Synthesis and radiolabelling of a N_2S_2-bifunctional chelate ligand with ^{77}As

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The element arsenic provides a range of interesting radioactive isotopes suitable for positron emission tomography (PET) and endoradiotherapy (ERT). ^{72}As (T½ = 26 h, 88 % β^+) and ^{74}As (T½ = 17.8 d, 29 % β^+) are the PET-isotopes of choice for the observation of slow metabolic processes and long term pharmacokinetics like the enrichment of antibodies in tumor tissue or the localisation of stem cells *in vivo*. ^{77}As (T½ = 38.8 h, 100 % β^-) is a particle emitter suitable for ERT due to its low γ-dose rate.
Our used labelling synthon [*As]AsI_3 has three free reaction sites and is able to form three covalent bonds from which the As-sulfur bond is the most stable one. To bind the radioactive arsenic stable to biomolecules we propose the use of bifunctional chelate ligands (BFC) with two or three sulfhydryls for the complexation of arsenic.

In a first experiment we synthesized a monoamine-monoamide-Ligand (MAMA', N_2S_2) **F** in 6 steps (Figure 1) that can be conjugated to a biomolecule via its secondary amine site (a) or its protected carboxylgoup (b).

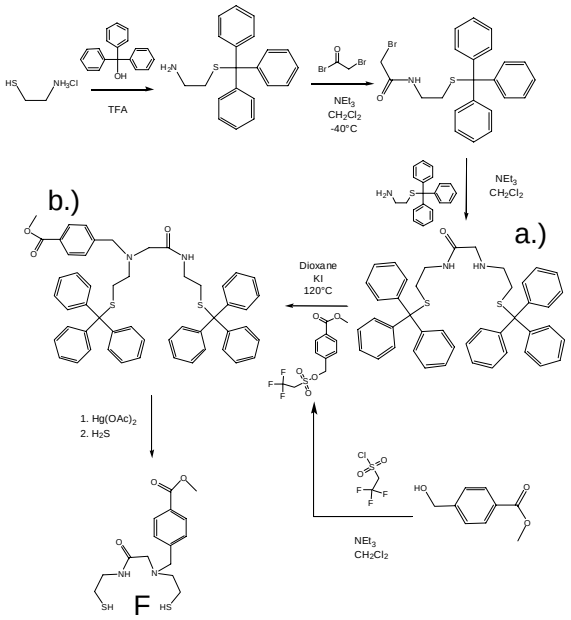

Figure 2: Reaction scheme for the synthesis of N_2S_2

Deprotection of the thiol was performed directly prior to labelling with $Hg(OAc)_2$ followed by precipitation of HgS with H_2S. The black solution was filtered through Celite and the ligand was purified via silica column chromatography ($CHCl_3$ / MeOH 100 / 3). Afterwards, the solvent was removed in vacuum to yield about 50% of unprotected ligand. 10 mg of the ligand were dissolved in 1 mL of dried chloroform and used as stock solution.

The [^{77}As]AsI_3 was isolated from a $^{nat}GeO_2$ target as irradiated for 6 h at the TRIGA reactor Mainz (φ = $4.2*10^{12}$ n/cm^{2}s) and eluted in 500 µL of dried chloroform [1]. 150 µL of the active solution were added to 850 µL of the unprotected ligand in chloroform and shaken vigorously for 10 seconds at room temperature. The radiochemical yields were monitored from 1 minute to 24 h by radio-TLC (chloroform / methanol 9 / 1) and compared with free [^{77}As]AsI_3.

Results:
The [^{77}As]AsI_3 reacts quantitatively with the ligand at RT after 1 minute (Figure 2). However, within 24 hours the increasing formation of a dimer is observed (25 % after 24 hours), resulting in the presence of the third free reaction site of [^{77}As]AsI_3.

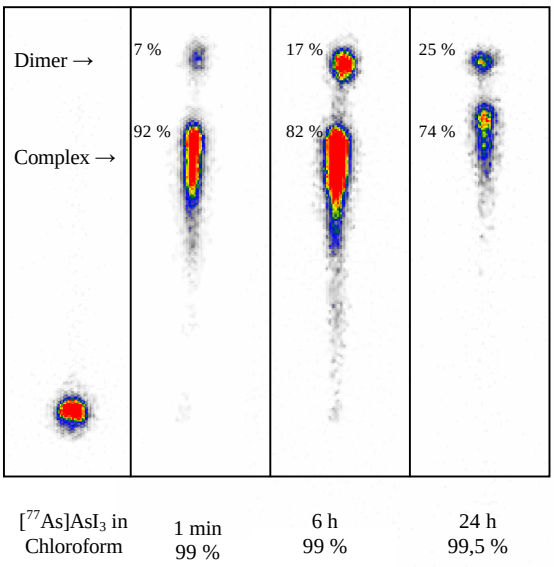

Figure 2: Free [^{77}As]AsI_3 and kinetic of the complexation of MAMA'-ligand

Conclusion:
As a first proof of principle we could show that [^{77}As]AsI_3 can be coupled to a BFC. The high radiochemical yields at RT are a promising evidence for the future radioarsenic labelling of BFC-conjugates. To avoid the formation of dimers a new NS_3-type BFC is under investigation.

References:

[1] Jennewein, M., et al., *A new method for radiochemical separation of arsenic from irradiated germanium oxide.* Appl Radiat Isot, 2005. 63(3): p. 343-51.