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Abstract

Synthesis and X-ray single crystal structure analysis of the compound $\{[Ag_2(\mu_2\text{-bpym})(\mu\text{-O-NO}_3)_2]\}_n$, **(1)**, (where bpym = 2,2'-bipyrimidine) are presented. Compound **(1)** has a (6,3)-2D honeycomb structure with a tetrahedral coordination geometry around the Ag(I) ion. In contrary to the solid state structural investigation, ESI-MS for **(1)** in solution shows a strong peak at *m/z* 423.0269 which indicates that the $[Ag(bpym)_2]^+$ cation is dominating instead of $[Ag_2(bpym)]^{2+}$. The anti-microbial activity of **(1)** was screened against 15 multi-drug resistant bacteria in comparison to silver(I) sulphadiazine and it showed a high activity against *Burkholderia mallei* which causes glanders; with a MIC value of 4μg/ml.

Keywords: silver(I) compounds, 2,2'-bipyrimidine, X-ray structure, anti-microbial activity.

Polymeric silver(I) compounds have recently attracted a great interest as versatile components in supramolecular compounds, [1-4] for photoluminescent [5], medicinal [6] and anti-microbial purposes [7-12]. The latter application has a long history even predating the discovery of microorganisms, [13-14] and before the introduction of modern antibiotics, silver in various forms was used for several medical indications. Our research group has synthesized and structurally characterized a number of monomeric, dimeric and 1D silver(I) compounds with N-donor heterocyclic ligands, most of which showed considerable anti-microbial activities against multi-drug resistant bacteria [15-22].

Since Ag(I) has the preference to form linear, trigonal planar or tetrahedral coordination geometries and often serves as simple spacer or connector (L-M-L coordination synthon), the geometry of the formed supramolecular structure depends mainly on the choice of polydentate

ligand [23]. Here we have chosen 2,2'-bipyrimidine (bpym) as a bis-bidentate ligand which can bridge several metal centres.

Compound **(1)** was synthesized[1] in a good crystalline form suitable for single crystal X-ray diffraction[2] upon direct mixing of $AgNO_3$ in water, and the corresponding organic ligand, (bpym) in ethanol, in a molar ratio Ag:L = 1:2. High resolution ESI-MS for **(1)** was performed in a DMSO/CH_3OH mixture to detect different cationic species in solution[3]. Antimicrobial activities of **(1)** are calculated as (MIC) values or Minimum Inhibitory Concentrations[4].

The structure of $\{[Ag_2(\mu_2\text{-bpym})(\mu\text{-O-}NO_3)_2]\}_n$ is shown in Fig. 1. The bpym ligand is (μ_2-N1,N1^i,N2,N2^i) chelating and bridging two silver(I) ions *via* its four nitrogen atoms forming two five-membered rings Ag1/N1/C2/C2^i/N2^i and N2/C2/C2^i/N1^i/Ag1^i. Each silver(I) atom is further coordinated to two nitrate groups forming a distorted tetrahedron defined by N1/N2^i/O33/O33^{iii}.

A CSD search [24] revealed 333 structures for bpym with different transition metals while only four Ag(I) structures were found: $[Ag_4(hfac)_4(\mu_2\text{-bpym})_3]$, [25] $\{[Ag(\mu_2\text{-bpym})]\}_n.nClO_4$, [25] $\{[Ag_2(\mu_2\text{-bpym})(\mu_2\text{-ox})]\}_n.4nH_2O$ [25] and $[Ag(\mu_2\text{-bpym})][Cr(\mu_2\text{-ox})_2(H_2O)_2].2H_2O$ [26] (where hfac = 1,1,1,5,5,5-hexafluoroacetylacetonate and ox = the oxalate anion $C_2O_4^{2-}$). $[Ag_4(hfac)_4(\mu_2\text{-bpym})_3]$ is a tetramer with two distorted square planar and two trigonal prismatic Ag(I) atoms, while compounds $\{[Ag(\mu_2\text{-bpym})]\}_n.nClO_4$ and $[Ag(\mu_2\text{-bpym})][Cr(\mu_2\text{-ox})_2(H_2O)_2].2H_2O$ have both 1D structure consisting of $[Ag(\mu_2\text{-bpym})]^+$ repeating units where the bpym ligand is chelating and bridging two Ag(I) atoms. The compound $\{[Ag_2(\mu_2\text{-bpym})(\mu_2\text{-ox})]\}_n.4nH_2O$ also has a 1D structure where $[Ag_2(\mu_2\text{-bpym})]^{2+}$ cationic units are connected by oxalate anions $(C_2O_4)^{2-}$. Selected bond lengths and angles for **(1)** are listed together with comparable structures in Table 1. The Ag-N bond distances (2.32 to 2.55Å) are longer than those found for L-Ag-L linear compounds [18-19] and are correlated to small N-Ag-N chelation angles for all these compounds (65 to 72°).

Weak interactions between the Ag(I) ion and adjacent oxygen atoms are also found; Ag…O32 and Ag…O33^{ii} are 2.981(6) and 2.989(5)Å, respectively [Symmetry codes: (i) –x, 1-y, -z; (ii) ½-x, -½+y, ½-z and (iii) ½-x, ½+y, ½-z]. The nitrate groups act as (μ-O) bridging Ag(I) ions through one oxygen atom (O33) to form 1D helices in b direction, see Fig. 2, with a weak interaction between the superimposed Ag(I) ions; Ag…Ag^v and Ag…Ag^{vi} is 3.5204(6)Å, [symmetry codes: (v) x, -1+y, z and (vi) x, 1+y, z]. Similar helices are found for the compound $[Ag(2,2'\text{-bipyridine})(NO_3)]_n$ [27] where nitrate groups are bridging the $[Ag(2,2'\text{-bipyridine})]^+$

units to form 1D chain of molecules with no Ag…Ag interactions. In case of **(1)** both bridging bpym ligands and nitrate groups extend the structure to (6,3)-2D honeycomb sheet (considering Ag(I) ions as nodes) in (b, c)- plane, see Fig. 3. Strong π-π stacking between the five-membered rings and the pyrimidine rings of same sheet is found, while no interactions between the pyrimidine rings themselves could be found; centroid–centroid distances are 3.520(2) and 3.390(3) Å with β angles (offset angle) 23 and 17°, respectively.

ESI-MS is a technique used for detection of different ionic species (cations or anions) possibly present in solution and/or in gas-phase and account for their relative stabilities under experimental conditions [28]. For compound **(1)**, a very strong peak is observed at *m/z* 423.0269 which is consistent with the calculated value for $[Ag(bpym)_2]^+$ (423.02 for $C_{16}H_{12}AgN_8^+$) instead of the expected cation $[Ag_2(bpym)]^{2+}$ found in the solid-state structure. Two minor peaks are also detected at *m/z* 264.9670 and 591.9208 which can be assigned to $[Ag(bpym)]^+$ and $[Ag_2(bpym)_2(NO_3)]^+$ cations; calculated values are 264.96 and 591.92 for $C_8H_6AgN_4^+$ and $C_{16}H_{12}Ag_2N_9O_3^+$, respectively. Also, the observation of a characteristic $^{107}Ag/^{109}Ag$ isotopic peak doublet (~52 : 48) further identified the 1:2 compound [29].

The compound in solution thus prefers the stoichiometry 1:2 (Ag:L) with a suggested tetrahedral coordination geometry around the Ag(I) ion as found in the previously mentioned compounds $\{[Ag(\mu_2\text{-bpym})]\}_n.nClO_4$ and $\{[Ag_2(\mu_2\text{-bpym})(\mu_2\text{-ox})]\}_n.4nH_2O$ [25]. The nitrate coordination to the Ag(I) centres in **(1)** is stabilizing the sheets formed in the solid-state with the stoichiometry 2:1 (Ag:L) while in solution the nitrates have been solvated giving the ligand more chance to directly attack the half naked $[Ag(bpym)]^+$ and form the 1:2 (Ag:L) cation $[Ag(bpym)_2]^+$.

In some related studies the ESI-MS of the silver(I) trifluoromethan sulfonate (AgO_3SCF_3) compound with 3,6-di(2-pyridyl)pyridazine in CH_3CN were consistent with X-ray crystallography where the same cations $[Ag(L)_2]^+$ (Ag:L = 1:2) were found [30]. Similarly, the ESI-MS for the compound $[Ag(4,5\text{-diazafluoren-9-one})_2]NO_3$ [21] showed only one strong peak representing the complex $[Ag(L)_2]^+$ with (Ag:L = 1:2). On the contrary, the ESI-MS for a solution containing $AgBF_4$ and excess bidentate 1,12-diazaperylene ligand indicate the formation of the 1:1 (90%) Ag:L complex while the expected 1:2 complex is only observed as a minor peak (10%) [31]. Thus the complexation behaviour of silver(I) ions in solution is complicated.

Compound **(1)** shows activities comparable with the commercially used silver(I) sulphadiazine against most Gram-positive bacteria used in this test, MIC values are listed in Table 2. The

highest activity recorded for **(1)** was against the Gram-negative *Burkholderia mallei* which causes glanders [32]; MIC value 4μg/ml.

In conclusion, we have synthesized and structurally characterized the compound $\{[Ag_2(\mu_2\text{-bpym})(\mu\text{-O-}NO_3)_2]\}_n$. The compound shows a broad spectrum antibacterial activity against all the test organisms with stronger effect against the Gram-negative *Burkholderia mallei* than silver(I) sulphadiazine under the same test conditions. This activity should be interpreted on the bases of solution chemistry of the compound, where $[Ag(bpym)_2]^+$ cation is detected by ESI-MS.

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Supplementary material

A Table and a Figure for weak C-H…O interactions are available. CCDC 797352 contains the supplementary crystallographic data for **(1)**. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.

Notes and References

[1] To an aqueous solution (20 cm^3) of $AgNO_3$ (0.34g, 2.0 mmol), an ethanolic solution of 4 mmol of 2,2'-bipyrimidine (0.60g) was added with continuous stirring . The mixture was then heated till boiling, followed by filtration. The clear filtrate was allowed to stand at room temperature for a couple of weeks. Colorless needles of **(1)** suitable for X-ray measurements were collected and dried in air, with a yield ~ 85% with respect to $AgNO_3$. IR was recorded on a Bruker IFS-125 model FT-IR spectrophotometer as KBr pellets; (v, very; s, strong; m, medium; w, weak; br, broad; sh, shoulder): 3090 s, 1609 w, 1560 vs, 1449 vs, 1408 sh, 1457 vs, br, 1283 vs, 1264 vs, 1142 m, 1104 m, 1015 s, 827 s, 807 m, 758 s, 685 w, 661 s, 593 m, 409 m, 388 m, 343 w, 317 w, 272 w. Elemental analyses (C, H, N) were carried out by Mikroanalytisches Laboratorium KOLBE, Mülheim an der Ruhr, Germany. Calculated values are: C, 19.22; H, 1.61 and N, 16.81%. Found values are: C, 19.17; H, 1.42 and 16.53%.

[2] Crystallographic measurements were made on a Siemens Smart CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073Å) at 153 K. The structure was solved by direct method and subsequent full-matrix least-squares refinement, including anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined isotropically with use of geometrical constrains. The calculations were carried out using SHELXTL program package. Empirical formula: $C_{16}H_{12}Ag_4N_{12}O_{12}$, F.W. 995.86, Crystal system: monoclinic, Space group: C2/c, a=20.940(2), b=3.5204(4), c=19.477(2)Å, β=122.017(2)°, V =1217.4(2)$Å^3$, Z=2, $D_{(calc)}$=2.177 Mg/m^3, μ=3.262mm^{-1}, F(000) = 952, Crystal size: 0.40x 0.08x 0.06 mm^3, θ range: 2.31 to 25.05°, Index ranges: -24<=h<=24, -4<=k<=4, -23<=l<=23, Reflections collected: 3998, Independent reflections: 1070 [R(int) = 0.0440], Completeness to θ=25.05°: 99.1%, Absorption correction: multi-scan, $T_{(Max)}$=0.8283, $T_{(min)}$=0.3553, Refinement method: full-matrix least-squares on F^2, Data/ restraints/ parameters: 1070/ 0/ 100, Goodness-of-fit: 1.006, Final R indices [I>2σ(I)]: R1 = 0.0537 and wR2 = 0.1604, R indices (all data): R1 = 0.0547 and wR2 = 0.1623, largest diff. peak and hole: 1.935 and -2.232 e.$Å^{-3}$.

[3] High-resolution ESI-MS analysis was performed on a Bruker APEX-Qe hybrid quadrupole Fourier transform ion cyclotron resonance (Q–FT-ICR) mass spectrometer, equipped with an Apollo-II ESI source and a 4.7-T superconducting magnet. We used as gentle conditions as possible to ascertain that the MS data would represent solution characteristics rather than dissociation products in the gas-phase. CapExit: 300 V, Skimmer1: 12 V, Ion-funnel1: 150 V, Skimmer2: 10 V, Ion-funnel2: 15 V, Drying gas: 180 °C, Drying gas: 5.0 bar and Nebul. Gas: 1.0 bar. The instrument was operated in positive ion mode only. Compound (**1**) was dissolved in DMSO and diluted with MeOH. This solution was infused into the ESI source at a flow rate of 1.5 µl/min and positive ions were detected. The instrument was operated with Bruker XMASS 7.0.8 software and spectra were processed/ analyzed with the use of Bruker Data Analysis 3.5 software.

[4] Antimicrobial activity of **(1)** was determined according to the recommendations of NCCLS (1999), National Committee for Clinical Laboratory Standard, by the use of broth microdilution method. Minimum inhibitory concentrations (MICs) for the tested compound were conducted using 15 different bacterial clinical isolates (Department of Vascular Surgery, Faculty of Medicine, Alexandria University, Egypt) and are all resistant strains for commonly used antibiotics. The test material was dissolved in DMSO to give a stock solution that subsequently diluted in the growth medium to give final concentrations of 256, 128, 64, 32, 16, 8, 2, 1, and 0.5 µg of compound/ml. A final concentration of 5% DMSO was present in all assays. Bacteria were cultured in Mueller Hinton broth (MHB) for 24 h at 35 °C. A toxicity bioassay against Daphnia was conducted using standard methods.

5 Table 2 footnote: The MIC values are corresponding to the lowest concentrations (µg/ml) that inhibited the bacterial growth.

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