0.56 g, 4.0 mmol) being stirred at 60 °C for 8 h. After cooling at ambient temperature, acetone (60 mL) was added and the mixture was stirred for at least 18 h. Filtration gave a white solid. Yield: 0.48 g, 0.93 mmol, 93%.

Mp: 94−96 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.50 (t, 4 H, CH_2CH$_2$CH$_2$OH), 1.95 (q, 4 H, CH$_2$CH_2CH$_2$OH), 3.42 (t, 4 H, CH$_2$CH$_2$CH_2OH), 4.31 (t, 2 H, CH$_2$CH$_2$CH$_2$OH) 5.57 (s, 4 H, CH$_2$), 7.07 (d, 2 H, J = 7.8 Hz, m-pyr), 7.23 (s, 2 H, NC(H)CH), 7.26 (s, 2 H, NC(H)CH), 7.65 (t, 1 H, J = 7.8 Hz, p-pyr). ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.3, 46.5, 52.6, 57.0, 122.1, 122.4, 123.1, 136.9, 138.9, 153.7.

FT IR (Nujol, cm^{-1}): 3345 (vs), 3037, 3135, 1598, 1559, 1452, 1156, 1091, 1076, 772, 645. FAB-MS *m*/*z*: 357 [M^+], 436 [$M - Br^+$].

Synthesis of Silver(I)−2,6-Bis(propanolimidazolemethyl)pyridine Hydroxide (4b). The synthesis procedure was same as for **4a,** with **3b** (1 mmol) and Ag_2O (1 mmol) being dissolved in methanol (70 mL) and stirring at ambient temperature for 2 h. The solution was filtered through Celite, and the volatile components were removed under reduced pressure, yielding **4b** as a yellow solid, which slowly changed to a tan color solid on long exposure to air. Yield: 0.40 g, 0.86 mmol, 86%. Anal. Calcd for $C_{19}H_{25}AgO_2N_5$: Ag, 22.50; C, 46.93; H, 5.66; N, 14.67. Found: Ag, 22.36; C, 46.85; H, 5.61; N, 14.60. FT IR (Nujol, cm^{-1}): 3304, 3089, 2939, 1739, 1660, 1594, 1459, 1366, 1232, 1077, 761. ^{1}H NMR (300 MHz, D_2O): δ 3.50 (t, 4 H, CH_2CH$_2$CH$_2$OH), 1.86 (q, 4 H, CH$_2$CH_2CH$_2$OH), 3.42 (t, 4 H, CH$_2$CH$_2$CH_2OH), 5.11 (s, 4 H, CH$_2$), 7.00 (d, 2 H, J = 7.8 Hz, m-pyr), 7.15 (s, 2 H, NC(H)CH), 7.20 (s, 2 H, NC(H)CH), 7.60 (t, 1 H, J = 7.8 Hz, p-pyr). ^{13}C NMR (75 MHz, D_2O): 181, 156.1, 139.4, 122.8, 121.8, 57.9, 55.6, 48.6, 33.5. FAB-MS *m*/*z*: 356 [M^+], 456 [M^+].

Synthesis of Dimer Silver(I)−2,6-Bis(ethanolimidazolemethyl)pyridine Hexafluorophosphate (4c). Ion exchange of **4a** (0.50 mmol) was in 5 mL solution of ammonium hexafluorophosphate. The water-insoluble **4c** was rinsed twice with distilled water and crystallized from acetonitrile/methanol.

Yield: 0.50 mmol, 100%. Mp: 162−164 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.76 (t, 4 H, CH_2CH$_2$OH), 4.17 (t, 4 H, CH$_2$CH_2OH), 5.07, (s, 2 H, CH$_2$CH$_2$OH), 5.32 (s, 4 H, CH$_2$), 7.12 (d, 2 H, J = 7.8 Hz, m-pyr), 7.51 (s, 4 H, NC(H)CH), 7.75 (t, 1 H, J = 7.8 Hz, p-pyr). ^{13}C NMR (75 MHz, DMSO-d_6): δ 53.8, 55.5, 60.9, 121.2, 122.4, 122.5, 138.7, 156.1. ^{19}F NMR (282 MHz, DMSO-d_6): δ −70.64 (d, $J_{(FP)}$ = 709.6 Hz, PF_6^-). ^{31}P NMR (121 MHz, DMSO-d_6 external Std H_3PO_4): δ 165.03 (m, $J_{(PF)}$ = 707.9 Hz). FAB-MS *m*/*z*: 434 [M^+], 474 [**3a** − PF_6^-], 328 [**3a**].

Antimicrobial Test. Sterilized LB Broth was measured (5 mL) into a sterile tube. A constant volume (20 μL) of stationary phase pure cultured microorganism (*E. coli*, *P. aeruginosa*, *S. aureus*) was introduced into the tube containing the LB Broth solution. The mixture was cultured overnight, at 37 °C in a shaking incubator.

In the next step, 3 mL of sterile solution of the silver compounds was transferred into a 10 mL sterile tube and marked A. Serial dilution was made to obtain a range of concentrations by transferring 1 mL of the 3 mL silver compound solution into a culture tube containing 2 mL of LB Broth, marked B. A well mixed solution B **(**1 mL) was transferred to a tube containing 2 mL of LB Broth, marked C. The same process was repeated for dilutions D and E.

Determination of Minimum Inhibition Concentration (MIC). The MIC was evaluated by visual inspection of growth/no growth of the above concentrations of the silver compounds marked A−E inoculated with 20 μL of the organisms respectively, after overnight incubation at 37 °C.

Filter Disk Testing. A filter paper disk (6 mm in diameter, Whatmann #3) was soaked with 20 μL of sterile silver solution and placed on a lawn of bacteria of an LB agar plate and incubated overnight at 37 °C. The diameter of clear zone around the filter disk size was measured.

Determination of Minimum Bactericidal Concentration (MBC). Culturing the clear (no growth) media with the lowest Ag compounds concentration was done by streaking 0.01 mL of the solution on an agar plate using a sterilized loop and incubated at 37 °C for 24−48 h. The number of colonies was visually counted, with the end point of the MBC as no growth on the agar plate

X-ray Structure Determination. Crystal data and structure refinement parameters are presented in Table 1. Crystals of **4a** and **4c** were each coated in paraffin oil, mounted on kryo loop, and placed on a goniometer under a stream of nitrogen. X-ray data were collected at a temperature of 100 K on a Bruker Apex CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å). Intensity data were intergrated using SAINT software, and an empirical absorption correction was applied using SADABS. Structures **4a** and **4c** were solved by direct methods and refined using full-matrix least-square procedures. All non-hydrogen atoms were refined with anisotropic displacement.

Acknowledgment. We thank the National Institute of Cancer, National Institute of Health (grant number 1R15 CA096739-01), The University of Akron, and the Ohio Board of Regents for Financial Support. We thank the National Science Foundation (CHE-0116041) for funds used to purchase the CCD Single Crystal X-ray diffractometer used in this work. We wish to express our thanks to Dr. Martha Kory of the Department of Biology, University of Akron, for the strains of organism used.

Supporting Information Available: Complete listing of crystallography data for **4a** and **4c**, synthetic details for the new compounds **3a**, **3b**, **4a**, **4b**, and **4c**, and their antimicrobial testing. Spectroscopic data and experimental details are included. Tables 3, 4, and 5 included.

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JM030262M