



Novel silver(I) compounds with 1-adamantanamine

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Abstract: In this work, three novel silver(I) complexes with an almost completely rigid and bulky monodentate ligand, 1-adamantanamine, were synthesized. The aliphatic amine, 1-adamantanamine, is the sole electron donor ligand in these complexes. In addition to spectroscopic characterization, the basic biological activities of the new compounds were investigated and their minimum inhibitory concentrations were determined. The antifungal and antibacterial activities indicate that these compounds could potentially be applied as new therapeutics.

Keywords: amantadine; silver(I) complexes; rigid and bulky ligand; NMR spectroscopy; biological activity.

INTRODUCTION

Adamantane is a hydrocarbon that consists of three connected cyclohexane rings, forming a cage-like structure. Although there are numbers of isomers with the formula C₁₀H₁₆, adamantane is the most stable one.¹ Moreover, it is peculiar since it is rigid considering its “armchair” configuration, but practically without strain. The lipophilic adamantyl group is interesting from the aspect of medicinal chemistry, since it is present in several compounds that are currently used for the treatment of neurodegenerative disorders, viral infections and type 2 diabetes.² Adamantane polymers have been patented as antiviral agents against HIV.³ It is important to emphasize that in many cases, the adamantyl group has improved the pharmacological properties of a parent compound, without increasing the toxicity.

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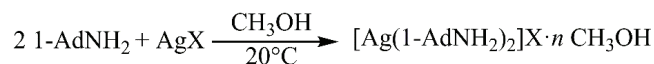
Different derivatives of adamantane, such as memantine, dopamantine and rimantadine have been utilized as therapeutics. Amantadine (1-adamantanamine), which can be obtained in a well-established way from adamantane,^{4–6} was used as an antiviral drug against different strains of influenza⁷ and in the treatment of Parkinson's disease.^{8,9}

It is well known that ligands having electron-donating atom(s) often show increased cytotoxicity due to their enhanced coordination capacity.^{10,11} Various research groups are devoted to development of novel coordination compounds that contain 1-adamantanamine as a ligand in order to improve the performances and potentially overcome the shortcomings of known therapeutics. So far, platinum, titanium and zinc complexes with adamantylamine ligand were synthesized, characterized and studied from the perspectives of therapy and biological interest.^{12–15} For example, platinum(IV) complexes with adamantylamine were thoroughly tested for their biological activity and have the potential to provide a significantly improved therapy for many types of tumors.¹³

To the best of our knowledge, a complex of 1-adamantanamine with silver(I) has not been described, although some similar compounds could be found in the literature.¹⁶ In addition, in these complexes, 1-adamantanamine is the sole electron donor ligand. Since silver(I) ion is very well recognized for its antibacterial activity,¹⁷ three novel silver(I) complexes with bulky, rigid 1-adamantanamine ligand were synthesized and characterized by spectroscopic measurements. The antifungal and antibacterial activities of these compounds were investigated and their minimum inhibitory concentrations were determined.

EXPERIMENTAL

An appropriate silver(I) salt was added dropwise during 30 min under stirring to a methanolic solution of 1-adamantanamine. The mixture was stirred for 2 h in total darkness. The mole ratio of the reactants was 2.1:1 in favor of the amine. The obtained clear solution was left to crystallize for 72 h in the dark. The formed photosensitive crystals were suction-filtered in the dark and dried in a light-protected desiccator. The synthetic procedure can be summarized by Scheme 1.



Ad= 1-adamantyl

X = NO₃⁻, ClO₄⁻ (*n* = 0.5), CSA = D (+)-10-Camphorsulphonate (*n* = 2.5)

Scheme 1. Overall synthesis of the silver(I) complexes.

Total silver content for the three novel compounds was determined by means of the atomic absorption method EPA 272.1, direct aspiration. The infrared (IR) spectra were recorded in the wavenumber range 4000–480 cm⁻¹ on a Nicolet 6700 FT-IR instrument (Thermo Scientific) using the KBr technique. The ¹H-NMR spectra were recorded on a Varian Gemini 2000 instrument at 200 MHz and the ¹³C-NMR spectra were recorded on a Bruker Avance III

instrument at 50 MHz. The agar-dilution method¹⁸ was used for the determination of the minimal inhibitory concentration (*MIC*) values of the synthesized complexes. The microorganisms were prepared in nutrient-rich agar plates without the tested substances to obtain single cell colonies, which were then transferred into nutrient-rich agar plates containing the tested substances (10 μL , range: 0.02 to 50 $\mu\text{mol L}^{-1}$). The inoculated agar-plates were incubated for 24 h and then the colonies were counted.

RESULTS AND DISCUSSION

Three novel silver(I) complexes, bis(1-adamantanamine)silver(I) nitrate hemimethanolate, bis(1-adamantanamine)silver(I) perchlorate hemimethanolate and bis(1-adamantanamine)silver(I) D-camphor-10-sulphonate hemipentamethanolate (Fig. 1), were synthesized and characterized by atomic absorption, IR and ^1H - and ^{13}C -NMR measurements.

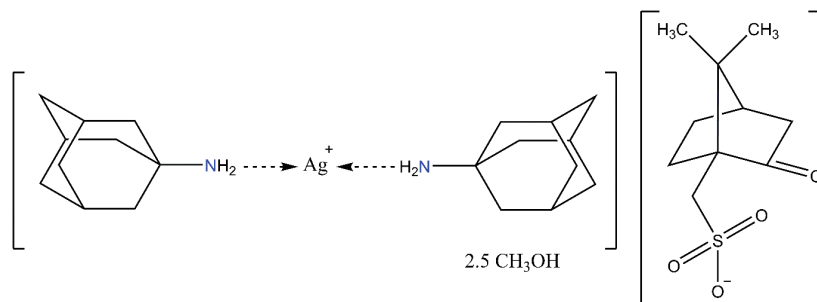


Fig. 1. The presumed structure of bis(1-adamantanamine)silver(I) D-camphor-10-sulphonate.

Elemental microanalysis measurements are not reliable for this type of compounds, since the studied complexes showed incomplete combustion. Moreover, reported sublimation and vaporization enthalpies showed significant discrepancies.^{19–24} The highly symmetric, globular ligand, 1-adamantanamine, shows a tendency to sublime. In order to determine accurately the combustion enthalpy of adamantane, its derivatives and complexes, the samples should be combusted in a calorimetric bomb under high pressure.²⁵ Thus, atomic absorption measurements were performed as a substitute. The calculated value for the total silver in bis(1-adamantanamine)silver(I) nitrate hemimethanolate is 22.09 %, while the determined value was 21.9 ± 0.1 %. In the case of bis(1-adamantanamine)silver(I) perchlorate hemimethanolate, the calculated value for the total silver is 20.51 % and the determined value was 20.56 ± 0.1 %. For the bis(1-adamantanamine)silver(I) D-camphor-10-sulphonate complex, the calculated and determined values were 14.94 % ($[\text{Ag}(1\text{-AdNH}_2)_2]\text{CSA} \cdot 2.5\text{CH}_3\text{OH}$) and 14.77 ± 0.1 %, respectively.

The infrared spectrum of 1-adamantanamine showed characteristic bands for primary amines: asymmetric and symmetric stretching bands (NH_2 group) at 3329.8 and 3252.7 cm^{-1} , respectively, N–H bend vibrations at 1587.7 cm^{-1} , C–N stretch (aliphatic amines) in the region of 1250–1020 cm^{-1} , located at 1098.8 cm^{-1} ,

and N–H wag vibration was found at 812.2 cm^{-1} . Moreover, in this spectrum two strong bands were observed at 2907.5 and 2848.7 cm^{-1} , presenting asymmetric and symmetric stretching bands, respectively (CH and CH_2 groups). In the IR spectrum of the synthesized complex of 1-adamantanamine with silver nitrate, the following bands were observed: 3435.2 cm^{-1} , wide stretching band; 1591.4 cm^{-1} , weak bending band that arises from the NH_2 group; 1348.1 cm^{-1} , strong stretching band of the NO_3^- ion; 2910.6 and 2847.1 cm^{-1} , strong stretching bands originating from the CH_2 groups and 1450.7 cm^{-1} , weak bending band, which is derived from the CH groups. In the IR spectrum of the synthesized complex of 1-adamantanamine with silver camphorsulfonate, the following bands were registered: 3457.1 cm^{-1} , wide stretching band; 1597.3 cm^{-1} , weak bending band originating from the NH_2 group; 2903.5 and 2846.5 cm^{-1} , strong stretching bands that originate from the CH_2 groups, 1451.6 and 1367.7 cm^{-1} , weak bending bands that originate from the CH groups; 1740.6 cm^{-1} , strong stretching band that comes from the C=O group; 1197.6 and 1047.0 cm^{-1} strong bands of the SO_3^- group. In the IR spectrum of the synthesized complex of 1-adamantanamine with silver perchlorate, the following bands were detected: 3426.0 cm^{-1} , wide stretching band; 1584.2 cm^{-1} , weak bending band that originates from the NH_2 group; 1097.0 and 621.5 cm^{-1} strong stretching bands that arise from ClO_4^- , 2906.7 and 2846.5 cm^{-1} , strong stretching bands that come from the CH_2 group and 1450.7 and 1363.6 cm^{-1} , weak bending bands originating from the CH group. Due to relatively low concentration of methanol, its IR bands were overlapped with the bands that belong to the NH_2 and CH_2 groups and counter ions.

In summary, two peaks assigned to stretching modes of NH_2 group (3329.8 and 3252.7 cm^{-1}) in the non-coordinated ligand had become one broad peak located around 3440 cm^{-1} in the spectra of all the investigated complexes, indicating that the coordination to the metal ion was successful.

Evidence for complexation of silver(I) to 1-adamantanamine could also be obtained from the NMR spectra. In the ^1H -NMR spectrum of 1-adamantanamine, two broad signals of carbon-bound hydrogen atoms could be seen – one at 2.05 ppm, corresponding to the methine protons, and the other at 1.59 ppm, corresponding to the methylene protons. Upon complexation, the methine proton signals and the methylene proton signals from hydrogens at carbons 4, 6 and 10 remain at the same chemical shift (as in the ligand), while the methylene proton signals from the hydrogens at carbons 2, 8 and 9 are shifted downfield, to 1.66–1.70 ppm (adequate numeration is shown in Fig. 2).

In the ^{13}C -NMR spectra, there is an important downfield shift of the quaternary carbon 1, from 47.2 ppm in the ligand to 48.8–50.1 ppm in the complex salts. This deshielding is the consequence of the electron-withdrawing effect of the silver(I) ion.

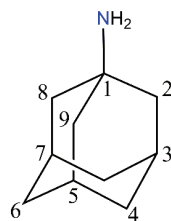


Fig. 2. Numeration of 1-adamantanamine.

Determination of *MIC* values was performed and all obtained complexes showed activity to the tested microorganisms. The antifungal activities are comparable with those of the test compound nystatin. Unfortunately, 1-adamantanamine is not soluble in water. Therefore, *MIC* values for the ligand were not determined.

The diminished activity of the studied complexes (Table I) compared to simple silver(I) salts was expected, considering the lower concentration of free silver(I) ions due to complexation. On the contrary, only in one case, *i.e.* *Aspergillus niger*, *MIC* values determined for $[\text{Ag}(1\text{-AdNH}_2)_2]\text{CSA}\cdot 2.5\text{CH}_3\text{OH}$ showed significant increases in activity. Although the percentage of silver(I) in bis(1-adamantanamine)silver(I) D-camphor-10-sulphonate complex is lower than in nitrate and perchlorate analogues, $[\text{Ag}(1\text{-AdNH}_2)_2]\text{CSA}\cdot 2.5\text{CH}_3\text{OH}$ showed comparable activity in the case of *Candida albicans*. The increased activity of the camphorsulphonate complex was probably caused by the greater lipophilicity of the complex.

TABLE I. *MIC* values ($\mu\text{mol L}^{-1}$) of the complexes and reference compounds

Compound	<i>Staphylococcus aureus</i> (ATCC 25923)	<i>Escherichia coli</i> (ATCC 25922)	<i>Micrococcus luteus</i> (ATCC 10240)	<i>Candida albicans</i> (ATCC 24433)	<i>Aspergillus niger</i> (ATCC 10249)
Streptomycin	<0.001	0.019	0.019	>0.617	>0.617
Nystatin	–	–	–	5.399	2.483
AgNO_3	0.188	0.188	0.188	0.765	0.005
$\text{AgClO}_4\cdot\text{H}_2\text{O}$	0.124	0.244	0.124	0.124	0.124
AgCSA	0.144	0.590	0.590	0.289	1.150
$[\text{Ag}(1\text{-AdNH}_2)_2]\text{NO}_3\cdot 0.5\text{CH}_3\text{OH}$	0.471	31.962	31.962	31.962	31.962
$[\text{Ag}(1\text{-AdNH}_2)_2]\text{ClO}_4\cdot 0.5\text{CH}_3\text{OH}$	29.420	29.420	29.420	29.420	4.393
$[\text{Ag}(1\text{-AdNH}_2)_2]\text{CSA}\cdot 2.5\text{CH}_3\text{OH}$	0.819	1.639	1.639	21.956	0.410

The antiviral effect of adamantane amines is well known, as well as the antibacterial effect of silver(I) ions.²⁶ The demonstrated antifungal and antibacterial activities of the newly synthesized complex compounds may have significance for their further application.

CONCLUSIONS

In this work, although being photosensitive, three novel compounds with a monodentate ligand, the almost completely rigid and bulky aliphatic amine (1-adamantanamine), were successfully prepared for the first time in a simple and low-cost way. All three compounds were characterized by atomic absorption, IR, and ^1H - and ^{13}C -NMR measurements. All three characterization methods evidenced that the complexation had been successfully achieved. Two characteristic bands that appear in the IR spectrum of the non-coordinated ligand became one broader peak positioned at higher energies in the spectra of the investigated complexes. In the NMR spectra, important downfield shifts were observed upon complexation. Since this amine is a bulky and rigid monodentate ligand, and silver(I) mostly forms linear compounds, the obtained complexes had coordination number 2. It should be noted that in these compounds, the amine ligand is the sole electron donor. The measured antifungal and antibacterial activities of the synthesized compounds, may have an impact on their further applications as therapeutics. Special attention should be paid to the nitrate and perchlorate complexes, although the lipophilic camphorsulphonate analogue gave satisfactory results despite having a lower percentage of silver(I). The obtained compounds are relatively unstable. However, these complexes could be observed as model systems in order to produce new derivatives with desired biological properties belonging to this class of compounds.

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ИЗВОД

НОВА ЈЕДИЊЕЊА СРЕБРА(I) СА 1-АДАМАНТАНАМИНОМ

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У овом раду су синтетисана три нова комплекса сребра(I) са јако ригидним и релативно великим монодентатним лигандом, 1-адамантанамин. Алифатични амин, 1-адамантанамин, једини је електрондонорски лиганд у овим комплексима. Поред спектроскопске карактеризације, испитиване су и основне биолошке активности и одређене су минималне инхибиторне концентрације. Антифунгалне и антибактеријске активности ових једињења указују да она потенцијално могу бити примењена као нови терапеутици.

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