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N-(2-Mercaptoethyl)picolylamine as a Diaminomonothiolate Ligand for the “*fac*-[Re(CO)$_3$]$^+$” Core

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N-(2-Mercaptoethyl)picolylamine (MEPAH) was studied as a potentially biologically relevant ligand for the “*fac*-[M(CO)$_3$]$^+$” core (M = Re, ^{99}Tc, ^{99m}Tc). To this end, the complex Re(CO)$_3$(MEPA) was synthesized. The reaction of MEPAH with *fac*-[Re(CO)$_3$(MeCN)$_3$]$^+$ took place over the course of seconds, showing the high affinity possessed by this ligand for the “*fac*-[Re(CO)$_3$]$^+$” core. A single-crystal X-ray diffraction study was performed confirming the nature of Re(CO)$_3$(MEPA), a rare mononuclear rhenium(I) thiolate complex. Additional exploration into derivatization of the ligand backbone has afforded the analogous *N*-ethyl complex, Re(CO)$_3$(MEPA-NEt). The high affinity of the ligand for the metal coupled with the ease of its derivatization implies that utilization of this ligand system for the purposes of ^{99m}Tc-radiopharmaceutical development is promising.

Over the last 20 years, much research in the area of ^{99m}Tc radiopharmaceuticals has been directed toward development of the chemistry of the “[TcO]$^{3+}$” core.[1] While the most successful ^{99m}Tc radiopharmaceutical, [^{99m}Tc(MIBI)$_6$]$^+$ (MIBI = 2-methoxyisobutylisonitrile),[2] is a Tc(I) compound, the chemistry and biology of Tc(V) has dominated the literature. Only recently, with the advent of Alberto’s elegant reduction of Tc(VII) to Tc(I) under 1 atm of CO,[3,4] has there been a resurgence in Tc(I) chemistry. Additionally, Alberto has made accessible a new core, namely, the “*fac*-[Tc(CO)$_3$]$^+$” moiety, which is available as reactive, but air-stable, *fac*-[TcCl$_3$(CO)$_3$]$^{2-}$. In coordinating solvents, the chlorides are replaced, yielding mixed carbonyl−chloro−solvento species. In water, methanol, and acetonitrile, all three chlorides are replaced to give tris(solvento)tricarbonyltechnetium(I) cations, which react with a variety of monodentate, bidentate, and tridentate ligands.[3−9]

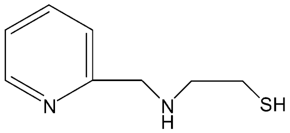

Figure 1. *N*-(2-Mercaptoethyl)picolylamine (MEPAH).

Given that the starting material is a cation with three open sites, it became desirable to develop a monoanionic tridentate ligand system. This allows for maximum stability due to the chelate effect along with neutrality of the overall complex. A ligand which has been used in the study of zinc enzyme active sites, *N*-(2-mercaptoethyl)picolylamine[10] (MEPAH; Figure 1), was found to be a good fit for these requirements. Other properties led us to select this system as well. Studies aimed at ascertaining what types of ligands are considered to have a high affinity for the “*fac*-[M(CO)$_3$]$^+$” core have found that those containing aromatic amines tend to show the fastest coordination to the kinetically inert d^6 metal centers.[11,12] Additionally, mononuclear thiolate complexes of this core had not been widely studied, and the one proton-bearing nitrogen appeared to be well-suited for potential derivatization and, eventually, bioconjugation. As a potentially monoanionic tridentate possessing an {NNS} donor set, it also provided a ligand somewhat comparable (at least in donor atoms present) to the well-developed {N$_2$S$_2$} ligands

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used in Re(V) and Tc(V) chemistry.[13−15] In this preliminary investigation into the chemistry of the ligand with respect to the "*fac*-$[M(CO)_3]^+$" core (M = Tc, Re), rhenium was used as a nonradioactive mimic of technetium.

The synthesis of $Re(CO)_3$(MEPA) is very straightforward. Reaction of MEPAH-NEt_3 with $[Re(CO)_3(MeCN)_3]^+$ takes place within seconds at room temperature in air to give a yellow solution. Precipitation of the neutral complex with water gives the product in good yield. It was desirable to extend this chemistry to aqueous conditions given the potential development of ^{99m}Tc radiopharmaceuticals from this ligand system, but all attempts to synthesize $Re(CO)_3$(MEPA) cleanly in water only gave a mixture of the expected product and an impurity which is likely to be oligomeric (FABMS). Presumably, the acidic nature of the aqua cation leads to protonation at the long Re−S bond (vide infra). Subsequent dissociation of the thiol from the metal center leaves an open site on the metal which is competed for in an ill-defined manner. These solutions cannot be neutralized, as the added base would react with $[Re(CO)_3(H_2O)_3]^+$ to give polynuclear hydrolysis products.[16,17] In fact, in the absence of NEt_3, the synthesis of $Re(CO)_3$(MEPA) in acetonitrile is also not clean, presumably due to the production of 1 equiv of unneutralized HBr. This acid sensitivity of $Re(CO)_3$(MEPA) is not expected to be a problem in ^{99m}Tc syntheses as $[^{99m}Tc(CO)_3(H_2O)_3]^+$ is the dominant species present in solution, even in basic solution as strong as pH 13.[4,11]

Crystals suitable for a single-crystal X-ray diffraction study[18] were grown by the slow evaporation of a saturated acetone−water solution. The crystal structure (Figure 2) clearly shows the binding of the tridentate {NNS} ligand to the "$[Re(CO)_3]^+$" core. Most bond lengths and angles are similar to those observed for other compounds of this core.[6,7,19] A notable structural characteristic is the relatively long Re−S bond length of 2.477(4) Å. It is approximately 0.2 Å longer than the corresponding Re−S bonds in $\{ReON_2S_2\}$ compounds,[13,14] but it is similar to Re−S bonds in Re(I) thioether compounds.[7] A search of the literature has produced only one other example of a mononuclear Re(I) thiolate complex.[20] The synthesis of $Re(CO)_3$(MEPA) and confirmation of the structure of this interesting diaminomonothiolate complex of the rhenium tricarbonyl core led to the subsequent investigation of the derivatization of MEPAH (Figure 3).

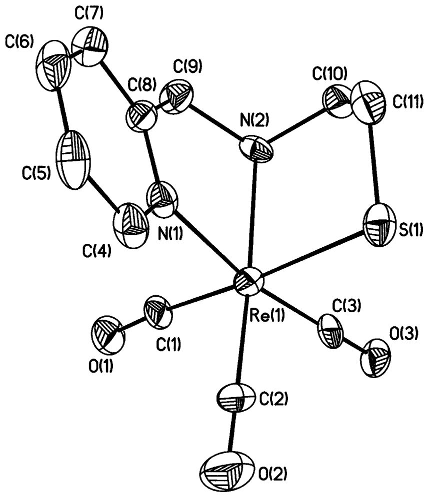

Figure 2. ORTEP diagram of $Re(CO)_3$(MEPA) showing 35% ellipsoids. Selected bond lengths (Å) and angles (deg): Re(1)−C(1) 1.905(13), Re(1)−C(2) 1.920(14), Re(1)−C(3) 1.926(15), Re(1)−N(1) 2.182(10), Re(1)−N(2) 2.204(9), Re(1)−S(1) 2.477(4), C(1)−Re(1)−C(2) 89.7(6), C(1)−Re(1)−N(1) 96.0(5), C(2)−Re(1)−N(2) 171.8(5), N(1)−Re(1)−N(2) 75.2(3), N(2)−Re(1)−S(1) 82.1(3).

Protection of the thiol of MEPAH with TFA and triphenylmethanol gave the trityl-protected thiol, MEPAH-STr, in good yield. Reaction of MEPAH-STr with bromoethane in refluxing acetonitrile in the presence of base gave the *N*-ethyl derivative, also in good yield. While the ethyl-derivatized ligand is not suitable for further reaction leading to potential bioconjugation, its synthesis demonstrates the ease of derivatization of the internal nitrogen of the ligand, as shown recently by others.[21] Furthermore, the deprotection of MEPAH-NEt-STr with TFA and Et_3SiH followed by reaction with $[Re(CO)_3(MeCN)_3]^+$ in the presence of NEt_3 gave $Re(CO)_3$(MEPA-NEt) after precipitation with water. This shows not only that the ligand can be derivatized but also that it is possible to deprotect the new form of the ligand and complex it to the metal center. This reaction also takes place quickly, indicating that the affinity of the ligand for the metal center has not decreased despite the derivatization.

The structure of $Re(CO)_3$(MEPA-NEt) has been confirmed by a single-crystal X-ray diffraction study.[22] The crystal structure (Figure 4) shows a similar Re−S bond length of 2.471(2) Å and a general structural similarity of this complex to the parent $Re(CO)_3$(MEPA).

New complexes containing the "*fac*-$[Re(CO)_3]^+$" core and a thiolate ligand with an {NNS} donor set have been synthesized. Current work is focused on derivatization of

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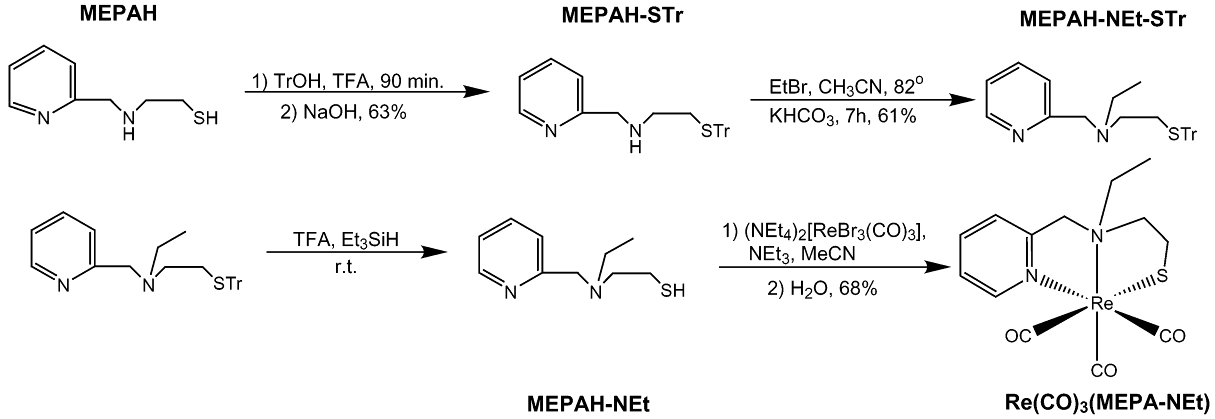

Figure 3. Reaction scheme for derivatization of MEPAH.

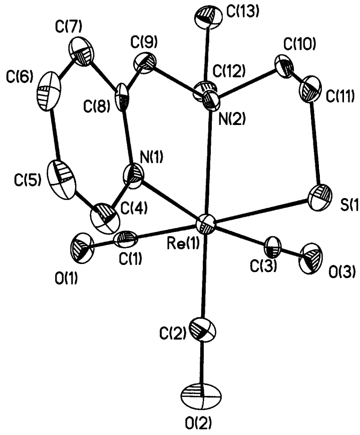

Figure 4. ORTEP diagram of $Re(CO)_3$(MEPA-NEt) showing 35% ellipsoids. Selected bond lengths (Å) and angles (deg): Re(1)−C(1) 1.907(9), Re(1)−C(2) 1.925(10), Re(1)−C(3) 1.926(11), Re(1)−N(1) 2.198(7), Re(1)−N(2) 2.253(7), Re(1)−S(1) 2.471(2), C(1)−Re(1)−C(2) 89.8(4), C(1)−Re(1)−N(1) 95.5(3), C(2)−Re(1)−N(2) 173.4(3), N(1)−Re(1)−N(2) 76.7(3), N(2)−Re(1)−S(1) 83.4(2).

the ligand to enable bioconjugation. Additionally, syntheses of the complexes $^{99m}Tc(CO)_3$(MEPA) and $^{99}Tc(CO)_3$(MEPA) are being investigated.

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Supporting Information Available: X-ray crystallographic file in CIF format, ORTEP of $Re(CO)_3$(MEPA) containing both (isostructural) molecules of the asymmetric unit and complete experimental, spectroscopic, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Crystal data for $C_{13}H_{15}N_2O_3ReS$: monoclinic space group $P2_1/n$, $Z = 4$, $a = 7.2999(4)$ Å, $b = 14.9969(8)$ Å, $c = 13.5499(8)$ Å, $\beta = 97.7420(10)°$, $V = 1469.93(14)$ Å^3, $\rho_{calc} = 2.104$ g/cm^3, $F(000) = 888$. A total of 5514 reflections were collected in the θ range 2.04−22.50° of which 1921 were unique ($R_{int} = 0.1225$). A face-indexed absorption correction was applied. The crystal was bounded by $(0,1,0)$, $(0,\bar{1},0)$, $(1,0,0)$, $(\bar{1},0,0)$, $(0,1,\bar{2})$, and $(0,\bar{1},2)$. The maximum and minimum transmissions were 0.5909 and 0.2536, respectively. Refinement was carried out by full-matrix least-squares on F^2, and the final refinement gave R1 = 0.0428 and wR2 = 0.1060 ($I > 2\sigma(I)$), and R1 = 0.0438 and wR2 = 0.1070 (all data), by using 1921 data per 183 parameters.