

DITHIOCARBAMATE BASED CHELATION UNITS FOR LINKING $M(\text{CO})_3^+$ ($M = \text{Tc}, \text{Re}$) SPECIES TO OTHER MOLECULES.

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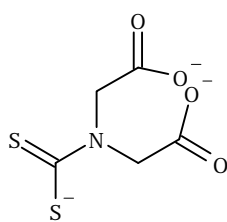
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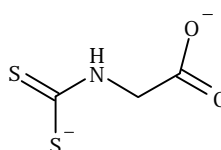
Technetium radiopharmaceuticals, as complexes of the ^{99m}Tc radionuclide, are of great importance in diagnostic nuclear medicine. Over the last few years, the chemistry of novel organometallic species, $M(\text{CO})_3^+$ ($M = \text{Tc}, \text{Re}$), has been intensively developed. Alberto et al. [1,2] reported methods for preparing of aqueous $M(\text{CO})_3^+$, at both the macroscopic level with Tc and Re and at the tracer level with ^{99m}Tc. We have also developed a simple method for the synthesis of aqueous metaltricarbonyl species ($M = \text{Tc}, \text{Re}$) by direct dissolution of $M(\text{CO})_5\text{X}$ ($\text{X} = \text{Cl}, \text{Br}$) in hot water [3]. More recently, we have disclosed an autoclave procedure for the carbonylation of MO_4^- , using a small microreactor that was specially designed to operate safely under high pressure and temperature [4].

As a result of the increasing availability of $M(\text{CO})_3^+$ ($M = \text{Tc}, \text{Re}$) species, a premium has been placed on identification of a suitable chelation system that could be used to link the $M(\text{CO})_3^+$ unit to biomolecules. In the present work we studied new dithiocarbamate based chelating systems. This class of ligands appears to be rather promising, since they are relatively compact, can be easily prepared, and form strong complexes with $M(\text{CO})_3$.

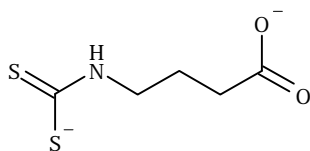
We examined the following ligands:



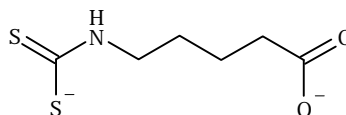
bis[carboxymethyl]dithiocarbamate ligand (L1)



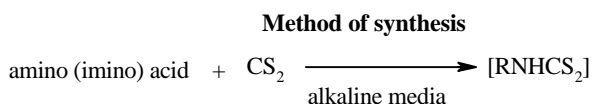
dithiocarbaminoacetic ligand (L2)



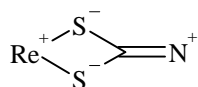
dithiocarbaminobutyric ligand (L3)



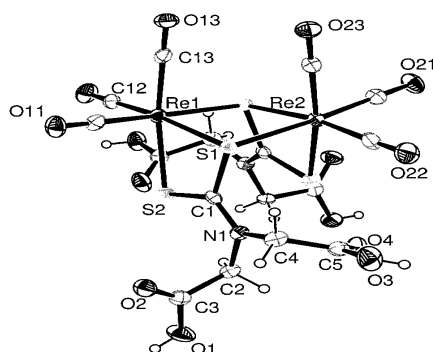
dithiocarbaminovaleric ligand (L4)



Reaction of aqueous $\text{Re}(\text{CO})_3^+$ with dithiocarbamo-carboxylate ligands (L1, L2) requires approximately 30 min at 50°C in contrast to $\text{Tc}(\text{CO})_3^+$ (few minutes) (TLC and UV-VIS control). Structure of complexes in polar organic solvents was determined by ^1H , ^{13}C NMR and IR spectroscopy. It was shown that these compounds are extremely stable for a long period in neutral, acid and basic aqueous solutions. The solid state structure of $[\text{Re}(\text{CO})_3\text{L1}]_2$ solved by single-crystal XRD consists of dimers with a plane location of the following fragment



with a shortened C-N bond, which was also confirmed by IR spectroscopy.

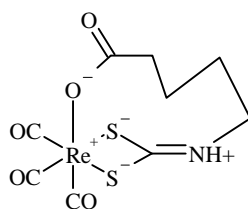


However, both FAB MS spectra of the methanol solution of crystalline $\text{Re}(\text{CO})_3(\text{L1})$ and ESI MS spectra of freshly prepared aqueous solution contain a molecular peak of $\text{Re}(\text{CO})_3(\text{H}_2\text{O})(\text{L1})$. These data show that the dimeric form is unstable in aqueous solution and in polar organic solvents and dissociates to form monomeric species with bidentate coordinated dithiocarbamate ligand. Thus, $\text{Re}(\text{CO})_3(\text{L1})$ complex has dimeric structure in solid state and monomeric structure in solutions.

Disadvantage of bidentate ligands is a presence of one coordination site occupied with a weak donor ligand, which can be readily substituted by stronger donor group in the biologically active media. As a result, the binding affinity of the resulting bioconjugate will be lower.

To block the coordination vacancy, which remains in the metal sphere of the monomeric complex, we designed new dithiocarbamate-carboxylate ligands with longer carbon chains (C_4 and C_5). In these new chelating systems, our goal was to provide a sufficiently long tether between the metal dithiocarbamate unit and the carboxylate, so that the carboxylate could reach back and coordinate with the same metal center within a monomeric complex. The complexes were isolated from aqueous solutions by precipitation with PPh_4Cl and characterized by ^1H and ^{13}C NMR spectrometry and FAB MS and ESI MS spectrometry. In the case of C_4 a mixture of tridentate and bidentate coordinated dithiocarbamate-carboxylic complex is formed. In the case of C_5 we found that both dithiocarbamic and carboxylic groups are coordinated to the metal atom. Moreover, this coordination pattern remains the same

under the conditions of mass spectrometric experiments (molecular peaks of $\text{Re}(\text{CO})_3(\text{L3-L4})$ were registered in the mass-spectra). So, we propose the following structure of the complex:

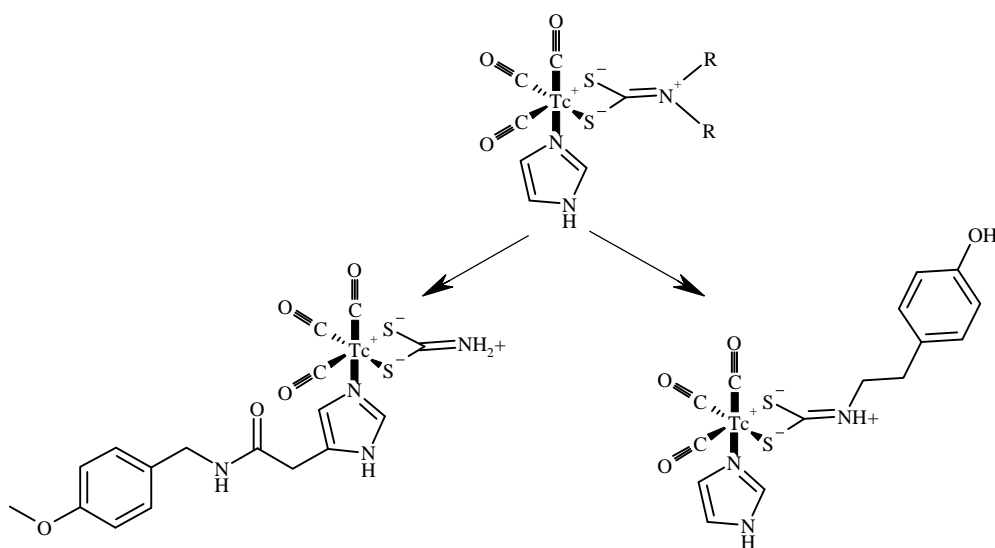


The next step of our study was the estimation of the stability of the isolated complexes to histidine challenge reaction.

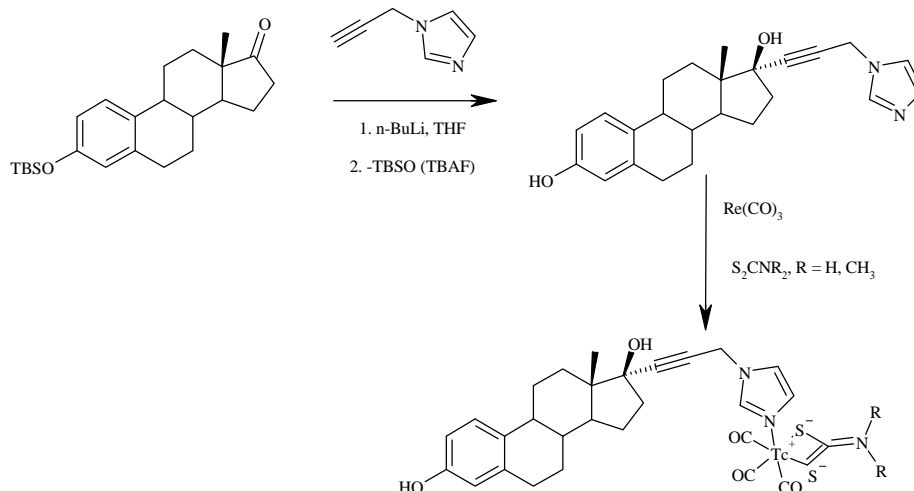
The stability of the "scorpion-like" complex with dithiocarbaminovaleric ligand (L4) was tested in reactions with histidine and hydroxyl ion at pH 7.5. It was found that the "scorpion-like" cyclic structure opens to form the corresponding mixed-ligand dithiocarbamato-histidine or dithiocarbamato-hydroxyl complex. Thus, we can conclude that the chelation effect of the long-chain "scorpion-like" ligands is rather weak due to the poor delocalization of the electron density.

To block free coordination vacancy in dithiocarbamate complexes we used the "2+1" approach. Dithiocarbamino acetate (L2) and bis[dicarboxymethyl]dithiocarbamate (L1) were used as bidentate ligands and a series of amines, thiols and their salts, thioethers, hydroxyl ion, water soluble phosphine, and some heterocycles were used as monodentate ligands. The stability of the resulting "2+1" $\text{M}(\text{CO})_3$ complexes to the interligand exchange with histidine was tested. This reaction was studied mainly by ^{99}Tc NMR spectroscopy. It was found that the complexes with imidazole and water soluble phosphine $\text{P}(\text{CH}_2\text{CH}_2\text{COO})_3^{3-}$ are the most stable. No exchange was observed for at least 24 h in solution with a large histidine excess. In all other cases the mixed-ligand dithiocarbamato-histidine complexes were detected.

Two possible ways for realization of "2+1" approach at the goal of labeling small molecules with dithiocarbamato-imidazole complexes of $\text{M}(\text{CO})_3$ were studied: attaching of biomolecule through imidazole fragment and attaching through dithiocarbamate unit.



Corresponding model compounds were prepared in a high yield and characterized by ^1H and ^{13}C NMR, MS, UV and IR spectroscopy. Imidazole attached 17 α -estradiol was prepared and reaction with $\text{Re}(\text{CO})_3^+$ and dithiocarbamate ligand was performed:



It was found that this reaction yields a target compound contaminated with a mixture of dimeric (*cis*- and *trans*-) dithiocarbamate-metaltricarboxyl species (identified by ^{13}C , ^1H , FAB MS) and starting steroid rather complex for separation.

Thus, we can conclude that “2+1” mixed ligand complexes of $\text{M}(\text{CO})_3$ based on dithiocarbamate chelators and imidazole are promising for labeling of smaller molecules than that of steroids. Probably, they can be used for labeling of serotonin receptor ligands, dopamine transporters and for creation new multidrugs.

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References:

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2. Alberto, R., Shihbli, R., Abram, U., et al., Radiochimica Acta 79: 597-601 (1997).
3. Miroslavov, A.E., Gorshkov, N.I., Lumpov, A.A., and Suglobov, D.N., Radiochemistry (Radiokhimiya) 42: 213-217 (2000)
4. Gorshkov, N. I., Lumpov, A. A., Miroslavov, A. E., and Suglobov, D. N., RF Patent 2125017, Method of synthesis of water soluble technetium(I) and rhenium(I) carbonyl complexes. BI, 1999, no. 2, p. 431.