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Synthesis and structural characterization of a novel Re[P][NN][S][SO] mixed ligand rhenium(III) complex

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Abstract

A novel mixed ligand hexacoordinated rhenium(III) complex of the general formula $Re^{III}[P][NN][S][SO]$ has been synthesized by reacting $Re^{V}OCl_{3}(PPh_{3})_{2}$ with 2,2'-bipyridine (NN), *p*-thiocresol (S) and *N*-acetyl-L-cysteine (SO) in a 1:1:1:1 ratio in methanol. During the reaction, the central rhenium atom undergoes reduction from Re(V) to Re(III). The complex was isolated as red crystals and characterized by elemental analysis, IR and NMR spectroscopies. X-ray crystallographic studies showed that the coordination geometry around rhenium is distorted octahedral. The equatorial plane is defined by the two nitrogen atoms of 2,2'-bipyridine, the sulfur of *N*-acetyl-L-cysteine and the sulfur of the aromatic thiol, while the phosphorous and the carboxylate oxygen of *N*-acetyl-L-cysteine occupy the apical positions.

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1. Introduction

Extensive research efforts on the inorganic chemistry of technetium have resulted in the preparation of a great number of novel Tc-99m compounds and has produced many useful radiopharmaceuticals with a tremendous impact on the development of diagnostic nuclear medicine [1]. Rhenium, a congener of technetium, exhibits many of the chemical properties of technetium and investigations of rhenium coordination chemistry are often performed in conjunction to technetium, providing thus a non-radioactive alternative to working with technetium radioisotopes [2]. Furthermore, the β emitting radionuclides of rhenium, ¹⁸⁶Re and ¹⁸⁸Re, are of great interest to nuclear medicine, as they possess physical and nuclear properties favorable for use in systemic radiotherapy [2]. Current efforts [1] are focus-

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ing on labeling small peptide receptor ligands that will specifically direct the radiopharmaceutical on a target tissue.

This work is part of our continuing investigations into mixed ligand bipyridyl-thiolato complexes of technetium and rhenium [3,4] with the aim to develop a new class of potentially useful diagnostic and therapeutic radiopharmaceuticals, respectively. In a previous work [3], we have synthesized hexacoordinated complexes of the formula Re^VO[NN][S][SO], where NN is 2,2'-bipyridine, S is an aromatic monothiol and SO is thiosalicylic acid. In an effort to develop bifunctional chelating agents [2b], we replaced thiosalicylic acid with Nacetyl-L-cysteine which can also act as an aliphatic SO ligand. N-Acetyl-L-cysteine can serve as a model for the incorporation of a peptide in the coordination sphere of rhenium since the acetyl group may, in principle, be replaced by a small peptide. However, instead of the expected oxorhenium(V) complex, a novel mixed ligand rhenium(III) complex, Re^{III}[PPh₃][NN][p-CH₃C₆H₄S]- $[SCH_2CH(NHCOCH_3)COO]$ (1), where NN is 2,2'-

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bipyridine, was isolated and characterized by IR, NMR, elemental analysis and X-ray crystallography. In this complex, as originally planned, *N*-acetyl-L-cysteine is incorporated in the coordination sphere of rhenium.

2. Experimental

2.1. Materials and methods

IR spectra were recorded as KBr pellets in the range 4000–500 cm⁻¹ on a Perkin–Elmer 1600 FT-IR spectrophotometer and were referenced to polystyrene. The NMR spectra were recorded in deuteriochloroform on a Bruker 500 MHz Avance DRX spectrometer using TMS as reference. Elemental analyses were performed on a Perkin–Elmer 2400/II automated analyzer.

All laboratory chemicals were of reagent grade. *N*-Acetyl-L-cysteine, 2,2'-bipyridine and *p*-thiocresol were purchased from Fluka and $\text{ReOCl}_3(\text{PPh}_3)_2$ was prepared according to the literature [5].

2.2. Synthesis of $Re[NN][PPh_3][p-CH_3C_6H_4S][SCH_2CH(NHCOCH_3)COO]$ (1)

To a stirred suspension of trichlorobis(triphenylphosphine)rhenium(V) oxide (334 mg, 0.4 mmol) in MeOH (10 ml) CH₃COONa in MeOH (2 ml, 0.4 mmol) was added. A mixture of 2,2'-bipyridine (63 mg, 0.4 mmol), *p*-thiocresol (50 mg, 0.4 mmol) and *N*-acetyl-L-cysteine (66 mg, 0.4 mmol) in MeOH (15 ml) was added under stirring. The mixture was refluxed for approximately 1 h. During heating the originally green reaction mixture became red-brown in color. After cooling to room temperature, CH₂Cl₂ was added in the mixture. The organic layer was washed with H₂O, collected and dried over MgSO₄. The volume of the solution was reduced to 5 ml and then 5 ml of MeOH was added. The yelloworange crystals formed were isolated and were shown by NMR to be the well characterized ReO(NN)(p-CH₃C₆H₄S)₃ complex [3] (yield: 17%, 49 mg). Upon standing and slow evaporation of the filtrate, red crystals of complex 1 were formed. Crystals suitable for X-ray crystallography were obtained by recrystallization from MeOH-CH₂Cl₂.

Yield: 95 mg (27%), $R_{\rm f} = 0.5$ (silica gel, CH₂Cl₂– MeOH, 9:1), IR (cm⁻¹, KBr): 1607, 1089, 806, 764, 697. *Anal.* Calc. for C₄₀H₃₇N₃O₃PReS₂: C, 54.04; H, 4.19; N, 4.73; S, 7.21. Found: C, 53.68; H, 4.32; N, 4.68, S, 6.95%.

2.3. X-ray crystallography

A red crystal of $1 (0.06 \times 0.18 \times 0.40 \text{ mm})$ suitable for X-ray analysis was mounted in air and covered with epoxy glue. Diffraction measurements were made on a

 $P2_1$ Nicolet diffractometer upgraded by Crystal Logic using graphite monochromated Cu Ka radiation. Unit cell dimensions were determined by using the angular settings of 25 automatically centered reflections in the range $22 < 2\theta < 54^{\circ}$ and they appear in Table 1. Intensity data were recorded using a $\theta - 2\theta$ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization and psi-scan absorption corrections were applied using CRYSTAL LOGIC software. The structure was solved by direct methods using SHELXS-86 [6] and refined by full-matrix least-squares techniques on F^2 using SHELXL-93 [7]. Further crystallographic details for 1: $2\theta_{\text{max}} = 118.3^{\circ}$, scan speed 1.5° min⁻¹, scan range $2.9 + \alpha_1 \alpha_2$ separation, reflections collected/unique/used 8545/8202 [R_{int} = 0.0206]/8202, 931 parameters refined, $[\Delta \rho]_{\text{max}}/[\Delta \rho]_{\text{min}} = 2.116/-0.913$ e Å⁻³, $[\Delta /\sigma]_{\text{max}} =$ 0.010, R_1/wR_2 (for all data) = 0.0492/0.1350. All hydrogen atoms were introduced at calculated positions as riding on bonded atoms, all non-H atoms were refined anisotropically (except of the solvent water molecules which were refined isotropically). The second water molecule was refined with the occupation factor fixed to 10.50.

3. Results and discussion

Refluxing of trichlorobis(triphenylphosphine)rhenium(V) oxide in the presence of 2,2'-bipyridine (NN), *p*-thiocresol and *N*-acetyl-L-cysteine in a neutral methanolic solution for 1 h (Fig. 1) yielded a red-brown solution which was diluted with CH₂Cl₂ and then washed with water. TLC analysis (silica gel, CH₂Cl₂-MeOH, 9:1) of the dichloromethane layer showed the existence of two complexes, one with $R_f \sim 0.8$ and a

Table 1 Summary of crystal, intensity collection and refinement data

	$1 \cdot 0.75 H_2 O$
Empirical formula	C40H38.5N3O3.75ReS2
Formula weight	902.53
Temperature (K)	298
Wavelength (Å)	Cu Ka 0.710730
Space group	$P2_1$
a (Å)	12.539(1)
b (Å)	20.274(2)
c (Å)	15.846(1)
β(°)	106.405(4)
$V(Å^3)$	3864.3(6)
Z	4
$D_{\text{calcd}}/D_{\text{meas}}$ (Mg m ⁻³)	1.551/1.53
Absorption coefficient μ (mm ⁻¹)	7.898
F(000)	1806
R indices	$R_1 = 0.0492$ ^a , $wR_2 = 1350$ ^a
Goodness-of-fit on F^2	1.050

^a For 8202 reflections with $I > 2\sigma(I)$.



Fig. 1. Reaction scheme of the formation of the rhenium complexes.

second with $R_f \sim 0.5$. The first product precipitated from the reaction mixture as yellow-orange crystals and proved to be the ReO[NN][*p*-CH₃C₆H₄S]₃ complex [3]. The second product precipitated subsequently from the filtrate as red crystals and turned out to be the Re^{III}[PPh₃][NN][*p*-

 $CH_3C_6H_4S][SCH_2CH(NHCOCH_3)COO]$ complex 1. The isolation of complex 1 indicates that Re(V) is partially reduced to Re(III) under the reaction conditions, a fact that has been reported in previous studies [8]. Complex 1 is soluble in CHCl₃ and CH₂Cl₂, slightly soluble in MeOH, EtOH and insoluble in ether, pentane and water. It is stable in the solid state and in solution as indicated by the NMR studies.

The infrared spectrum of complex 1 is free of any IR band in the v(ReO) region in agreement with the absence of the ReO core. The PPh₃ group shows a P-sensitive absorption at 1089 cm⁻¹ and a strong band at 697 cm⁻¹. Furthermore, the peaks found at 806, 764 and 1607 cm⁻¹ are indicative of the existence of the aromatic thiol, 2,2'-bipyridine and N-acetyl-L-cysteine, respectively.

The NMR spectra of complex 1 consisted of sharp peaks typical of a diamagnetic complex. ¹H and ¹³C spectra as well as integration of ¹H peaks were in agreement with the assigned structure. ¹H and ¹³C NMR chemical shifts for 1 in CDCl₃ at 25 °C are given in Table 2. Assignments were based on a series of 1D and 2D homonuclear and heteronuclear experiments. Fig. 2 shows part of the ¹H–¹H correlation spectrum (COSY) of complex 1.

An ORTEP diagram of 1 is given in Fig. 3 and selected bond distances and angles are listed in Table 3. Compound 1 crystallizes in the monoclinic space group $P2_1$ with two independent molecules in the asymmetric unit, thereafter referred as mol 1 and mol 2. The coordination geometry around rhenium is distorted octahedral. The equatorial plane of the octahedron is defined by the two nitrogen atoms of 2,2'-bipyridine, the sulfur of N-acetyl-L-cysteine and the sulfur of the aromatic thiol, while the phosphorous and the carboxylate oxygen of N-acetyl-L-cysteine occupy the apical positions. The equatorial plane of the distorted octahe-

Table 2 ^{1}H and ^{13}C NMR chemical shifts (ppm) for complex 1 in CDCl_3 at 25 $^{\circ}\text{C}$

H-1	4.33, 2.87	C-1	63.58
H-2	3.92	C-2	55.20
H-5	1.84	C-3	178.98
H-6	8.24	C-4	168.42
H-7	6.86	C-5	23.59
H-8	7.29	C-6	153.39
H-9	8.08	C-7	123.51
H-12	7.99	C-8	139.03
H-13	7.21	C-9	120.26
H-14	6.80	C-10	152.75
H-15	7.82	C-11	153.46
H-17 (H-21)	7.49-7.41	C-12	119.92
H-23 (H-27)		C-13	139.08
H-29 (H-33)		C-14	123.30
H-18 (H-20)	7.26 - 7.22	C-15	152.15
H-24 (H-26)		C-16, C-22, C-28	148.55
			$({}^{1}J_{\rm CP} = 47.7 \text{ Hz})$
H-30 (H-32)		C-17 (C-21)	133.49
			$(^2 J_{\rm CP} = 9.5 \text{ Hz})$
H-19, H-25, H-31	7.21 - 7.18	C-23 (C-27)	
		C-29 (C-33)	
H-35 (H-39)	7.38	C-18 (C-20)	127.94
			$({}^{3}J_{\rm CP} = 9.2 \text{ Hz})$
H-36 (H-38)	7.20	C-24 (C-26)	
H-40	2.29	C-32 (C-30)	
NH	6.83	C-19, C-25, C-31	128.89
		C-34	132.09
		C-35 (C-39)	129.85
		C-36 (C-38)	130.07
		C-37	135.33
		C-40	21.09

Numbering of the atoms is according to the ORTEP diagram of Fig. 3.

dron is almost parallel to the planar five membered ring defined by the N-C-C-N chelating atoms of the bipyridine and the metal ion (5.1 and 5.8° for mol 1 and mol 2, respectively). The N-C-C-N dihedral angle of 2.2'-bipyridine is very small $(2.1^{\circ} \text{ for mol } 1 \text{ and } 3.9^{\circ}$ for mol 2). The six membered ring in the coordination sphere adopts the rarely occurring unstable half chair conformation with the acentric carbon atom being out of the best mean plane of the remaining five atoms (0.85 Å for C2 in mol 1 and 0.74 Å for C42 in mol 2). The angles around the metal within the tetragonal plane of the octahedron range from 72.5(3) to $104.1(1)^{\circ}$ for mol 1 and from 72.7(4) to $105.0(1)^{\circ}$ for mol 2, whereas those involving the apical atoms range from 82.2(3) to $95.7(2)^{\circ}$ for mol 1 and from 80.1(3) to $98.7(3)^{\circ}$ for mol 2. As expected, the bite angle of 2,2'-bipyridine (N-Re-N) is the smallest one in the coordination sphere. The Re-N, Re-S and Re-P bond distances are in the ranges observed for analogous complexes [3,9].

In conclusion, reaction of trichlorobis(triphenylphosphine)rhenium(V) oxide with 2,2'-bipyridine, *p*-thiocresol and *N*-acetyl-L-cysteine in methanol resulted in the





Fig. 2. Part (8.34–6.73 ppm) of the ${}^{1}H{-}^{1}H$ correlation NMR spectrum of complex 1 in CDCl₃ at 25 °C. The numbering of the protons that appear as separate peaks is noted.



Fig. 3. ORTEP diagram of complex 1.

isolation of a novel neutral $Re^{III}[PPh_3][NN][p-CH_3C_6H_4S][SCH_2CH(NHCOCH_3)COO]$ complex, where the cysteine residue has been incorporated in

Table 3 Selected bond distances (Å) and angles (°) for 1

Mol 1		Mol 2	
Bond distances			
Re(1) - O(1)	2.151(6)	Re(2) - O(4)	2.154(8)
Re(1) - N(1)	2.189(9)	Re(2) - N(4)	2.187(9)
Re(1) - N(2)	2.211(9)	Re(2) - N(5)	2.20(1)
Re(1)-S(2)	2.258(3)	Re(2) - S(4)	2.262(4)
Re(1) - S(1)	2.266(3)	Re(2) - S(3)	2.250(3)
Re(1) - P(1)	2.324(3)	Re(2) - P(2)	2.326(3)
Bond angles			
O(1) - Re(1) - N(1)	83.3(3)	O(4) - Re(2) - N(4)	84.2(3)
O(1) - Re(1) - N(2)	82.2(3)	O(4) - Re(2) - N(5)	80.1(3)
N(1)-Re(1)-N(2)	72.5(3)	N(4) - Re(2) - N(5)	72.7(4)
O(1) - Re(1) - S(2)	95.7(2)	O(4) - Re(2) - S(4)	93.6(2)
N(1)-Re(1)-S(2)	92.2(3)	N(4) - Re(2) - S(4)	91.6(3)
N(2)-Re(1)-S(2)	164.7(3)	N(5)-Re(2)-S(4)	163.5(3)
O(1) - Re(1) - S(1)	89.8(3)	O(4) - Re(2) - S(3)	92.0(2)
N(1)-Re(1)-S(1)	162.8(3)	N(4) - Re(2) - S(3)	163.2(3)
N(2)-Re(1)-S(1)	91.1(2)	N(5)-Re(2)-S(3)	90.5(3)
S(2) - Re(1) - S(1)	104.1(1)(1)	S(3) - Re(2) - S(4)	105.0(1)
O(1) - Re(1) - P(1)	174.7(2)	O(4) - Re(2) - P(2)	177.8(2)
N(1)-Re(1)-P(1)	94.6(3)	N(4) - Re(2) - P(2)	93.8(2)
N(2)-Re(1)-P(1)	92.5(3)	N(5)-Re(2)-P(2)	98.7(3)
S(2) - Re(1) - P(1)	89.3(1)	S(4) - Re(2) - P(2)	87.1(1)
S(1)-Re(1)-P(1)	90.8(1)	S(3)-Re(2)-P(2)	89.8(1)

the coordination sphere of the metal. This [P][NN][S][SO] system is a versatile system because of the coordination of different ligands, able to bear functional groups, at the metal center and may prove useful in the development of rhenium(III) and technetium(III) radiopharmaceuticals.

4. Supplementary material

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 189967 for complex **1**. Copies of the data may be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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