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# Anticancer and antibacterial properties of trinuclear Cu(I), Ag(I) and Au(I) macrocyclic NHC/urea complexes

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ABSTRACT

Synthesis and characterisation of the first macrocyclic Cu(I), Ag(I) and Au(I) tricarbene/urea *N*-heterocyclic carbene (NHC) complexes is described and their fluorescence properties are compared to related tetracarbene complexes. The newly described silver and gold complexes show luminescence with emission maxima at $\lambda_{em,max}$ = 481 nm and $\lambda_{em,max}$ = 334 nm, respectively. Moreover, their ability to inhibit the growth of bacteria (*S. aureus* and *E. coli*) and cancer cells (HeLa and MCF7) is investigated. A strong influence of the metal is observed. While the copper and gold complexes are inactive against bacteria, the silver complex depicts a moderate activity (MIC ≈ 30 µM). The copper and silver complexes exhibit antiproliferative activity in both cell lines, ranging from 25.1 µM to 3.03 µM.



## 1. Introduction

The first isolable and stable *N*-heterocyclic carbene (NHC) complexes were described by Wanzlick and Öfele in 1968, followed by Arduengo, who synthesized the first isolable free carbene in 1991 [1–3]. At this point NHCs emerged as promising ligands for transition metal complexes for various applications in laboratory as well as in industry. [4] Originally they were mainly applied in catalysis as promising replacements of phosphine ligands. In general, NHCs are considered as strong $\sigma$-donors, usually resulting in strong metal bonds and a better oxidation and thermal stability, compared to phosphines. [5] Moreover, the steric and electronic properties of NHCs can be varied easily [4, 6–10]. Nowadays NHC complexes of late transition metals such as Cu, Ag, Au, Pd or Pt have also gained attention in the field of bioinorganic and medicinal chemistry as antibacterial or anticancer agents [11-14]. NHCs exhibit distinct advantages compared to phosphines, since they are nontoxic and exceptionally stable, also under physiological conditions [13-16]. Due to the higher stability of Ag(I)-NHC complexes, the silver ions are released more slowly, thus, being therapeutically active for a longer time [17-20]. Gold complexes emerged as promising alternatives due to their different mechanism of action, compared to the well-established metallodrug cisplatin and its derivatives [13, 20-22]. The antiproliferative properties of active Au compounds are assigned to specific inhibition of thioredoxin reductase (TrxR), being overexpressed in many cancer cells. [23, 24] Moreover, gold complexes can also inhibit the growth of certain bacteria, attributable to a certain specificity to TrxR [25-29]. Berners-Price *et al.* reported that Au(I)-*bis*-NHC complexes can selectively accumulate in the mitochondrial membrane of cancer cells due to their delocalized lipophilic cationic character (DLCs) [30-32].

Recently, bi- or multi-dentate NHC complexes gained attention, also in the field of bioinorganic chemistry, due to high stability under physiological conditions and against thiols. This outstanding stability might prevent a decomposition by blood proteins (e.g. glutathione). [33, 34] Some of those complexes show luminescence in solution due to $d^{10}$-$d^{10}$ interactions (aurophilic/argentophilic interactions), being advantageous for cell imaging studies. [35, 36] In contrast to the frequently applied modification with an organic fluorophore substituent, which may affect the biological properties, the ligand is not modified. [37, 38] Recently, a 16-membered

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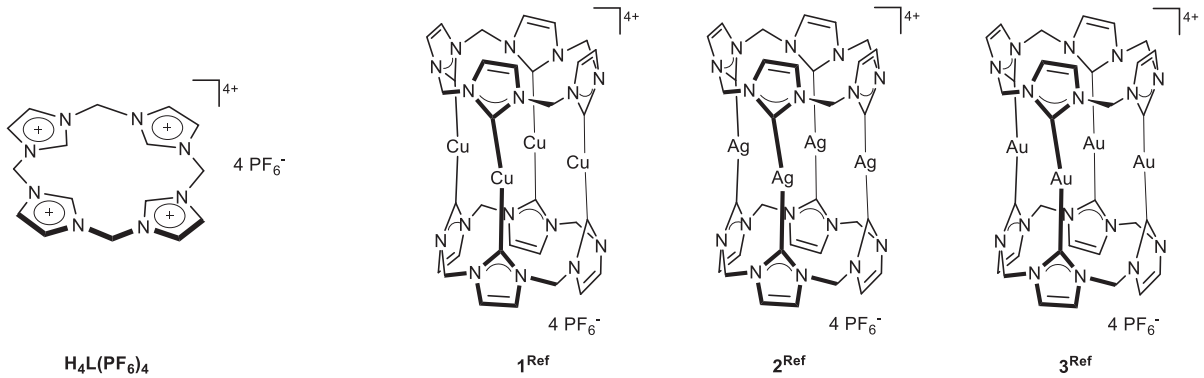
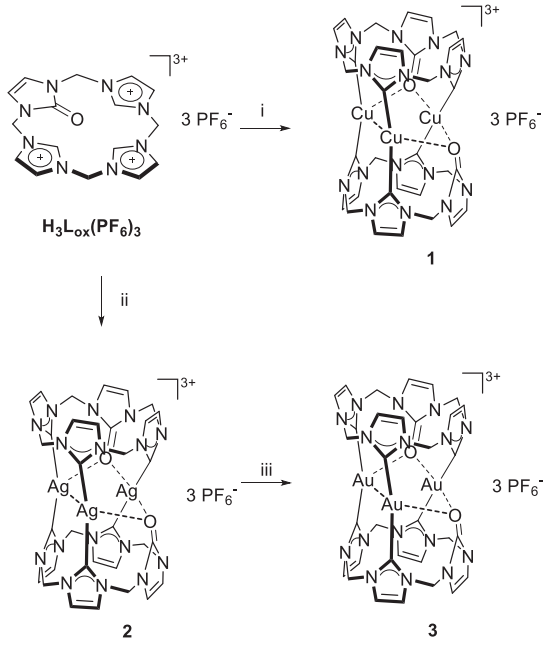



**Scheme 1.** Previously reported Cu(I), Ag(I) and Au(I) tetracarbene complexes [39, 41].




**Scheme 2.** synthesis of complexes **1**, **2** and **3**. i) according to the respective literature procedure [41], ii: 3.0 equiv. $Ag_2O$, r.t., 16 h in MeCN (44% yield): iii) 1.1 equiv. Au(tht)Cl r.t. 16 h in MeCN (61% yield).

macrocyclic imidazolylidene tetracarbene ligand $\mathbf{H_4L(PF_6)_4}$ and its corresponding linear molecular box-type copper(I)-, silver(I)- and gold(I)-complexes were synthesized (scheme 1) [39-41]. Only the gold complex is reported to exhibit photoluminescence with an emission maximum at $\lambda_{em,max}$ = 442 nm and presents a moderate cytotoxicity against various cell lines ($IC_{50}$-values ranging from 44.5 µM in HeLa cancer cells to 99.7 µM in MCF7 breast cancer cells after 48 h incubation time). [39, 42]

The corresponding Cu(III) and Au(III) complexes of the same ligand feature a square planar structure of the ligand, as observed for the Fe(II/III), Co(III), Ni(II), Pd(II) and Pt(II) derivatives. [41, 43, 44] [39, 45] Interestingly, upon reaction of the Cu(III) complex with acetic acid, one imidazole moiety is oxidized to a cyclic urea, forming a tricationic macrocyclic imidazolium salt $\mathbf{H_3L_{Ox}(PF_6)_3}$ (scheme 2). [41] Although, a variety of different macrocyclic ligands is reported, the amount of cyclic ligands bearing three NHCs is scarce, since they cannot be obtained by simple condensation reactions of two *bis*-imidazoles, making $\mathbf{H_3L_{Ox}(PF_6)_3}$ an interesting motif for further investigations. So far, only the Cu(I) NHC complex **1** is reported with this type of ligand. Besides copper NHC bonds the compound also features interactions between copper and the oxygen atoms of the cyclic urea moieties (scheme 2). However, no application for this type of complexes has been reported yet. [41]

In this work, the synthesis and characterization of the related Ag(I) and Au(I) complexes as well as the assessment of their cytotoxic and antibacterial properties is reported. These three M(I) NHC complexes (M = Cu (**1**); Ag (**2**); and Au (**3**)) are tested against two common cancer cell lines (MCF7 breast- and HeLa cervix- carcinoma cells) and two bacteria strains (*Escherichia coli* (*E. coli*) and methicillin-resistant *Staphylococcus aureus* (*S. aureus*)). To investigate the influence of the cyclic urea ligand $\mathbf{L_{Ox}}$ compared to **L** on the photoluminescence properties as well as $d^{10}$-$d^{10}$ interactions, UV/Vis and fluorescence spectra of all compounds are reported.

## 2. Results and Discussion

The silver (I) complex **2** is synthesized by reacting the imidazolium salt $\mathbf{H_3L_{Ox}(PF_6)_3}$ with $Ag_2O$ (scheme 2). Absence of the imidazolium proton resonances in the $^1$H-NMR spectrum and characteristic Ag-carbene resonances in the range 186 ppm - 183 ppm in the $^{13}$C-NMR spectrum support the successful complex formation. For each carbene two resonances are observed, due to coupling with the two silver isotopes with relative abundances of 51.8% ($^{107}$Ag, S = 1/2) and 48.2% ($^{109}$Ag, S = 1/2). [46] The resonances of the backbone- and methylene bridge protons are slightly high-field shifted compared to the imidazolium salt ligand precursor $\mathbf{H_3L_{Ox}}$. [41] Owing to the formation of the molecular box-type complex and the resulting rigid conformation the protons of the methylene bridges and imidazole backbones are not equivalent, leading to additional resonances in the $^1$H-NMR spectrum. Every signal is observed as a doublet, due to the $^3J_{HH}$-coupling of the backbones and the geminal $^2J_{HH}$-coupling of the methylene bridges. However, many resonances are overlapping. The resonance splitting is in accord with the already reported Cu(I) complex **1**. The carbene resonances in the $^{13}$C-NMR spectrum are slightly downfield shifted compared to the copper complex **1** and are in the typical range for Ag-carbenes. [17, 47] Regarding the silver carbene resonances no notable difference is observed compared to $\mathbf{2^{Ref}}$. ESI-MS and elemental analysis are in accordance with the theoretical values for the complex **2** and thus, prove the successful formation.

The gold complex **3** is formed by transmetallation of the respective silver complex **2** (scheme 2). In the $^1$H-NMR spectrum the above mentioned signal pattern is observed, indicating a similar structure, however slightly shifted. Interestingly, the doublets overlap to a lesser extent compared to the silver complex **2**. Furthermore, one resonance of the $CH_2$-bridge is significantly shifted downfield to 8.1 ppm. Compared to the carbene resonances of **2**, no notable shifts are observed for the corresponding signals of **3**. However, these resonances are observed as singlets, indicating a

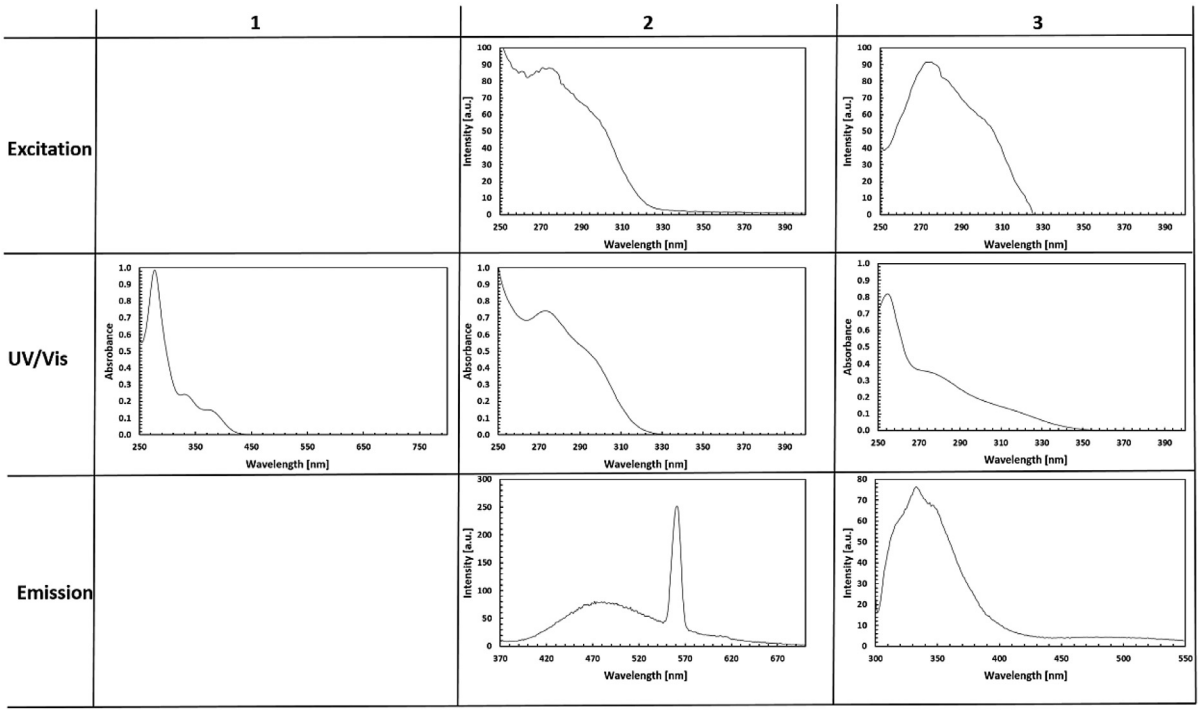



**Figure 1.** Excitation (top row), UV/Vis (middle row) and emission spectra (bottom row) of **1** (left), **2** (middle) and **3** (right). As Cu(I) complex **1** does not show fluorescence properties, excitation spectra and emission spectra are not displayed. Concentrations: 20 μM; solvent: MeCN.

successful transmetallation. ESI-MS and elemental analysis are in accordance with the theoretical values for **3**.

To investigate potential luminescence caused by $d^{10}$-$d^{10}$ metal interactions, UV/Vis-, emission- and excitation spectra are recorded (Figure 1).

Complex **1** shows three absorption maxima in the UV/Vis spectrum at 280 nm, 329 nm and 338 nm. However, the compound does not exhibit any fluorescence properties, in contrast to its silver(I) and gold(I) derivatives (Figure 1). Complex **2** depicts two absorption maxima in the UV/Vis spectrum at $\lambda_{abs,max1}$ = 276 nm and $\lambda_{abs,max2}$ = 295 nm. $\lambda_{abs,max,2}$ represents a shoulder of the more intense band $\lambda_{abs,max,1}$. According to the respective excitation spectrum, both maxima are decisive for the fluorescence of compound. The emission spectrum shows one broad maximum at $\lambda_{em,max}$ = 481 nm, which is typical for argentophilic $d^{10}$-$d^{10}$ interactions (Figure 1). Those often result in fluorescence with broad emission bands ranging from 400 nm to 600 nm [48-50]. Interestingly, in contrast to **2**, the tetranuclear Ag (I) tetra-NHC complex $2^{Ref}$, which also features Ag–Ag interactions as demonstrated by SC-XRD, does not show luminescence properties. [39] Therefore, the appearance of luminescence in the case of **2** presumably is a result of the interaction with the urea moieties of the macrocyclic ligand. This assumption is supported by the previously reported effect of urea-substituted macrocycles on silver(I) triflate, leading to fluorescence. [51] The second maximum in the emission spectrum at 552 nm represents an artifact caused by irradiating the sample at $\lambda_{max,1}$ = 276 nm (2 × 276 nm = 552 nm) and does not resemble 2 (Figure 1).

The UV/Vis spectrum of complex **3** shares similarities with the spectrum of complex **2**, as it also features two absorption maxima. However, those appear blue-shifted- and correspond to $\lambda_{abs,max,1}$ = 256 nm and $\lambda_{abs,max,2}$ = 278 nm, respectively. According to the excitation spectrum, only the latter maximum is responsible for the fluorescence properties of **3**. Although, in contrast to compound **2**, the emission spectrum of **3** shows a maximum at $\lambda_{em,max}$ = 334 nm, which lies in the ultraviolet range, weak emission in the visible violet range from ca. 380 nm to 410 nm is also observed (Figure 1). The observed emission and excitation maxima are in the typical range of other Au(I) NHC complexes, featuring aurophilic $d^{10}$-$d^{10}$ interactions. [52, 53] Such Au–Au interactions and the resulting photoluminescence were also reported for the related tetranuclear Au (I) tetra-NHC complex $\mathbf{3^{Ref}}$, which fluoresces blue light with an emission maximum of 442 nm. [39]

**Table 1**
$IC_{50}$- and MIC-values of the compounds **1, 2** and **3**. $IC_{50}$ and MIC values were determined after 24 h and 18 h, respectively.

| Compound | 1 | 2 | 3 | Reference |
|---|---|---|---|---|
| HeLa | 25.1 μM | 3.61 ± 1.04 μM | n.a. | 39.9 ± 4.6 |
| MCF7 | 12.23 ± 1.08 μM | 3.03 ± 1.06 μM | n.a. | 18.1 ± 5.1 μM |
| *E. coli* | n.a. | 25-50 μM | n.a. | 37 μM |
| *S. aureus* | n.a. | 30 μM | n.a. | 33 μM |

*Compounds with $IC_{50}$/MIC > 100 μM are considered as not active (n.a.). Error deviations are expressed as standard error. Cisplatin and $AgNO_3$ are included as reference compounds for the anticancer and antibacterial properties, respectively [54–56].

Since, Cu(I), Ag(I) and Au(I) are often applied as anticancer or antibacterial agents, compounds **1, 2** and **3** are tested against two cancer cell lines, namely HeLa (cervix) and MCF7 (breast), and two bacteria strains (*E. coli* (Gram negative) and *S. aureus* (Gram positive)) (Table 1). The antiproliferative activity against HeLa and MCF-7 is expressed as $IC_{50}$-values. They are obtained *via* a colorimetric method with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT assay). The antibacterial activity is expressed as MIC- (minimum inhibitory concentration) values.

The antiproliferative activity of the complexes strongly depends on the metal. Copper complex **1** only presents a moderate activity against cancer cells and no activity against bacteria. While silver complex **2** shows a high anti-proliferative activity against cancer cell lines and a moderate activity against bacteria, the gold complex **3** is always inactive. When comparing the gold complex **3**

to the previously reported tetranuclear complex $\mathbf{3}^{\mathbf{Ref}}$, a loss in activity is observed. $\mathbf{3}^{\mathbf{ref}}$ presents moderate antiproliferative activity ($IC_{50}$ = 44.5 ± 20 µM and 97.7 ± 22 µM after 48 h incubation in HeLa and MCF7, respectively). [42] It seems that less incubation time and lowering the amount of gold nuclei leads to a reduction of the already low activity. The cyclic urea moiety has no positive effect. Although many gold and copper complexes inhibit the growth of bacteria, compounds **1** and **3** do not. Neither the gold, nor the copper complex show a growth inhibition of selected Gram-negative (*E. coli*) or -positive bacteria (*S. aureus*). The Ag(I) NHC complex **2** gives the most promising results, with a moderate activity against bacteria and a good activity against cancer cells. No dependence on the Gram- positive or -negative bacteria strains is observed. In both cases the MICs are around 30 µM, which is comparable to the reference $AgNO_3$. In contrast to the moderate activity against bacteria, **2** exhibits significant antiproliferative activity against both cancer cell lines with $IC_{50}$-values around 3 µM after 24 h incubation time, being superior to cisplatin and comparable to many other reported silver complexes. [12, 17]

## 3. Conclusion

Novel trinuclear macrocyclic gold(I) and silver(I) NHC complexes bearing a cyclic urea moiety were synthesized and characterized by ESI-MS, elemental analysis, NMR spectrometry, UV/Vis spectrophotometry and fluorescence spectroscopy. Unlike the non-luminescent related silver tetra-NHC complex $\mathbf{2}^{\mathbf{Ref}}$, the trinuclear silver complex **2** exhibits luminescence properties with an emission maximum at $\lambda_{em,max}$ = 481 nm as a result of argentophilic interactions. A similar behavior is observed for the gold complex **3**. However, the emission maximum is blue-shifted to $\lambda_{em,max}$ = 334 nm. In addition, their ability to inhibit the growth of cancer cells and bacteria is investigated. The copper complex shows moderate activity against HeLa (25.1 µM) and MCF7 (12.2 ± 1.08 µM), which is nevertheless still better than cisplatin. The silver complex **2** shows better antiproliferative activity than the reference drug cisplatin and the copper complex **1** against breast- (MCF7) and cervix- (HeLa) carcinoma cell lines with $IC_{50}$-values of 3.06 ± 1.06 µM and 3.61 ± 1.04 µM, respectively. Moreover, it presents moderate MIC-values against gram- positive and -negative bacterial strains *S. aureus* and *E. coli*. In contrast to the Cu and Ag compounds, Au complex **3** is inactive against all tested cancer cell and bacteria lines.

## Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2020.121643.

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