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Mono- and binuclear chloride complexes of bismuth(III) with 2-aminopyrimidine cations depending on specific synthetic route

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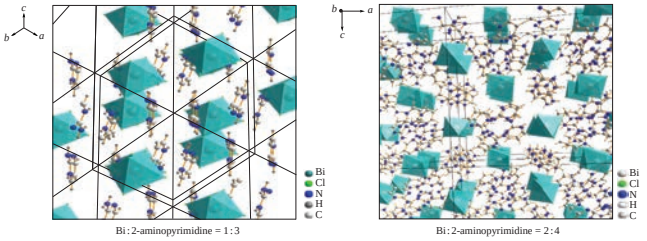
Complexes of Bi^{III} with 2-aminopyrimidine cations with metal-to-ligand ratios of 1 : 3 or 2 : 4 (depending on reaction conditions) were synthesized and characterized by elemental analysis, ^1H NMR spectroscopy, and single crystal X-ray crystallography. The possibility of conversion of the latter complex into the former one was demonstrated. The determined cytotoxicity depended on the structure of these complexes.



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Developments in the antitumor therapy have resulted in active studies of transition and heavy metal compounds, which significantly improved understanding of their properties. A substantial impetus to this was given by the successful clinical administration of cisplatin and its subsequent derivatives. There is another reason for the intent attention to metals and their complexes: the design of radiopharmaceuticals of new generation.[1] In both cases, bismuth is of extreme interest since it has demonstrated remarkable results in oncological studies, although the mechanism of action for its compounds is still unclear. Moreover, there are attractive radionuclides of bismuth. In medicine, the most popular are Bi^{III} complexes, however they remain less explored for cytotoxicity and antitumor potential as compared with the complexes of other metals.[2,3] The potent antitumor activity of some Bi^{III} compounds has already been reported.[4,5]

In the present work, two new Bi^{III} complexes with 2-aminopyrimidine (2-AP) have been synthesized, which may be of interest for radiomedical research. Herein, their structures and features depending on the synthetic routes are reported. The chemistry of organic-inorganic hybrid bismuth compounds is currently of considerable interest also in advanced materials studies.[6] Among hybrid tetraiodobismuthates, single and double charged cations were found in derivatives of aliphatic and aromatic heterocyclic compounds.[7,8] In the case of isomeric 2-, 3- and 4-aminopyridinium cations, the increased positive charge on the amino group for 4-substituted isomer leads to the formation of stronger N–H···I hydrogen bonds.[9] Mixed products were formed in solutions containing simultaneously two halide ions, *e.g.*, solid products enriched with iodine were isolated in the case of both Br^- and I^- ions.[10] For chlorine and iodine pair, a compound possessing the halogen ratio of 2 : 3 was precipitated from the solution.[11] At high pH values, partial hydrolysis of Bi^{III} occurs with the formation of polymer cations and Bi–O–Bi bridges.[12]

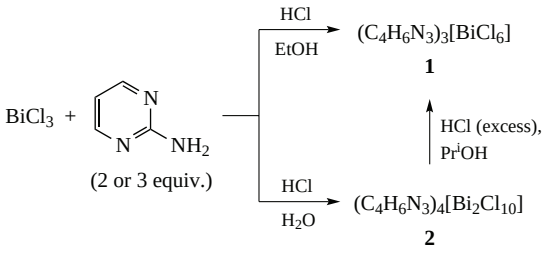
The interaction of bismuth with 2-AP can yield complexes of the two types possessing the Bi : 2-AP ratios of 1 : 3 (**1**) and 1 : 2 (*i.e.*, 2 : 4) (**2**) as was revealed by the elemental analysis (Scheme 1).† NMR data have confirmed that the resulting compounds containing 2-AP ligands remains preserved during various manipulations. Results acquired by XRD method

† *Synthesis of complex* **1** *in ethanol.* The initial Bi : 2-AP ratio was 1 : 3. 2-AP (0.14 g, 1.5 mmol) dissolved in EtOH (4 ml) was added dropwise to a solution of $BiCl_3$ (0.16 g, 0.5 mmol) in EtOH (4 ml) with added HCl (1 ml, 36%). White crystalline precipitate was formed. The reaction mixture was stirred at room temperature for 2 h, and the precipitate was filtered off. Yield of **1** 88%. Mp 227–228 °C. Calc. for $C_{12}H_{18}BiCl_6N_9$ (%): C, 20.30; H, 2.56; N, 17.75. Found (%): C, 20.30; H, 2.66; N, 17.43.

In case of the initial Bi : 2-AP ratio of 1 : 2, the reaction was performed analogously using 0.09 g (1 mmol) of 2-AP. Yield of **1** 87%. Mp 226–227 °C. Calc. for $C_{12}H_{18}BiCl_6N_9$ (%): C, 20.30; H, 2.56; N, 17.75. Found (%): C, 20.15; H, 2.62; N, 17.54.

Synthesis of complex **2** *in aqueous HCl.* The initial Bi : 2-AP ratio was 1 : 3. $BiCl_3$ (0.32 g, 1 mmol) was dissolved in aqueous HCl (2 ml, 36%). A solution of 2-AP (0.28 g, 3 mmol) in HCl (2 ml, 36%) was added dropwise (Bi : 2-AP = 1 : 3). White crystalline precipitate started to form immediately. The reaction mixture was stirred at room temperature for 3 h and cooled to –6 °C, and the precipitate was filtered off. Yield of **2** 74%. Mp 182–184 °C. Calc. for $C_{16}H_{24}Bi_2Cl_{10}N_{12}$ (%): C, 16.61; H, 2.09; N, 14.53. Found (%): C, 16.85; H, 2.05; N, 14.46.

For initial Bi : 2-AP ratio of 1 : 2, the reaction was performed similarly using 0.19 g (2 mmol) of 2-AP. The white crystalline precipitate started to form after 10 min of stirring. The mixture was stirred for 3 h, cooled to –6 °C, and the precipitate was filtered off. Yield of **2** 76%. Mp 182–184 °C. Calc. for $C_{16}H_{24}Bi_2Cl_{10}N_{12}$ (%): C, 16.61; H, 2.09; N, 14.53. Found (%): C, 16.93; H, 2.15; N, 14.63.



Scheme 1

(Figures S4–S6) have demonstrated that polycrystalline samples may contain compounds **1** or **2**, or their mixture at various ratios and some impurity substances, depending on the synthetic conditions. The impurity phases could not be identified using the PDF-2 ICDD database, but it was demonstrated that they did not include chloro-, oxo- nor hydroxo-bismuth derivatives, neither 2-AP nor 2-AP hydrochloride. The samples of compound **2**, which are relatively pure according to XRD, can be synthesized in aqueous HCl at the Bi : 2-AP ratio of 1 : 2. However, if this compound is prepared at the Bi : 2-AP ratio of 1 : 3 (also in aqueous HCl), it would not be possible to isolate its polycrystalline sample without any noticeable impurity phase content (the ratio of **2** : **1** was 67.7 : 32.3). The structures of isolated complexes were dependent primarily on the used medium, as well as on the initial ratio of reactants. In the case ethanol HCl solutions, complex **1** was always isolated (regardless of the initial ratio of reagents). In aqueous HCl solutions, the structure of formed product depends on the ratio of reagents as well as on the reaction conditions. It is important, that compound **2** (Bi : 2-AP = 2 : 4) can be 'saturated' with 2-AP. Thus, a reaction mixture containing rapidly precipitated compound **2** can be treated with isopropanol at low temperature, yielding complex **1**, within 3 days, *i.e.*, **2** converts into **1**. This process reflects a complex kinetics of the precipitation formation (related probably to the solubility of complexes), and the resulting precipitate corresponded to structure **1** (Bi : 2-AP = 1 : 3).

Figure 1‡ shows the structure of compound $(C_4H_6N_3)_3[BiCl_6]$ **1**, which crystallizes in monoclinic system with space group $P2_1$. The asymmetric unit in the crystal structure contains four $[BiCl_6]^{3-}$ anions and twelve protonated 2-AP moieties [see Figure 1(*b*)]. Each Bi atom is surrounded by six Cl atoms forming distorted octahedral configuration, whereas Bi–Cl bond lengths range from 2.568(9) to 2.911(9) Å, and Cl–Bi–Cl bond angles vary from 84.7(3) to 99.5(3)° and from 171.3(3) to 177.7(3)° for *cis*- and *trans*-arrangements, respectively. These parameters are in a good agreement with other reported data.[15–18] Numerous hydrogen bonds are formed between the cations (C–H···N and N–H···N) as well as between cations and anions (N–H···Cl and C–H···Cl).

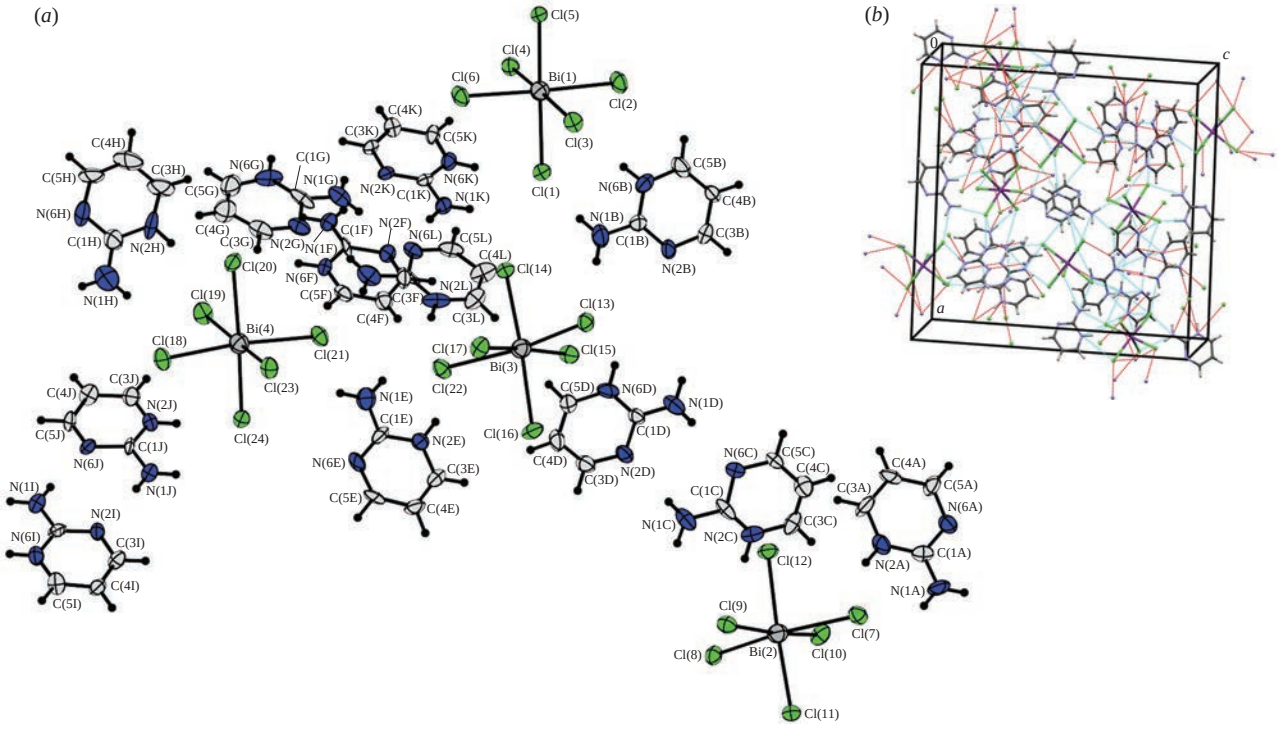


Figure 1 (*a*) Molecular structure of complex **1** showing thermal ellipsoids at the 50% probability level; (*b*) hydrogen bonds formed between cations and between cations and anions in the crystal cell.

Conversion of **2** *into* **1**. A solution of 2-AP (0.28 g) in aqueous HCl (6 ml, 36%) was added to a solution of $BiCl_3$ (0.32 g, 1 mmol) in aqueous HCl (2 ml, 36%). The mixture was stirred at room temperature for 3 days, cooled to –6 °C, then isopropanol (100 ml) was added. A white crystalline precipitate of **1** was formed. Yield 69%. Mp 225–227 °C. Calc. for $C_{12}H_{18}BiCl_6N_9$ (%): C, 20.30; H, 2.56; N, 17.75. Found (%): C, 20.42; H, 2.69; N, 17.66.

‡ *Crystal data for* **1**. $C_{12}H_{18}BiCl_6N_9$ (M = 710.03), monoclinic, space group $P2_1$, at 295 K: a = 24.7839(5), b = 7.5284(1) and c = 17.3295(17) Å, β = 91.456(2)°, V = 4614.45(15) Å^3, Z = 8, d_{calc} = 2.044 g cm^{-3}, μ(MoKα) = 8.355 mm^{-1}, F(000) = 2704. Total 113159 reflections were measured, and 21179 independent reflections (R_{int} = 0.1043) were used in a further refinement. The final R_1 = 0.0512 (wR_2 =0.0972) was calculated for 10339 observed reflections with $I > 2\sigma(I)$. GOF = 0.821.

Crystal data for **2**. $C_8H_{12}BiCl_5N_6$ (M = 578.47), triclinic, space group $P\bar{1}$, at 295 K: a = 8.8840(3), b = 10.0229(4) and c = 11.1040(4) Å, α = 114.815(3), β = 108.674(3) and γ = 91.409(3)°, V = 835.54(6) Å^3, Z = 2, d_{calc} = 2.299 g cm^{-3}, μ(MoKα) = 11.348 mm^{-1}, and F(000) = 540. Total 23529 reflections were measured, and 4007 independent reflections (R_{int} = 0.0589) were used in a further refinement. The final R_1 = 0.0360 (wR_2 = 0.0778) was calculated for 3028 observed reflections with $I > 2\sigma(I)$. GOF = 1.028. The data were collected using a STOE diffractometer equipped with Pilatus100K detector operating at mono capillary collimation MoKα (λ = 0.71073 Å) radiation, plane graphite monochromator, rotation method mode. STOE X-AREA 1.67 software was used for cells refinement and data reduction. Intensity data were scaled in LANA program (implemented in the X-AREA) to minimize

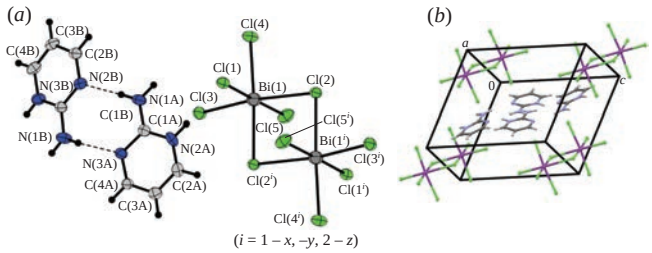


Figure 2 (*a*) Molecular structure of complex **2** showing thermal ellipsoids at the 50% probability level; (*b*) the packing of the molecules in a crystal.

In compound $(C_4H_6N_3)_4[Bi_2Cl_{10}]$ **2**, which crystallizes in triclinic[15] system with space group *P*1, the corresponding atoms of $(Bi_2Cl_{10})^{4-}$ anion are linked by an inversion center, *i.e.* the structure of anion consists of centrosymmetric dimeric $[BiCl_5]^{2-}$ units, wherein two Cl ligands bridge the bismuth atoms forming a four-membered ring [Figure 2(*a*)].‡ The Bi atom is octahedrally coordinated by chlorine atoms, whereas Bi–Cl distances range from 2.531(3) to 2.934(2) Å and the Cl–Bi–Cl angles range from 85.26(7) to 96.00(10)° and from 171.82(8) to 175.77(10)° for *cis*- for *trans*-arrangements, respectively. These parameters are in a good agreement with the reported data on structures containing $[Bi_2Cl_{10}]^{4-}$ anion.[19–25] Cations form dimers *via* N(1)Bi–H(1)Bi···N(3A) and N(1A)–H(1A)···N(2B) hydrogen bonds. Hydrogen atoms of the N(1A)–H(1)···Cl(1) amino groups and protons at the N(2A) atom [N(2A)–H(2)···Cl(1)] of the A cations bind adjacent anions and thus form an endless rod of anions running along the *b* axis. The bonding of neighboring rods occurs with the participation of the B cations N(2B)–H(3)···Cl(4). Thus, a layer consisting of anionic rods and ribbon of cations A and B connected to each other in dimers appears. Note that there is a π–π interaction between cations in the layer. The layers are interconnected *via* C–H···Cl hydrogen bonds, thus forming a 3D-structure. Figure 2(*b*) shows packing of the molecules in a crystal.

We have found that obtained bismuth complexes are low-toxic towards normal lymphocytes but more toxic towards Jurkat cell line according to the data of MTT-test[26,27] (Table 1). Compound **2** was an order of magnitude more cytotoxic towards leukemic cells as compared to **1** due to the higher relative concentration of contained bismuth, which is a strong cytotoxic agent.

In conclusion, we have demonstrated the dependence of structure of formed bismuth complexes on the differences in the synthetic route, which causes a change in the pH value, solubility of bismuth compounds, acid concentration and, consequently, the formation or breaking of bridging bonds.

Table 1 Cytotoxicity of bismuth complexes towards normal lymphocytes (HD) and Jurkat cells.

Complex	LC_{50} (μmol ml^{-1})		
	Mononuclear cells of healthy donors	Jurkat	[LC_{50}(HD)/ LC_{50}(Jurkat)]
1	7.3 ± 1.5	0.7 ± 0.2	10.4
2	1.7 ± 0.3	0.05 ± 0.01	34

differences of intensities for symmetry-equivalent reflections (multi-scan method). The structures were solved and refined using SHELX program. The non-hydrogen atoms were refined using the anisotropic full matrix least-square procedure. All the hydrogen atoms were placed at the calculated positions and allowed to ride on their parent atoms [C–H 0.93; U_{iso} = 1.2U_{eq} (parent atom)]. Molecular geometry calculations were performed using the SHELX program,[13] and the molecular images were prepared using DIAMOND[14] software.

CCDC 1907486 and 1907487 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.024.

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