‘2+1’ TRICARBONYLTECHNETIUM(I) AND -RHENIUM(I) MIXED-LIGAND COMPLEXES WITH N-METHYLPYRIDINE-2-CARBOXYAMIDE – THE COMPOUNDS MODELLING PRECURSORS OF RADIOPHARMACEUTICALS

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In a series of three papers published recently we have presented results of our studies on the ‘2+1’ tricarbonyl complexes of technetium(I) and rhenium(I) with a neutral bidentate ligand N-methylpyridine-2-carboxyamide, L\textsubscript{NO} – and with H\textsubscript{2}O, Cl\textsuperscript{−} or tert-butyl 3-isocyanopropanoate – bicp as monodentate ligands [1-3]. Physicochemical characteristics of the complexes have been obtained and the molecular structure of the rhenium complex studied. The objective of this work was to check if precation tricarbonyl complexes of technetium(I) and rhenium[I] with the neutral bidentate N,O-donor ligand may be considered promising candidates for radiopharmaceutical precursors. Alberto \textit{et al.} preferred instead of N,O-bidentate anionic ligands which form very stable neutral tricarbonyl complexes of these metals [4]. Quantum chemical calculations can significantly extend our studies because electronic structure of the complexes is clearly connected with their other properties (e.g. reactivity) [5,6].

Literature concerning structural features and physicochemical properties of transition metal complexes with various picolinamide derivatives is rather poor. At present, except three publications from our group [1-3], we have found only 12 other papers related. Because the picolinamide molecules contain three potential donor atoms (N, N’ and O) they are able to coordinate cations either bidentely, or monodentely. In the case of bidentate coordination, a five-membered ring is formed by the Tc\textsuperscript{5+}/Re\textsuperscript{3+} cation and either \textit{via} the pyridine and the amide nitrogen atoms (further on called the N,N’-complex) or \textit{via} the pyridine nitrogen and the amide oxygen atoms (N,O-complex). Two paper deal with the equilibrium between the N,N’- and N,O-structures [7,8].

N-methylpyridine-2-carboxyamide was synthesized in the Department of Chemistry, University of Warsaw and tert-butyl 3-isocyanopropanoate – purchased from Sigma-Aldrich. Synthesis of fac-[\textsuperscript{99m}Tc(CO)\textsubscript{3}(OH\textsubscript{3})\textsubscript{4}]\textsuperscript{+} precursor was accomplished according to Alberto’s procedure [9] improved by Zhang \textit{et al.} [10], fac-[\textsuperscript{188}Re(CO)\textsubscript{3}(OH\textsubscript{3})\textsubscript{4}]\textsuperscript{+} was obtained using IsoLink kits (Mallinckrodt, Netherlands) according to the manufacturer’s procedure. Further details of the experiments and calculations can be found in [1-3]. Synthetic pathway, together with the abbreviations of names for the complexes is shown in Fig.1. Compounds of the b series are assumed to be similar to a but they contain Re\textsuperscript{3+} instead of Tc\textsuperscript{5+} (Table 1).

Table 1. Conditions and yields (not optimized) of the n.c.a. [M(CO)\textsubscript{3}(L\textsubscript{NO})(H\textsubscript{2}O)]\textsuperscript{+} and [M(CO)\textsubscript{3}(L\textsubscript{NO})(bicp)]\textsuperscript{+} complexes synthesized in two-step procedure at 1 mM concentrations of L\textsubscript{NO} and bicp.

\begin{tabular}{|c|c|c|c|c|c|}
\hline
M(I) & L & Product & t [min] & T [°C] & Yield [%] logP\textsubscript{oct/aq} \\
\hline
\textsuperscript{99m}Tc & H\textsubscript{2}O & 2a & 60 & 40 & 75 & 0.43 \pm 0.02 \\
\textsuperscript{99m}Tc & bicp & 3a & 60 & 40 & 73 & 1.3 \pm 0.2 \\
\textsuperscript{188}Re & H\textsubscript{2}O & 2b & 50 & 30 & 47 & 0.76 \pm 0.04 \\
\textsuperscript{188}Re & bicp & 3b & 50 & 30 & 37 & 1.2 \pm 0.1 \\
\hline
\end{tabular}

Obtained already experimental results [1,2] can be summarized as:

- X-ray diffraction studies show that the Re(CO)\textsubscript{3}(L\textsubscript{NO})Cl molecule (1b) has the N,O-structure. It is not impossible that under other conditions ...

Fig.1. Tricarbonyltechnetium(I)/tricarbonylrhenium(I) complexes studied in presented work.
the complex may crystallize in the N,N′-conformation.

- Cationic tricarbonyltechnetium(I) and tricarbonylrhenium(I) cores with three water molecules (precursors) are not very stable and they start to re-oxidaze within several hours, the rhenium complex being significantly more stable. In the deareated reaction mixture (pH 7~8; RT) the complexes slowly decompose to $^{99m}$TcO$_4^-$/ReO$_4^-$, respectively. Detectable amounts of pertechnetate were observed already after 4 h, while the perrhenate – after 6 h.

- The bidentate ligand gives moderate lipophilicity to the complex molecules 3a and 3b.
- The substitution of tert-butyl 3-isocyanopropionate ligand for the labile water molecule in 3a/3b results in remarkable stabilization of the formed molecules 4a/4b and increases their lipophilicity.
- The rhenium complexes studied are much more resistant against ligand exchange than their technetium analogues. The compounds obtained withstand the histidine/cysteine challenge tests to a different degree, but even the less stable complex 4a is fairly resistant against binding with proteins in rat serum.

To make a deeper insight into the structural and electronic properties of the 1a/b-4a/b compounds, quantum chemical calculations were performed at the DFT level. It was shown that the calculations reflect sufficiently well structural features of the transition metal complexes [11]. It has been found that:

- The energy calculated in vacuum for the N,O-structure of the bidente ligand $L_{NO}$ is ca. 12 kcal/mol higher than the N,N'-structure with two nitrogen atoms in the cis position. So, the latter is the ground state of the molecule. The N,N'-conformer seems to be stabilized by formation of an intramolecular hydrogen bond N-H…N because the calculated distance between the amide proton and pyridine nitrogen atoms is 2.568 Å. The N,N'-conformer is a planar molecule (N-C-C-N dihedral angle equals 180°), while the N,O-conformation appeared to be considerably twisted (calculated N-C-C-O dihedral is about 50°). Molecular structures of both conformers are shown in Fig.2. All the molecular structure parameters are close to the found by X-ray diffraction for picolinamide – a molecule of very similar structure to that of our the $L_{NO}$ ligand [12].

![Fig.2. Two conformers of the bidente ligand, N-methyl-2-pyridinecarboxyamide.](image-url)
the labile water molecule in 3a/3b results in remarkable stabilization of the formed molecule 4a/4b and that the rhenium complexes studied are much more resistant against ligand exchange than their technetium analogues. So, one can conclude that the thermodynamic factor – binding energy – may determine the experimentally observed properties of the studied tricarbonyl-rhenium(I)/tricarbonyltechnetium(I) complexes.

In conclusion, the new ‘2+1’ tricarbonyltechnetium(I) and -rhenium(I) complexes with the neutral N,O-bidentate ligand and the monodentate ligands studied, in particular with the isocyanide derivative, may be considered models for promising radiopharmaceutical precursors.

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References
MOLECULAR STRUCTURES OF TWO TRICARBONYLRHENIUM(I) COMPLEXES WITH N-METHYL-2-PYRIDINECARBOXYAMIDE

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Technetium-99m (T1/2 = 6 h, Eγ = 140 keV) has optimal properties for diagnostic nuclear medicine. Two rhenium isotopes Re-186 (T1/2 = 89 h, Eγ = 107 MeV, Eγ = 137 keV) and Re-188 (T1/2 = 18 h, Eγ = 2.12 MeV, Eγ = 155 keV) have good nuclear properties for targeted radiotherapy of cancers. Aquaiions [M(H2O)5(CO)3]4+ (M = Tc, Re), formed by dissolving of [NEt4][M(CO)5X5] (X = Cl, Br) salt in aqueous solution, are used as precursors of tricarbonyl complexes of rhenium(I) and technetium(I) [1]. The carbonyl groups in these complexes are strongly bound with the metal centre, and the lability of the coordinated water molecules makes it possible the preparation of a wide range of tricarbonyl complexes. Monodentate, bidentate or tridentate ligands can be coordinated to fac-[M(CO)3]+ core to enhance its stability, improve lipophilicity or to connect it with a biomolecule which can lead the radionuclide to pathologically changed cell or tissue.

N-methyl-2-pyridinecarboxyamide (LH) is a compound belonging to amide derivatives of picolinic acid [2]. The molecule of this ligand contains three donor atoms: nitrogen atom of aromatic ring, oxygen atom of carbonyl group and nitrogen atom of amide part. In spite of three donor atoms, the bidentate way of complexation with metal ions is only possible.

The synthesis and the structures of two tricarbonyl complexes of rhenium(I) with bidentate ligand N-methyl-2-pyridinecarboxyamide and bromide anion or imidazole (im) molecule are presented in this work. The structures of [Re(CO)3LH4Br] (1) and [Re(CO)3LN4(im)] (2) compounds were determined by single crystal X-ray diffraction (Figs. 1 and 2). The first complex was synthesized by warming an aqueous solution of [NEt4][Re(CO)3Br] with a methanol solution of N-methyl-2-pyridinecarboxyamide. Yellow crystals of [Re(CO)3LH4Br] were obtained after a few days. Then, in the reaction with imidazole in warm water/methanol solution, the compound 1 was transformed into [Re(CO)3LH4N(im)] complex which was grown in the form of yellow crystals after a few months.

Fig. 1. Molecular structure of [Re(CO)3LH4N(im)] (1). Selected bond lengths [Å] and angles [°]: Re(1)-C(1) 1.904(8), Re(1)-C(2) 1.903(9), Re(1)-C(3) 1.921(8), Re(1)-O(1) 2.174(5), Re(1)-N(1) 2.185(6), Re(1)-Br(1) 2.6097(8), N(1)-Re(1)-O(1) 74.7(2), N(1)-Re(1)-Br(1) 84.41(17), C(1)-Re(1)-C(2) 87.6(3), C(1)-Re(1)-C(3) 90.7(3), C(2)-Re(1)-C(3) 89.8(3), C(3)-Re(1)-O(1) 97.7(3).