Introduction to the Scientific Community – Inorganic Chemistry

Coinage metal bis-NHC complexes for medicinal applications – synthesis and stability tests

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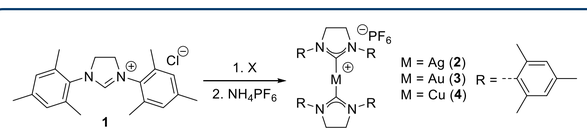
Introduction

Today, cancer is among the most common causes of death and thus a lot of research has been dedicated to the development of antitumor drugs. And while available drugs are quite effective, they can show problems with selectivity, leading to severe side effects, as well as ineffectiveness against multi-resistant tumor cell lines. This resistance can possibly be attributed to significantly increased glutathione (GSH) levels.[1]
Several bis-NHC Au(I) complexes have been shown to be highly selective towards certain tumor cell lines. Their inhibitory effects on tumor growth can be attributed to the inhibition of the mitochondrial protein thioredoxin (Trx) and Trx reductase (TrxR), leading to oxidative stress within the cell and ultimately self-induced cell death.[2]
In this poster, the stability of triazole based bis-NHC Au(I) complexes against the biologically active substances GSH and *L*-cysteine under physiological conditions is presented
Furthermore, imidazoline-based coinage metal bis-NHC complexes were synthesized and characterized.

Synthesis of imidazole-based bis-NHC complexes

The bis-NHC complexes were synthesized via direct synthesis from **1** or via transmetalation of **2**.



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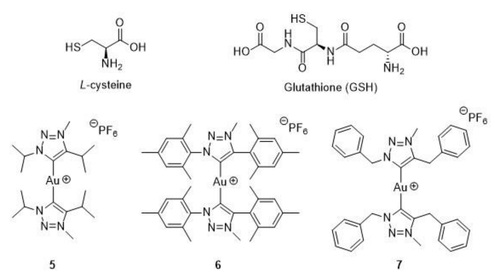
General reaction of imidazolinium salt (**1**) towards Ag(I), Au(I) and Cu(I) complexes (**2-4**).

Reaction conditions	Yield	Comments
1+CuOAc+KHMDS, RT, 16 h	28 %	Purest product obtained
1+CuCl+KOtBu, RT, 16 h	41 %	Around 10 % residual ligand left in the pro-duct after purification
1+Cu_2O, RT, 24 h	---	Highly impure mix of **4**, **1** and possibly mono-NHC species
2+CuCl, RT, 24 h	53 %	Small amounts of **2** in product, no full conversion
2+CuCl, 50°C, 72 h	56 %	Higher conversion, but side products formed

Tested synthetic pathways towards the novel Cu(I) complex **4**.

The Ag(I) complex **2** was synthesized stirring **1**, potassium-*tert*-butoxide and silver(I)acetate overnight, leading to an improved reaction time. For the Au(I) complex **3** no pure product could be obtained.

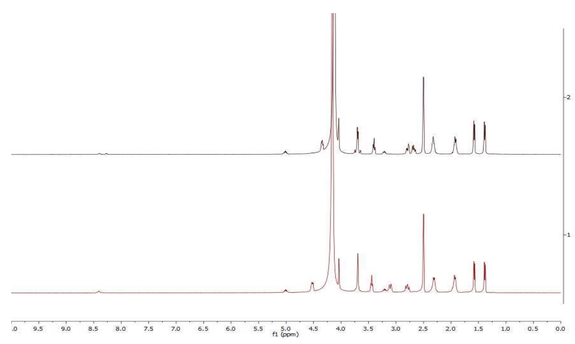
Stability of triazole-based Au(I) bis-NHC complexes



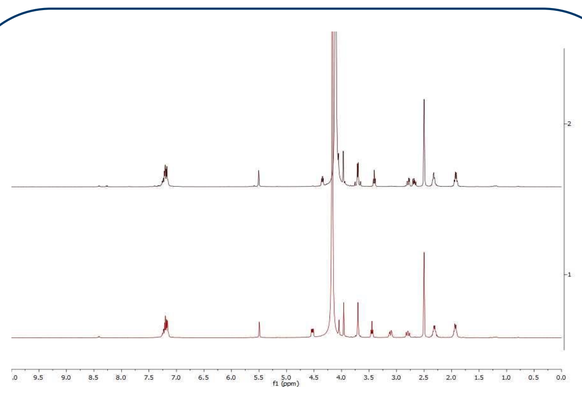
L-Cysteine, GSH and tested complexes *bis*-1,4-diisopropyl-3-methyl-triazolium gold(I) hexafluorophosphate (**5**), *bis*-1,4-dimesityl-3-methyl-triazolium gold(I) hexafluorophosphate (**6**), *bis*-1,4-dibenzyl-3-methyl-triazolium gold(I) hexafluorophosphate (**7**).

The stability tests were carried out in a mixture of deuterated phosphate-buffered saline (PBS), deuterated dimethyl sulfoxide (DMSO-d_6) and GSH or *L*-cysteine respectively under physiological conditions.
All tested complexes were stable over 72h, shown using ^{1}H-NMR and ESI-MS measurements. However solubility issues after 72h lead to decreased resolutions in some of the ^{1}H-NMR spectra.

Stability test spectra



^{1}H-NMR spectra of **5** against GSH after 0h (top) as well as 72h (bottom). No degradation can be observed.



^{1}H-NMR spectra of **7** against GSH after 0h (top) as well as 72h (bottom). No degradation can be observed.

Conclusion

The stability of the triazole-based Au(I) complexes **5-7** against GSH and *L*-cysteine over a period of 72h under physiological conditions was shown. Looking ahead, in vitro testing of these complexes against various tumor cell lines as well as healthy ones to determine their toxicity as well as selectivity against tumor cells can be performed.
Furthermore, synthetic routes towards a novel imidazoline-based Cu(I) bis-NHC complex **4** were presented, as well as an improved synthetic pathway towards the previously known imidazoline-based Ag(I) bis-NHC complex **2**. Their stability can be tested in future research, as was done with complexes **5-7**.

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[1] A.-M. Florea, D. Büsselberg, *Cancers* **2011**, 3, 1351.
[2] S. J. Berners-Price, A. Filipovska, *Metallomics,* **2011**, 3, 863.