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Research Article

Synthesis of pincer type carbene and their Ag(I)-NHC complexes, and their antimicrobial activities

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ABSTRACT

In this study, theophylline (1) compounds were synthesized with addition of 2-bromoethanol, 2-bromoacetamide and methyl-2-bromoacetate to attain symmetric connections to *NHCs* (2a–c). New complexes containing the symmetric N-heterocyclic carbene (NHC) ligands were synthesized using azolium salts in dimethyl formamide (DMF). After the NHC predecessor compounds reacted with Ag_2O, Ag(I)-NHC complexes were synthesized in the following: 7,9-di-(2-hydroxyethyl)-8,9-dihydro-1,3-dimethyl-1*H*-purine-2,6(*3H,7H*)-dionedium silver(I)bromide (3a), 7,9-di(acetamide)-8,9-dihydro-1,3-dimethyl-1*H*-purine-2,6(*3H,7H*)-diondium silver(I)bromide (3b) and 7,9-di(methylacetate)-8,9-dihydro-1,3-dimethyl-1*H*-purine-2,6(*3H,7H*)-diondiumsilver(I)bromide (3c). Both synthesized NHC predecessors (2a-c) and Ag(I)-NHC complexes (3a-c) were described by FTIR, ^{1}H-NMR, ^{13}C-NMR, liquid and solid-state conductivity values, TGA analysis, melting point analysis and XRD spectroscopy. *In-vitro* antibacterial activities of NHC-predecessors and Ag(I)-NHC complexes were tested against gram-positive bacteria (*Staphylococcus Aureus* and *Bacillus Cereus*), gram-negative bacteria (*Escherichia Coli* and *Listeria Monocytogenes*), and fungus (*Candida Albicans*) in Tryptic Soy Broth method. Ag(I)-NHC complexes showed higher antibacterial activity than pure NHC predecessors. The lowest microbial inhibition concentration (MIC) value of compound 3a was obtained as 11.56 µg/ml for *Escherichia Coli* and 11.52 µg/ml for *Staphylococcus Aureus*. All tested complexes displayed antimicrobial activity with different results.

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1. STRUCTURE

Cyclic diamine carbenes allow the provision of σ-donor-π-receiver complexes [1, 2] that have powerful chemical stability in terms of water and oxygen tolerance according to complexes relying on phosphine ligands and they have generally lower toxicity [3]. After sporadic studies, concerning the cellular toxicity of these kind NHC compounds, the cytotoxic effects [4] and mechanisms of action against bacteria it was identified [5, 6].

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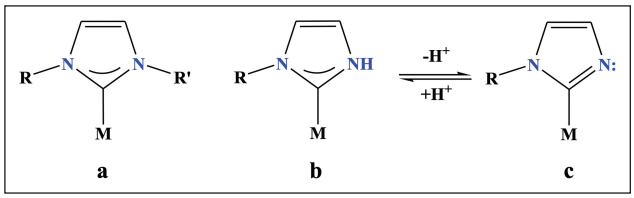

Figure 1. Complexes designed as general NHC **(a)**, pNHC **(b)**, and C-metalized azolato ligands **(c)**.

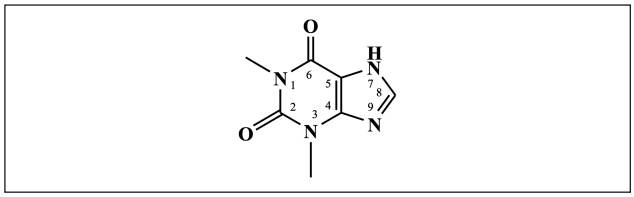

Figure 2. Numerical terminology of theophylline.

NHCs with minimum one NH functional group within the carbene heterocyclic structure are called protic NHCs or pNHCs [7]. These NHCs are not stable, in the free form because of rapid tautomerization to the suitable azole [8]. Additionally, they may be stabilized as ligands in different transition-metal complexes [9], and the synthesis of these pNHC complexes received interest and were prepared by many applications [10]. One feasible route for the adjustment of complexes with protic pNHC ligands is the oxidative supplementation of [11] *N*-alkyl halogen azoles [12] or unsubstituted azoles to different kind low-valent transition metals, such as Ni, Pd, and Pt. As a proton resource, this reaction gives pNHC complexes of type I, as an example [13].

While most NHCs used in inorganic chemistry act as observer ligands (Fig. 1a) that do not join directly in chemical transformations [14, 15], the development of NHCs exhibiting detrimental or assisting functionality were raised recently [16].

One lower class of these ligands are protic NHCs that have an acidic proton on one of the nitrogen atoms in the diamine heterocyclic compound [17]. In addition, they are deprotonated compounds containing a basic ring-nitrogen atom [18] (Fig. 1c).

The protonation method was extended to complexes of pNHC ligands, such as caffeine [19]. Even 2-halogenoazoles with a proton in place of an alkyl substituent on the azole ring nitrogen atom transport the protonation reactions with Pd (0) or Pt (0) to yield [19] the metal complexes with NH and NH-NHC ligands (IV) [20].

As model compounds, transition metal complexes of theophylline allow researched into the correlation between metal ions and nucleic acid oxo purine bases [21]. Theophylline is a monodentate ligand in a fundamental or neutral medium and it coordinates to metal ions through the N7 atom. In some samples, it functions as a bidentate N(7)/O(6) chelating ligand or as a bridging ligand with N(7)/O(6) chelation and N(9) coordination [22, 23].

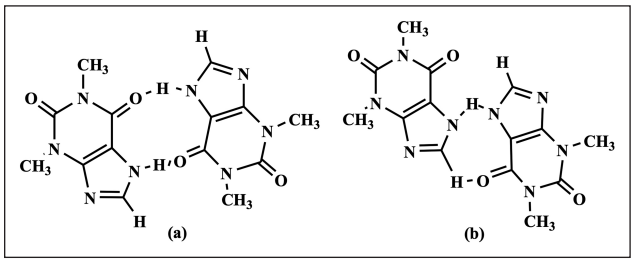

Figure 3. Hydrogen bond structure of theophylline.

Theophylline (1,3-dimethyl-3,7-dihydro-1*H*-purin-2,6-dione) is a natural *N*-methylated xanthine, consumed in beverages and food (Fig. 2). It is a purine alkaloid, 1,3-dimethylxanthine, with important biological properties [24]. It may be used as a respiratory stimulant for the treatment of lung disease and asthma [25]. Thanks to studies showed that theophylline will effectively block human immunodeficiency virus-1(HIV-1) [26].

Theophyllinium-derived compounds were obtained by binding tails with different properties to nitrogen atoms at positions 7 and 9 of the purchased theophylline compound, and their structure was characterized by spectroscopic methods. The XRD characterization of the theophylline molecule revealed strong interactions within crystal structures, such as, C–H···π, C=O···H and N···H···O (Fig. 3) [27].

Included among other health-related uses of theophylline, it has anti-inflammatory properties [28], antitumor potential [29, 30], and a role in neurodegenerative diseases [31]. In recent years, diverse fungi and bacteria have improved their resistance against drugs generally used in clinical studies; thus, there is a need to enhance the chemical and physical properties of drugs [32].

The synthesis and characterization of Ag (I) metal complexes with theophylline were investigated as a ligand for biological usage. Co-crystallization of a drug with another conformers greatly influences its physicochemical features, while it is hoped that metal complexes of theophylline will change the physiological structure of the drug by means of coordination bonds [33]. Alkali metal ions play a very important role in diverse biological subjects, such as within cellular diversity, pH, and tuning electrolyte balance [34–36]. In this study, it was proved that mono sodium salts possess a larger spectrum of antibacterial activity and they are effective especially against *Staphylococcus Aureus*, with over the range of pH 5.0 to 9.0 as bactericides.

Formation reactions for complex compounds involve the breaking of electron-rich olefins [37] by way of transition metals with low oxidation. The presentation of Ag(I)-NHC complexes, the transmetallation pathway [38] and stabilized *N*-heterocyclic carbine [39] make synthesis of functionalized carbene complexes possible in dissimilar studies. Amide, carbene donor polydentate ligand structures, pincer systems and tripodal have received great attention.

NHCs are synthesized in materials and modern medicine science because of their strong σ-transmitter and poor π-receiver characteristics. They were proven to be important compounds for coordination complexes with catalytic and medical activities [40].

Ag(I)-NHC complexes were recognized to have effective anticancer as antimicrobial agents not only with *in-vitro*, but also with *in-vivo* studies. In recent years, antimicrobial activities of Ag^+ ion against microorganisms have been used in medical studies. There are many studies about metal complexes of NHC compounds for dissimilar applications, including antimicrobial, antimitochondrial and anticancer studies in the literature [41, 42].

The synthesis and characterization of antimicrobial applications of new carbene complexes (3a-c) were presented in this paper. A number of bidentate theophyllinium, which are constitutional NHCs ligand pioneers, and their Ag(I)-NHC complexes were prepared. Sigma has a significant effect on reactivity due to electron-donating property in the environment where it is located. Ag(I) complexes were acquired by in-situ deprotonation of NHCs. Not only increasing chain length, but also methyl substituents in the theophylline ring increase the usage of Ag(I) complexes in bio-potential practice. Additionally, aryl bonding and two silver centers contributed to their antimicrobial action. Synthesized compounds were investigated with different techniques, such as FTIR, ^{1}H-NMR, ^{13}C-NMR, TGA, SEM, XRD, and elemental analysis [43].

Theophylline was acquired by the reaction of different substituents as ethanol, methyl acetamide and methyl acetate in a medium. Sodium carbonate was present as a base, and the theophyllinium cation resulted from this reaction. While 3a compound has small bulky bromide anion, 3b and 3c compounds have big bulky hexafluorophosphate anion. 3a, 3b and 3c compounds were obtained as Ag(I) complexes with interactions as a consequence of ligands 2a-c, with Ag_2O in C_2H_5OH or DMF. Ag(I)-NHC complexes, with symmetrical structure, were conjugated with hexafluorophosphate or bromine anions. Because of this arylation, compounds of theophylline derivatives with dissimilar properties were diverse in the sense of yield, conductivity, solubility and antimicrobial activity. NHCs and Ag(I)-complexes were tested against gram-positive and gram-negative bacteria, and fungi.

2. MATERIALS AND METHODS

2.1. Materials

Theophylline ($C_7H_8N_4O_2$, ≥99.00%), 2-bromoethanol (C_2H_5BrO ≥99.50%), 2-bromo acetamide (C_2H_4BrNO ≥99.50%) and methyl-2-bromo acetate ($C_3H_5BrO_2$ ≥97.00%) were supplied from Sigma-Aldrich (Poole, Dorset, UK). Dichloromethane (CH_2Cl_2 ≥99.9%), diethyl ether ($C_4H_{10}O$ ≥99.9%), deuterium oxide (D_2O ≥99.95%), deuterochloroform ($CDCl_3$ ≥99.80%), dimethyl formamide (DMF ≥99.80%), ethanol (C_2H_5OH ≥99.90%), potassium hexafluorophosphate (KPF_6 ≥99.50%), sodium carbonate (Na_2CO_3 ≥99.50%), and silver(I) oxide (Ag_2O ≥99.0%) were purchased from Merck (Germany). In addition, hexane (C_6H_{14} ≥99.00%) and ethyl acetate ($C_4H_8O_2$ ≥99.50%) were purchased at technical purity from local markets. All synthesized compounds were performed under Ar atmosphere using Schlenk line methods.

Minimum inhibition concentration (MIC) tests for each compound were investigated against reference bacterial strains: *Escherichia Coli* (ATCC 25922), *Listeria Monocytogenes* (ATCC 19115), *Salmonella Typhimurium* (ATCC 14028) as gram-negative bacteria, *Staphylococcus Aureus* (ATCC 25923), *Bacillus Cereus* (ATCC 11778), and a type of yeast *Candida Albicans* (ATCC 10231) [44]. Microorganisms were obtained from Technology Research-Development Application and Research Center in Trakya University (TUTAGEM, Edirne, Turkey). Bacterial strains and fungal strains were tested in sub-cultures.

2.2. Instrumentation

FTIR spectra were recorded with KBr pellets in an ATI Unicam 1000 spectrometer. Scanning electron microscope (SEM, Fei Quanta FEG 250) and Four-point probe device (Qiatek, FFP 4) were used to obtain surface images and solid state conductivity measurements, respectively. A pellet machine using a steel die (Desk-Top presser, Model: YLJ-24 MTI Corporation) under a pressure of ~10 tons was used to form a pellet. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Varian As 300 Merkur spectrometer operating at 300 MHz (^{1}H-NMR) and 75 MHz (^{13}C-NMR) in $CDCl_3$.

Thermogravimetric analysis (TGA-DTA) TGA 400 was performed by using EXSTAR 6300 at Akkim Kimya Company. A vacuum oven (Nuve Company, vacuum capacity of 760 mmHg with adjustment of temperature of 250 °C) was used for synthesis procedures. X-ray diffraction (XRD) analysis was done by using a Malwern Panalytical Empryean (PANalytical Netherlands) at Ataturk University. Elemental analysis was done by using 836 Series Elemental Analyzer at Trakya University (TUTAGEM). Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus.

2.3. Antimicrobial Activities of NHC Complexes

Antimicrobial activities of NHC complexes were tested using the agar dilution procedure proposed by the Institute of Clinical Laboratory Standards. For this purpose, *Escherichia Coli* (ATCC 25922), *Listeria Monocytogenes* (ATCC 19115), *Staphylococcus Aureus* (ATCC 25923), *Bacillus Cereus* (ATCC 11778), *Salmonella Typhimurium* (ATCC 14028), and a type of yeast *Candida Albicans* (ATCC 10231) were incubated in Tryptic Soy Broth (TSB) for 24 h at 37 °C. The McFarland Scale was set to 0.5 [45]. Ampicillin was used in cultures as antimicrobial control. Antimicrobial and soluble material stock solutions were filtered using 0.45

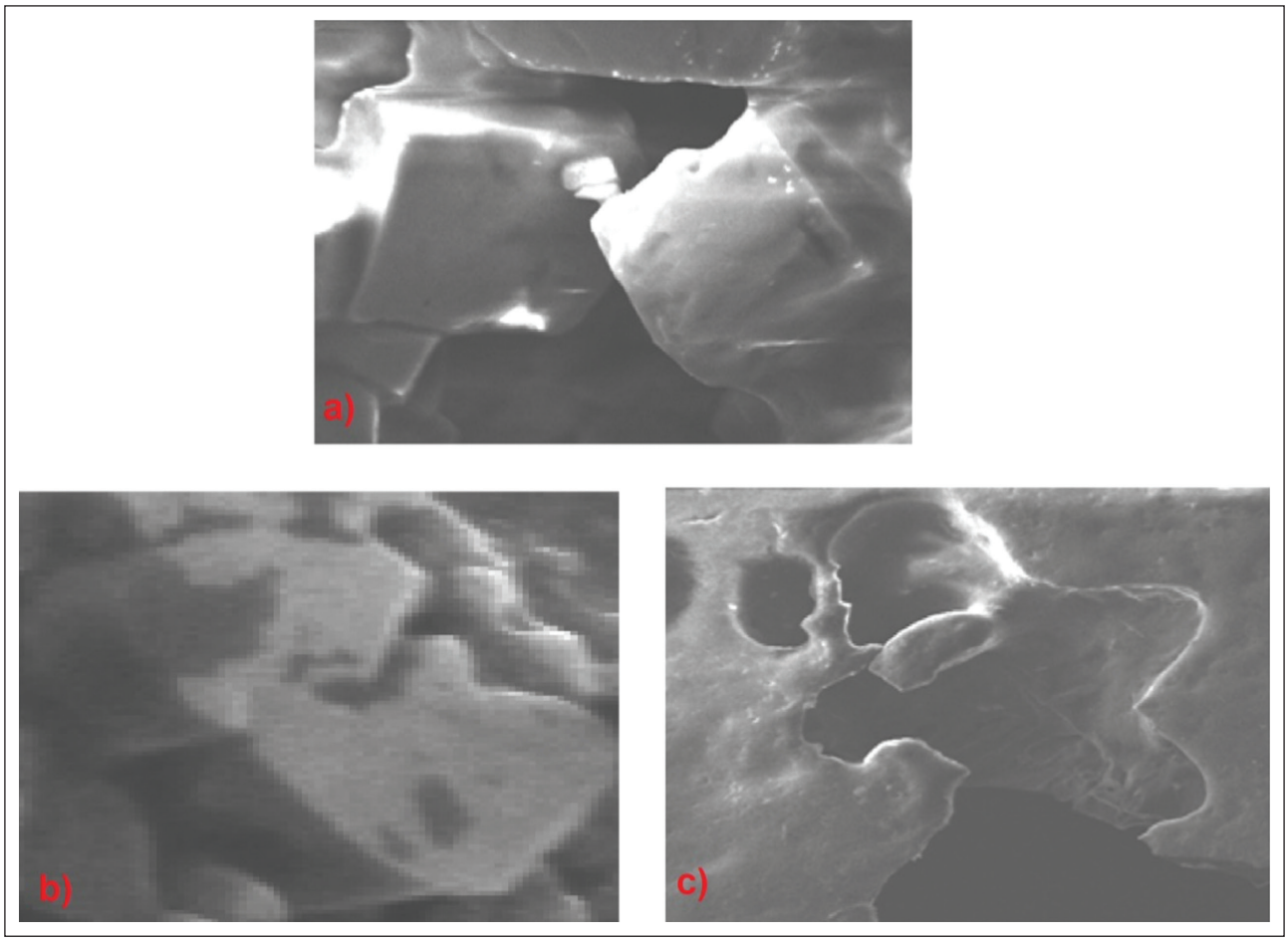

Figure 4. SEM images of NHC complexes, compounds (a) 3a, (b) 3b and (c) 3c. Inset: Time of sample gathering (days) **(a)** 500 µm, **(b)** 300 µm and **(c)** 500 µm scale bar.

µm sterile filter. The results were evaluated for bacteria and yeast after incubation periods of 24 and 48 h. Absorbance was measured at 600 nm and vitality % values were determined. Stock solutions of whole compounds were prepared in DMSO and dilutions were made with deionized water. Concentrations of tested whole compounds were prepared at 100, 50, 25 and 12.5 µg/mL. All inoculated plates were incubated and assessed for bacteria and yeast after incubation periods of 24 and 48 h. The lowest concentrations of compounds preventing growth were determined as MICs [46].

3. RESULTS AND DISCUSSION

3.1. Synthesis of NHCs

Theophylline (1) compound was added to 2-bromoethanol, ethyl-2-bromoacetate and methyl-3-bromopropanoate compounds, respectively. Each of these compounds were connected to NHCs for symmetrical attainment (2a-c). The obtained NHC predecessors (2a-c) were characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR, melting point analysis, liquid and solid-state conductivity, TGA analysis, XRD spectroscopy and SEM analysis.

3.2. SEM Images of NHC Complexes

SEM images of NHC in NHC-Silver(I)-Bromide = 1:1 are illustrated in Figure 4a. The surface area relative to NHC and Ag(I)-bromide is given in Figure 6a. This uneven surface of bromide has many nucleation regions for the growth of silver bromide nanoparticles. SEM images of NHC in NHC-Silver(I)-Bromide = 1:1 are shown in Figure 4b. The large porous structures were enhanced on the surface area relative to NHC and Ag(I)-bromide. SEM images of NHC in NHC-Silver(I)-Bromide = 1:1 can be seen in Figure 4c. The porous spherical nanoparticles were enhanced on the surface area relative to NHC and Ag(I)-NHC bromide (compound 3c) [47].

3.3. TGA and XRD Analysis

Thermal gravimetric analysis (TGA) measurements of Ag(I)-NHC complexes (3a, 3b and 3c) and weight loss of compounds occurred in 4 steps (Fig. 5). In the first step, temperature was between 150 and 400 °C. The weight loss came from dehydration of components. In this step for water molecule lost is 2 mole. In the second step, the temperature was between 400 and 510 °C and is due to primary carbonization. There was higher weight loss (58.73%) at 510 °C due

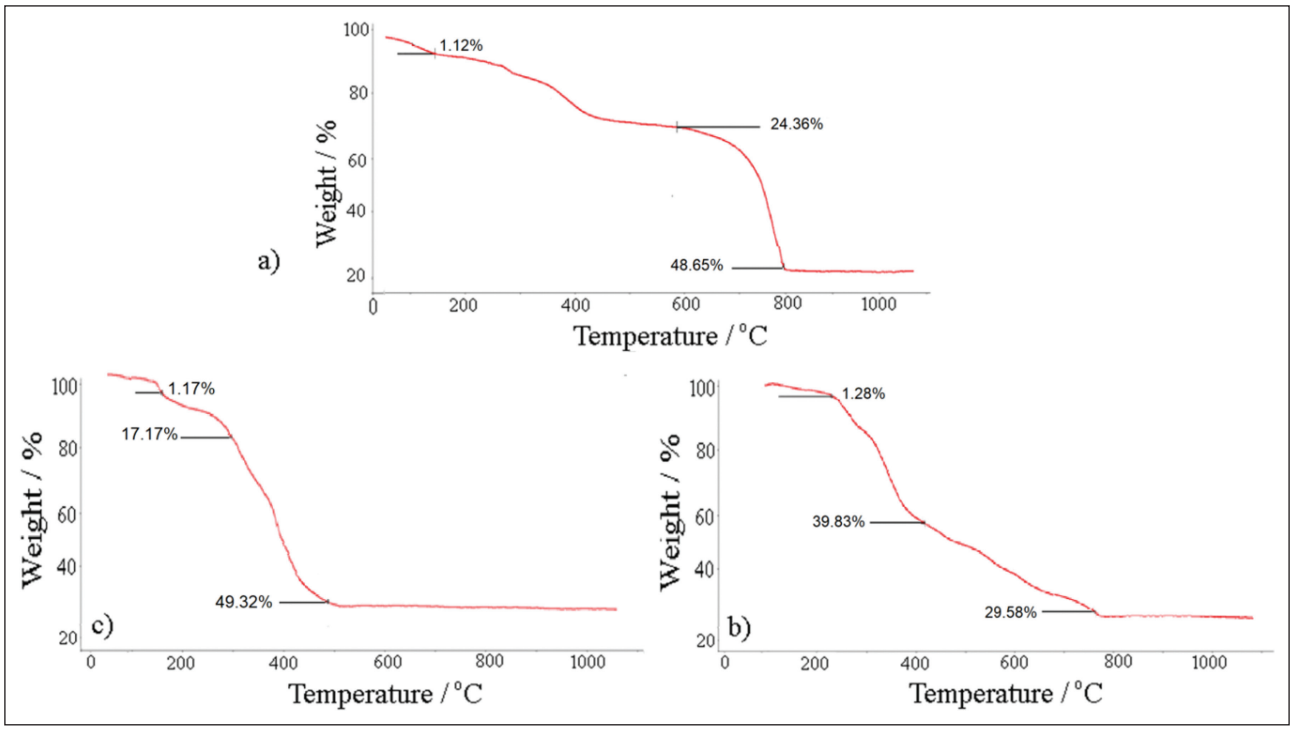

Figure 5. TGA measurements for NHC complexes, compounds **(a)** 3a, **(b)** 3b and **(c)** 3c.

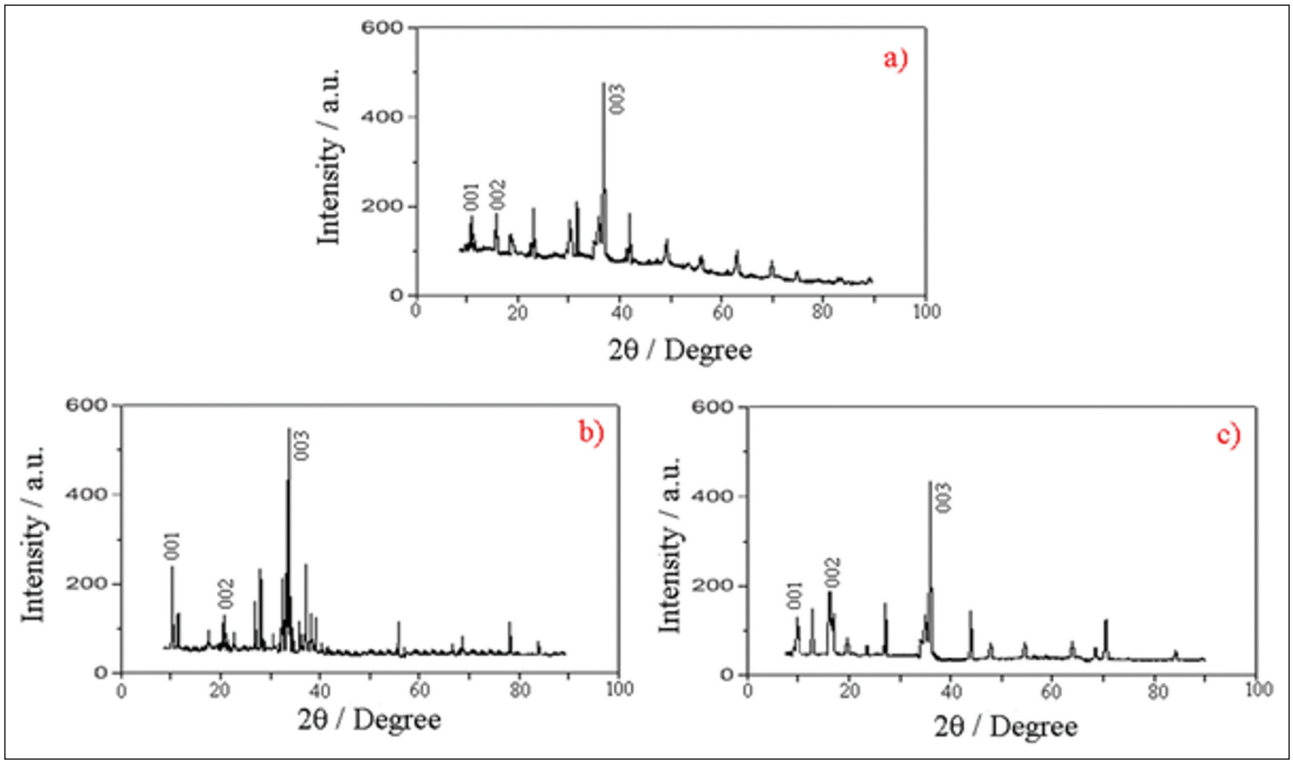

Figure 6. XRD measurements of NHC complexes, compounds **(a)** 3a, **(b)** 3b and **(c)** 3c.

to major volatiles and tar elimination. In the third step, the temperature was between 510 and 795 °C and the compound was nearly completely carbonized (weight loss = 39.83%). The ashes content of NHC is about 24.36%. The results of elemental analysis supported the TGA results. The weight loss of inorganic elements was obtained as 1–1.5% [48].

Table 1. MIC values of compounds (2a-c and 3a-c) for bacterial resistance in antimicrobial tests

	MIC (µg/ml)				
	Gram-negative		Gram-positive		Fungal
NHC complex	*Escherichia Coli*	*Listeria Monocytogenes*	*Staphylococcus Aureus*	*Bacillus Cereus*	*Candida Albicans*
2a	60.00	80.06	90.50	97.53	60.80
3a	11.56	28.36	11.52	44591	22.41
2b	99.02	52.50	85.03	99.00	53.95
3b	20,59	30.47	21.73	32.75	48.45
2c	87.10	58.29	99.00	99.20	57.65
3c	26.43	48.74	44.86	33.86	19.26
Ampicillin	5.00	5.00	10.00	10.00	–

In analysis of TGA plots of compounds 3a, 3b and 3c (Fig. 7a–c) were indicated an initial weight loss above 150 °C, based on the removal of water molecules. Respectively, this weight losses are higher than 1.12, 1.17 and 1.28% for impregnation degrees lower than 101% weight and reaches 8% for NHC, which confirms that these carbons are less hydrophilic in good agreement with their low oxygen surface contents. The second weight loss was followed on the step between 150 and 585 °C and is determined to decomposition of the oxygenated surface groups. In these step water losses for compounds are equivalent to 0.5, 1 and 2 moles, respectively. In the third step, when the temperature reached 500 to 800 °C, bigger weight loss occurred due to the carbonization of the NHC pioneer. Over generally 797 °C, the compound is nearly carbonized. In these step weight losses for compounds are equivalent to 74.13%, 67.66% and 70.69%, respectively.

XRD measurements of the NHC complexes of compounds 3a, 3b and 3c are illustrated in Figure 8. The XRD spectrum gives information depending on two phases with inorganic and organic structure for compound 3a. In this NHC-based Ag(I)-complex, hydrogen, nitrogen and carbon elements were pivotal components and silver and bromide ions were preserved compounds. The XRD peaks were acquired as 2θ= 12.78, 16.11 and 47.81°. In the designed NHC-based Ag(I)-complex of compound 3b, the hydrogen, nitrogen and carbon elements were central components and silver and hexafluorophosphate ions were preserved compounds. The XRD peaks at 2θ= 12.18, 12.84, 14.61 and 45.64° can be observed in Figure 8b. This can also be due to the structured formation of NHCs [49].

In the prepared NHC-based Ag(I)-complex of compound 3c, nitrogen, hydrogen and carbon elements were central components and silver and hexafluorophosphate ions were preserved compounds (Fig. 8c). The XRD peaks at 2θ= 12.36, 12.42, 14.81, and 45.27° were observed due to the structure of NHCs.

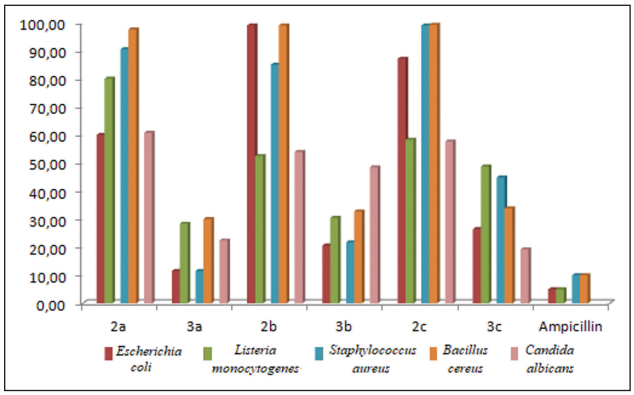

Figure 7. Antimicrobial activities of carbenes and Ag(I)-NHC ligands.

3.4. Conductivity Tests of NHCs and Their Complexes

Conductivity measurement tests of NHCs and their complexes were taken at molar concentration of 10^{-3} M in H_2O medium. The conductivity values for compounds 2a, 2b and 2c were acquired as 21.80, 23.20 and 25.90 µS/cm, respectively. But the conductivity values of NHC complexes increased to 78.25, 82.40 and 108.70 µS/cm for compounds 3a, 3b and 3c, respectively.

Solid-state conductivity of compounds 2a, 2b, 2c, 3a, 3b, and 3c was measured by Four-point probe device. All materials are pressed into a pellet form using the pellet machine. The highest conductivity was acquired as 5.94 $\mu S \times cm^{-1}$ for compound 2b. Other conductivity results are 0.36, 0.58, 4.10, 5.89 and 3.96 $\mu S \times cm^{-1}$ for compounds 2a, 2c, 3a, 3b and 3c, respectively. NHC complexes have conductivity of 4.10, 5.89 and 3.96 $\mu S \times cm^{-1}$ for compounds 3a, 3b and 3c, respectively. Inclusion of Ag metals in the complex form increases the conductivity results [50].

4.4. Microbial Activity of NHCs Complexed or Similar

The utility of Ag(I)-NHC complexes 3a, 3b and 3c for antimicrobial strains has been studied in more detail (Table 1). Compounds 3a, 3b and 3c displayed parallel activities

against both gram negative and gram positive bacteria and fungi. According to these results were more effective than the Ag(I)-NHC complexes carbenes of theophyllinium. Results are beneficial for synthesis of NHC compounds with high antimicrobial activities [51–54].

5. CONCLUSIONS

Thanks to the synthesis methods determined in the literature, derivatives of the theophyllinium cation were obtained by alkylation of theophyllinium. NHC cyclic complexes were synthesized as a result of the interaction of this theophyllinium cation with Ag_2O. The structural analyses of compounds 3a-c were performed with ^{1}H-NMR, ^{13}C-NMR, FTIR and mass spectrometry.

A serial of recent NHC predecessor complexes include symmetrical NHC ligands, which were obtained and characterized by various methods, such as ^{1}H-NMR, ^{13}C-NMR, FTIR liquid and solid-state conductivity, TGA analysis, XRD spectroscopy and melting point analysis. The antimicrobial activities of these Ag(I)-NHC complexes were published for the first time in the literature. NHC compound 3a displayed better antimicrobial activity against bacteria and fungi compared to another complexes, at lower concentrations.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FINANCIAL DISCLOSURE

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PEER-REVIEW

Externally peer-reviewed.

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