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Structure and vibrational spectra of *fac*-$Re^{I}(CO)_3^+$ complex with *N*-methyl-2-pyridinecarbothioamide

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Abstract

Syntheses of a bidentate ligand L = *N*-methyl-2-pyridinecarbothioamide and its tricarbonylchlororhenium(I) complex, [*fac*-$Re(CO)_3LCl$], are described. Physico-chemical characteristics of the novel species are presented. The molecular structures of both complex and ligand have been established by means of X-ray single crystal diffraction, and confirmed by FT-IR spectroscopy. UV–Vis absorption spectra of the complex have shown that it is stable in aqueous solutions at least for several days. Partition coefficients of the ligand and the complex in the *iso*-octanol–water systems have been determined. Lipophilicity of both is moderate: $\log(P) \approx 1.1$.

Keywords: Tricarbonylrhenium(I); *N*-methyl-2-pyridinecarbothioamide; Structural studies; Lipophilicity

1. Introduction

Two rhenium radionuclides, ^{186}Re and ^{188}Re, are considered as candidates for radiotherapeutical applications because of their favorable nuclear properties, in particular the latter, which can be obtained from the $^{188}W/^{188}Re$ generator system [1–3] available in the increasing number of nuclear medicine departments and clinics. Especially the ^{188}Re radioisotope is suitable for preparation of radiopharmaceuticals for therapeutic applications, due to its favorable nuclear properties. This nuclide decays through the emission of a β^- particle ($E_\beta = 2.2$ MeV, $T_{1/2} = 16.9$ h), which has energy appropriate for penetrating and destroying abnormal tissues, and of γ-rays ($E_\gamma = 155$ keV), which can be efficiently used for imaging and calculations of radiation doses. Rhenium eluted from the generator in the form of stable perrhenate anions ($^{188}ReO_4^-$) does not form therapeutically active complexes. Compounds in lower oxidation states, in turn, are relatively easily re-oxidized back to perrhenate. Due to this fact, the rhenium radiopharmaceuticals are difficult to prepare under clinical conditions.

The major advantage of $[Re(OH_2)_3(CO)_3]^+$ emerges from high stability of the [*fac*-$Re(CO)_3]^+$ moiety in water and its ability to exchange labile solvent ligands, H_2O. Moreover, the d^6 electronic configuration of the M(I) center in the octahedral field makes the complexes kinetically inert. The discovery of simple preparative procedure for production of [*fac*-$^{188}Re(CO)_3(H_2O)_3]^+$ (**1**) as a precursor of radiopharmaceuticals [4–7] has opened novel routes in labelling biomolecules [8]. However, even relatively simple derivatives of **1** may be of interest for radiopharmacy. Interaction of hydrophilic

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complexes [$^{188}Re(CO)_3(H_2O)L$] (**2**) (L = bidentate ligand) with plasma components, presumably due to exchange of the remaining water molecule in **2** for peptides [8] leads to supposing that more lipophilic species **2** would easily cross the brain-blood barrier or blood cell membrane to be trapped in the cell where the peptide concentration is high.

The aim of our work was to synthesize and physicochemically characterize novel tricarbonylrhenium(I) complexes with *N*,*S*-bidentate ligands – derivatives of thiopicolinic acid amide. Due to the presence of two soft donor atoms in the ligand molecules, sulfur and pyridinic nitrogen, the Re(I) chelates were expected to be sufficiently stable. In the presented paper *N*2-methyl-2-pyridinecarbothioamide (**3**) and tricarbonyl(*N*2-methyl-2-pyridinecarbothioamide)chlororhenium(I) (**4**) were synthesized and studied as the first compounds in the series.

2. Experimental

2.1. Synthesis of N2-methyl-2-pyridinecarbothioamide, $C_7H_8N_2S$ (3)

The ligand **3** was obtained according to the general procedure described in [9]. Sulphur (6.4 g, 0.2 mol) and *N*-methyformamide (11.8 g, 0.2 mol.) were added to 50 cm^3 of freshly distilled α-picoline. After heating the above mixture under reflux for 30 h, the excess of solvent was evaporated under reduced pressure. Crude product was dissolved in chloroform, purified on a silica gel column (Merck, 200–300 mesh) by elution with chloroform, and twice re-crystallized from ethyl acetate. 12.3 g (40.4% yield) of pure **3** was obtained.

M.p.: 75–79 °C; solubility in water (determined by HPLC): 3×10^{-5} mol/l. Elemental analysis Calc. (for $C_7H_8N_2S$, M = 152): 55.26%C, 5.26%H, 18.42%N. Found: 55.15%C, 5.33%H, 18.30%N. ^1H NMR (δ, $CDCl_3$): 10.244 (1H, m); 8.674 (1H, dd, $J_1 = 10$ Hz, $J_2 = 7.9$ Hz); 8.457 (1H, dt $J = 4$ Hz); 7.802 (1H, dt, $J_1 = 1.8$ Hz, $J_2 = 7.8$ Hz); 7.407 (1H, dq, $J_1 = 1.4$ Hz, $J_2 = 4.8$ Hz, $J_3 = 7.8$ Hz); 3.392, 3.365 (3H, $2 \times$ s). ^{13}C NMR (δ, $CDCl_3$): 191.632; 150.951; 146.887; 137.163; 125.974; 124.459; 32.601.

2.2. Synthesis of tricarbonyl(N2-methyl-2-pyridinecarbothioamide)chlororhenium(I) (4)

[$Re(CO)_3LCl$] (**4**), where L = (**3**) was obtained in two different ways (according the procedures given in [10,11] and [12], respectively):

1. 19.5 mg (0.128 mmol) of (**3**) was dissolved in 1 cm^3 of methanol. Then 56 mg (0.088 mmol) of the $(Et_4N)_2$-$Re(CO)_3Cl_3$ (synthesized in the Paul Scherrer Institute Villigen, Switzerland by low pressure procedure) was added and the color has changed immediately from yellow to purple. The solution was stirred for 20 min, until a red precipitate appeared, and then placed in a refrigerator for 2 days. The red crystals obtained were vacuum-dried. TLC (ethyl acetate/*n*-hexane; 30:70): $R_f = 0.62$.
2. $Re(CO)_5Cl$ (Aldrich, 126 mg, 0.333 mmol) and **3** (54 mg, 0.354 mmol) were dissolved in 13 cm^3 deaerated (argon) THF, and stirred for 24 h.. The orange residue that appear after solvent evaporation was dissolved in 15 cm^3 *n*-pentane/dichloromethane mixture (1:1), stirred for 12 h, filtered, and dissolved in a small amount of methanol. TLC (ethyl acetate/*n*-hexane, 30/70): $R_f = 0.64$. Crystals suitable for X-ray diffraction analysis were obtained after evaporation of methanol and slow crystallization from methanol/dichloromethane mixture (1:1).

M.p.: 279 °C (decomp.); solubility in water (determined by HPLC): about 4×10^{-2} mol/l. For the IR spectra and crystallographic data – see below.

Solvents for synthesis, crystallization, and TLC (p.a., POCh, Gliwice, Poland) were used without further purification.

3. Vibrational spectroscopy and X-ray diffraction studies

IR spectra of **3** and **4** either in solid pellets in KBr (about 1% of the samples; 4.000–400 cm^{-1}) or in THF solutions (ATR – 4.000–650 cm^{-1}) were recorded using ATI-Mattson Genesis and Bruker Equinox 55 FT-IR spectrophotometers.

X-ray reflections of (**4**) were measured at room temperature using the KUMA KM4 four circle diffractometer operating in $\omega - 2\theta$ mode. Crystal of (**3**) after picking up from the mother liquid at room temperature appeared to be unstable upon action of the X-ray and became to be amorphous within few hours. Going down with the temperature of crystal to 100 K radically decreased the decay rate and enabled us to collect a number of reflections sufficient for determining crystal structure of (**3**).

Three standard reflections were monitored every 200 reflections. Unit cell dimensions and standard deviations were obtained by least-squares fit to 25 reflections ($15° < 2\theta < 30°$). Reflections were processed using profile analysis and corrected for Lorentz factor and polarization effect. Re(I) (heavy atom) was located by Patterson's method while the positions of other non-hydrogen atoms were determined in the course of successive refinement using SHELXLS program [13]. Final refinement on F^2 by full-matrix least squares method was done on positional parameters of all atoms, anisotropic temperature factors of all non H-atoms and

isotropic temperature factors of hydrogen atoms. Weighting scheme was used in the form: $w = 1/[\sigma^2(F_o^2) + (A \times P)^2 + B \times P]$, where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$. The parameters A and B are listed in Table 1. Calculations were carried out using SHELXL97 program [14,15]. Summary of the experimental details is presented in Table 1.

3.1. Determination of partition coefficients

Partition coefficients, P_n, defined as the ratio of molar concentrations of n in the organic (*iso*-octanol) and aqueous (water or aqueous 0.9% NaCl solution) phases at equilibrium serve as a measure of lipophilicity of **3** and **4**,

$$P_n = \frac{[n]_{org}}{[n]_{aq}} = \frac{[n]_{org}}{[n]^0_{org} - [n]_{org}},$$

where, n stands for **3** or **4**, $[n]^0_{org}$ is the initial concentration of n in the organic phase, and $[n]_{org}$ and $[n]_{aq}$ are the equilibrium concentrations of n in the organic and aqueous phases, respectively. The *iso*-octanol (water saturated) solutions were saturated with either (**3**) or (**4**) by overnight stirring, then shaken with water or saline until the equilibrium was reached. After centrifugation (4000 rpm for 15 min) the concentration of (**3**) or (**4**) in the organic layer was spectrophotometrically determined: by UV–Vis and FT-IR, respectively. The concentrations of (**3**) were determined at four wavelengths: 260, 270, 280 and 300 nm (Fig. 1) both in the initial *iso*-octanol solution and in the organic phase at equilibrium with water or saline (V_{org}:V_{aq} = 1:1). In turn, the relative concentrations of (**4**) in the *iso*-octanol solutions were determined using two distinct bands assigned to the coordinated CO molecules: 2015 and 1913 cm^{-1}. A linear dependence of the absorbance on the concentration of (**4**) up to the saturated solution has been observed. The equilibrium concentration of (**4**) in the aqueous phase was determined as a difference between its concentrations in the initial and equilibrium organic phases. Due to the high P_4 values ($P_4 > 10$) in order to minimize experimental errors the V_{org}:V_{aq} = 1:10 ratio was used in the partition experiments with (**4**).

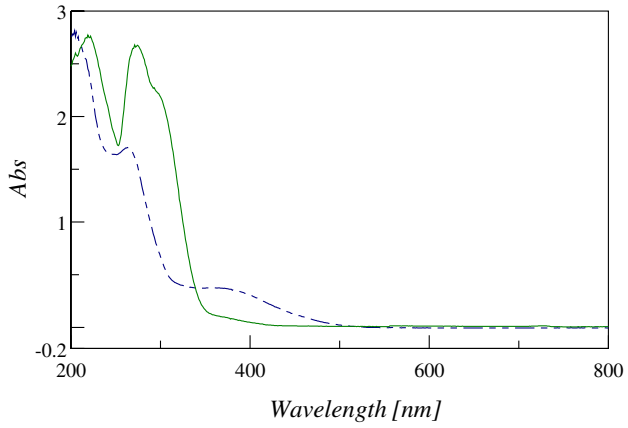


Fig. 1. UV–Vis spectra of the ligand (**3**, solid line) and the title complex (**4**, dotted line) registered as the *iso*-octanol solutions.

Table 1
Summary of the structure refinement parameters

	Ligand (**3**)	Complex (**4**)
Temperature (K)	100(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Calculated density	1.405	2.302
μ(Mo Kα)	0.37	9.55
F(000)	480	428
Crystal size (mm)	$0.13 \times 0.14 \times 0.38$	$0.10 \times 0.12 \times 0.30$
Max 2θ for data collection	56.26	60.12
Index range	$-7 \leqslant h \leqslant 0$	$-11 \leqslant h \leqslant 0$
	$-12 \leqslant k \leqslant 11$	$-11 \leqslant k \leqslant 11$
	$-26 \leqslant l \leqslant 25$	$-15 \leqslant l \leqslant 15$
Number of measured reflections	5702	4104
Number of unique reflections with $F_o > 4\sigma(F_o)$	1846	3838
R_{int}	0.0278	0.0174
Method of structure solution	Direct method	Direct method
Method of structure refinement	Full-matrix least-squares on F^2	
Number of parameters refined	330	168
Goodness-of-fit on F^2	1.315	1.125
Final R_1 [$F_o > 4\sigma(F_o)$]	0.0796	0.0484
Final wR_2 index	0.3501	0.1301
Largest difference peak and hole	1.18, −0.62	3.91, −2.79
Weight parameters (A, B)	0.1058, 4.40	0.1022, 0.34
Mean shift/esd	0.031	0.007

4. Results and discussion

The infrared spectra of solid **3** or **4** are shown in Fig. 2. The detailed assignment of the peaks was made according to [11] and [13], as well as those cited therein. The main FT-IR bands of **3** or **4**, ν(cm^{-1}) are listed in Table 2 together the proposed assignments. All the main bands of **3** can be found in both spectra. Two characteristic peaks of the C–O vibrations clearly appear in the spectrum of **4** (the complex) and confirm the existence of the entire rhenium–tricarbonyl core. The ATR spectra of THF solutions of **3** and **4** do not significantly differ from those of the solid species.

Both the ligand (**3**) and the complex (**4**) exhibit two characteristic bands in the range of 1570–1430 cm^{-1}, assigned to ν(CN) vibrations [16–18]. These bands determine the N–C [N(2)–C(7)thiocarbonyl] bond order, which is intermediate between the single bond, of characteristic frequency of 1350–1250 cm^{-1}, and the double bond of 1690–1640 cm^{-1} [19,20]. The appearance of the IR signals in the intermediate region indicates that amongst the possible resonance structures, e.g.,

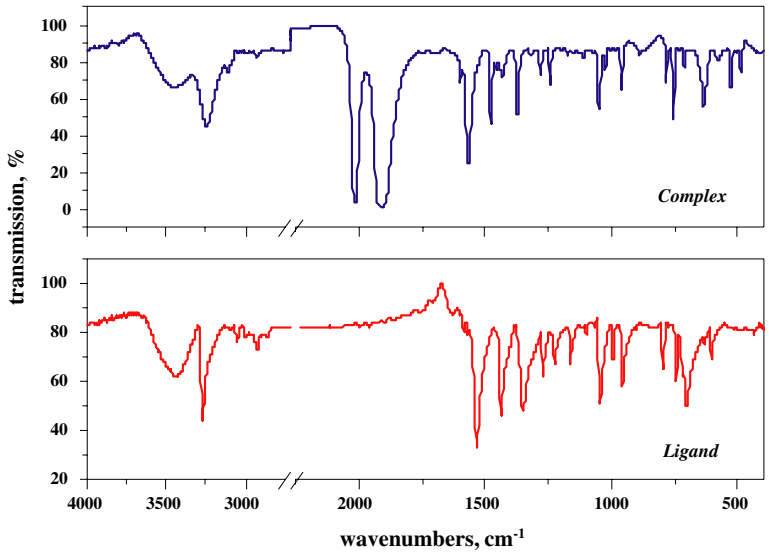
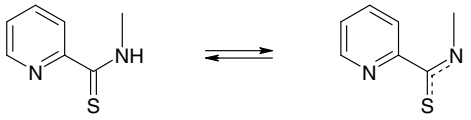


Fig. 2. FT-IR spectra of the ligand **3**, and the title complex **4**.

Table 2
Selected IR bands (cm^{-1}) and their possible assignments (KBr pellets)

Assignments	Ligand (**3**)	Complex (**4**)
$\nu_{NH_2,as}$	3450	3451
$\nu_{NH_2,sym}$	3272	3251
ν_{CH} (aromatic ring)	3049	3114
$\nu_{CH_3,as}$	2922	2927
ν_{CO}	–	2015
ν_{CO}	–	1913
ν_{CN}	1533	1567
ν_{CN}	1438	1478
$\nu_{C=S}$	1352	1374
ν_{CN}	1272	1257
A_1 cumulative vibration of the pyridine ring	1101	1111
B_1 cumulative vibration of the pyridine ring	957	960
δ_{C-H} (2H vibration of the 2-substituted pyridine ring)	796	783
$\delta_{N-C=S}$	743	731
ν_{C-S}	436	487

ν, stretching; δ, bending modes.



a contribution of the *thioenol* form must be considered. The signals at about 1250 cm^{-1} (Table 2) can be attributed to the presumably single N–CH_3 [N(2)–C(8)] bond.

The molecular structure of $Re(CO)_3LCl$ (**4**) is presented in Fig. 3. As it was expected, ligand (**3**) coordinates the cation bidentately: via the pyridine nitrogen and the sulphur atoms forming a five-member plane ring with the metal center. Axis of the

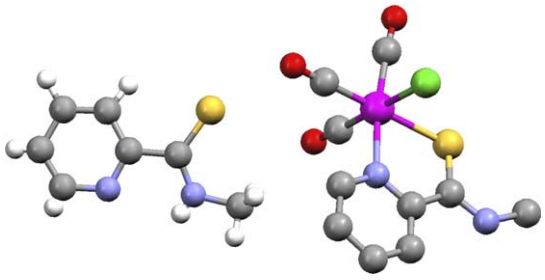


Fig. 3. Molecular structure of the ligand (**3**, left) and the title complex (**4**, right). (Hydrogen atoms in **4** are not shown for clarity).

octahedron is formed by the chloride anion and the CO molecule. Main crystallographic data are presented in Tables 3 and 4.

The crystallographic data (Table 4) can be used to solve the problem of existence of the *thioketo* and *thioenol* forms of the ligand, discussed above. The short

Table 3
Unit cell parameters for the ligand (**3**) and $Re(CO)_3LCl$ complex (**4**)

	Ligand (**3**)	Complex (**4**)
Empirical formula	$C_{14}H_{16}N_4S_2$	$C_{10}H_7ClN_2O_3ReS$
Formula weight	304.43	456.89
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a (Å)	5.9768(12)	7.8270(16)
b (Å)	9.239(18)	7.9740(16)
c (Å)	20.626(4)	10.903(2)
Unit cell dimensions		
α (°)	88.48(4)	77.35(4)
β (°)	89.19(4)	84.39(4)
γ (°)	1.44(4)	88.12(4)
V (Å^3)	1079.32(4)	660.7(2)
Z	3	2

Table 4
Selected bond lengths (pm) and angles (°) in the ligand (**3**) and $Re(CO)_3LCl$ complex (**4**)

Ligand (**3**)		Complex (**4**)	
Bond lengths			
S1–C7	167.3(8)	C6–N1	136.1(9)
C7–N2	129.(10)	C6–C7	147.1(9)
N2–C8	145.7(22)	S1–C7	166.9(7)
C6–C7	150.7(12)	C7–N2	132.7(9)
N1–C6	132.4(11)	N2–C8	145.6(12)
		Re–C1	189.2(8)
		Re–C2	192.7(9)
		Re–C3	190.1(8)
		Re–N1	219.2(6)
		Re–S	244.4(2)
		Re–C1	247.6(2)
Angles			
N2–C7–C6	115.1(7)	N1–Re–S1	79.02(17)
N2–C7–S1	123.1(6)	N1–C6–C7	116.3(6)
S1–C7–C6	121.8(6)	C7–S1–Re	101.0(2)
C7–C6–N1	114.3(7)	C6–C7–S1	121.5(5)
		C6–N1–Re	121.7(5)
		N2–C7–C6	117.3(6)
		N2–C7–S1	121.2(6)

distance between C(7) and N(2) atoms, of ca. 130 pm observed in both free and coordinated ligand (**3**), compared to ca. 150 pm for the single C–N and ca. 120–130 pm for the double C=N bond [21], supports the conclusion based on the IR spectra, that the conribution of the *thioenol* form of the ligand is significant.

An important feature of drugs, which determines their biodistribution, is lipophilicility. Diffusion processes in the human body are controlled by the difference in the composition of the intra- and extracellular liquids. In the present work, partition coefficients of (**3**) and (**4**) have been determined between *iso*-octanol and an aqueous phase being the pure water or 0.9% of NaCl aqueous solution, respectively. Pure water in the first system corresponds to the intracellular liquid, whereas 0.9% NaCl [1] in the second to the extracellular liquid [22,23]. It has been found, that for both (**3**) and (**4**) the P_n values are not affected (within the experimental error) by the given difference in the composition of the aqueous phase: $\log P_3 = 1.14 \pm 0.17$ and 1.11 ± 0.08, while $\log P_4 = 1.01 \pm 0.08$ and 1.11 ± 0.11, for *iso*-octanol–water and *iso*-octanol–0.9% NaCl, respectively.

Stability of **4** in aerated aqueous solution towards oxidation has been studied by registering its UV–Vis spectrum (Fig. 1) vs. time. Within 48 h (which corresponds to ca. three half-life periods of ^{188}Re) no distinct change in the spectrum has been detected.

[1] Commercial peritoneal injection solution produced by Baxter Terpol, Ltd. (Sieradz, Poland) contains 154 mmol dm^{-3} of natrium and 154 mmol dm^{-3} of chloride ions (pH 6.7).

5. Conclusions

A novel soft donor *N*,*S*-bidentate ligand, L = *N*2-methyl-2-pyridinecarbothioamide (**3**), has been synthesized. Its tricarbonylchlororhenium(I) complex, $Re(CO)_3(L)Cl$ (**4**), can easily be prepared from pentacarbonylrhenium(I) chloride. Structural studies of **4** confirm that ligand (**3**) coordinates the Re(I) cation bidentatly by the S and N atoms. The existence of **3**, both free and coordinated,in the *thioenol* form has been concluded from the IR spectra and structural data. The complex (**4**) is stable in aerated solutions for at least 2 days.

6. Supplementary material

Crystallographic data (excluding structural factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre and allocated the Deposition Nos. CCDC 242919 andCCDC 224857 for **3** and **4**, respectively.

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