Polyhedron 40 (2012) 153-158

Contents lists available at SciVerse ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly



Tricarbonyltechnetium(I) and -rhenium(I) complexes with *N*′-thiocarbamoylpicolylbenzamidines

Elisabeth Oehlke^a, Hung Huy Nguyen^b, Nils Kahlcke^a, Victor M. Deflon^c, Ulrich Abram^{a,*}

^a Freie Universität Berlin, Institute of Chemistry and Biochemistry, Fabeckstr. 34-36, D-14195 Berlin, Germany ^b Department of Chemistry, Hanoi University of Science, 19 Le Thanh Tong, Hanoi, Viet Nam ^c Instituto de Química de São Carlos, Universidade de São Paulo, 13566-590 São Carlos, SP, Brazil

ARTICLE INFO

Article history: Received 9 February 2012 Accepted 11 April 2012 Available online 24 April 2012

Keywords: Technetium Rhenium Carbonyl complexes Tridentate ligands Structure analysis

1. Introduction

The radionuclides of technetium and rhenium play an important role in the field of nuclear medicine [1–3]. ^{99m}Tc (pure γ -emitter, E_{γ} = 140 keV, $t_{1/2}$ = 6 h) is the most used isotope for diagnostic radiopharmaceuticals [2]. The β -emitting rhenium isotopes ¹⁸⁶Re and ¹⁸⁸Re are under consideration as therapeutic agents for various forms of cancer or arthritis [3]. One focus of recent research in this field is the radiolabelling of biomolecules or pharmacophores, which rapidly and efficiently transport the radionuclide to the target site. The most common way to incorporate the radiometals is the use of a strong chelator which coordinates the metal and serves at the same time as linker to the biomolecule [4]. The tricarbonyl complexes $[M(CO)_3(H_2O)_3]^+$ (M = ^{99m}Tc, ⁹⁹Tc, Re) are excellent starting materials for this purpose. A low-pressure synthesis of $[M(CO)_3(H_2O)_3]^+$ (M = ^{99m}Tc, ⁹⁹Tc, Re) has been developed which can be performed in aqueous media [5]. The three aqua ligands can easily be replaced by chelating ligands while the facial binding carbonyl ligands are largely inert against ligand exchange. Suitable ligand systems for the $[M(CO)_3]^+$ core should preferably be monoanionic, tridentate and facial coordinating in order to form neutral complexes, which are thermodynamically stable and kinetically inert.

Recently, the synthesis of a number of tridentate derivatives of *N*,*N*-[(dialkylamino)-*N*'-(thiocarbonyl)]benzamidines, such as the

ABSTRACT

N,*N*-Dialkylamino(thiocarbonyl)-*N*'-picolylbenzamidines react with $(NEt_4)_2[M(CO)_3X_3]$ (M = Re, X = Br; M = Tc, X = Cl) under formation of neutral $[M(CO)_3L]$ complexes in high yields. The monoanionic *NNS* ligands bind in a facial coordination mode and can readily be modified at the $(CS)NR^1R^2$ moiety. The complexes $[^{99}Tc(CO)_3(L^{PyMor})]$ and $[Re(CO)_3(L)]$ (L = L^{PyMor}, L^{PyEt}) were characterized by X-ray diffraction. Reactions of $[^{99m}Tc(CO)_3(H_2O)_3]^*$ with the *N*'-thiocarbamoylpicolylbenzamidines give the corresponding ^{99m}Tc complexes. The ester group in HL^{PyCOOEt} allows linkage between biomolecules and the metal core. © 2012 Elsevier Ltd. All rights reserved.

> compounds shown in Scheme 1, have been reported. They are prepared by reactions of benzimidoyl chlorides with functionalized amines [6], and can readily be varied in their periphery which helps to tune their properties or couple them to biomolecules [7]. The coordination chemistry of such ligands with technetium(V) and rhenium(V) cores has been extensively studied [6– 8]. Similar complexes with the $[M(CO)_3]^+$ core are only known with bidentate *N*-[(dialkylamino)(thiocarbonyl)]benzamidines up to now [9].

2. Results and discussion

Reactions of $(NEt_4)_2[Re(CO)_3Br_3]$ with 1 eq. HL^{PyMor} or HL^{PyEt} give $[Re(CO)_3(L)]$ (L = L^{PyMor}, L^{PyEt}) complexes in almost quantitative yields. The ESI⁺ mass spectra of the products show intense signals corresponding to the expected [M+H]⁺ ions. The spectrum of [Re $(CO)_3(L^{PyMor})$] displays an extra peak for the $[M+Na]^+$ ion. Infrared spectra of both complexes show the typical pattern for a facial arrangement of CO ligands ($v_{C=0}$: 2206, 1906 and 1865 cm⁻¹ for $[Re(CO)_3(L^{PyMor})];$ 2009, 1899 and 1884 cm⁻¹ for $[Re(CO)_3(L^{PyEt})].$ The $v_{C=N}$ stretches are bathochromically shifted with respect to those of the non-coordinated benzamidines from 1620 to 1607 cm^{-1} for [Re(CO)₃(L^{PyMor})] and 1605 cm^{-1} for [Re(CO)₃(L^{PyEt})]. These shifts are relatively small compared to those, which were observed for rhenium(V) and technetium(V) complexes (up to 120 cm⁻¹) [6]. Apparently, the large degree of π -electron delocalization within the chelate rings, which results in large bathochromic shifts in the IR spectra and an almost perfect C-N



^{*} Corresponding author. Tel.: +49 30 838 54002; fax: +49 30 838 52676. *E-mail address*: ulrich.abram@fu-berlin.de (U. Abram).

^{0277-5387/\$ -} see front matter @ 2012 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.poly.2012.04.008



Scheme 1. Ligands used throughout this paper.

bond-length equalization in the rhenium(V) and technetium(V) complexes does not apply to $[\text{Re}(\text{CO})_3(\text{L})]$ ($\text{L} = \text{L}^{\text{PyMor}}, \text{L}^{\text{PyEt}}$) due to the facial coordination of the tridentate ligands. The ¹³C NMR spectrum of $[\text{Re}(\text{CO})_3(\text{L}^{\text{PyMor}})]$ shows three signals for the carbon atoms of the carbonyl ligands at 198.8, 196.4 and 193.3 ppm, reflecting some influence of the trans-bonded donor atoms. For the other compounds, unfortunately, ¹³C NMR of satisfactory quality could not be obtained due to their lower solubility.

not be obtained due to their lower solubility. The technetium complex [⁹⁹Tc(CO)₃(L^{PyMor})] was synthesized from (NEt₄)₂[⁹⁹Tc(CO)₃Cl₃] and HL^{PyMor} in methanol. Its infrared spectrum shows the $v_{C=N}$ stretch at 1609 cm⁻¹ and the bands of the CO ligands at 2017, 1921 and 1886 cm⁻¹. The absence of absorptions in the regions around 3350 and 3400 cm⁻¹ (in which the v_{NH} stretch is detected in the spectrum of the uncoordinated HL^{PyMor}) indicates the expected deprotonation of the ligand during complex formation. The ⁹⁹Tc NMR spectrum shows a signal at -1220 ppm with a half-width of 596 Hz ((NEt₄)₂[⁹⁹Tc(CO)₃Cl₃]: $\delta = -870$ ppm, $\Delta v_{1/2} = 29$ Hz in H₂O). Single crystals of [Re(CO)₃(L^{PyMor})], [Re(CO)₃(L^{PyEt})] and

Single crystals of $[\text{Re}(\text{CO})_3(\text{L}^{\text{PyMor}})]$, $[\text{Re}(\text{CO})_3(\text{L}^{\text{PyE}})]$ and $[^{99}\text{Tc}(\text{CO})_3(\text{L}^{\text{PyMor}})]$ were obtained either directly from the reaction solutions or by recrystallization of the initially formed pale-yellow powders from acetone. Fig. 1 illustrates the molecular structure of $[^{99}\text{Tc}(\text{CO})_3(\text{L}^{\text{PyMor}})]$. Since the structure of $[\text{Re}(\text{CO})_3(\text{L}^{\text{PyMor}})]$ is virtually identical, no extra figure is presented for the rhenium compound. The structure of $[\text{Re}(\text{CO})_3(\text{L}^{\text{PyMor}})]$ is shown in Fig. 2. Selected bond lengths and angles of all three complexes are presented in Table 1. The metal atoms show distorted octahedral coor-



Fig. 1. Ellipsoid representation [16] of the molecular structure of $[^{99}Tc(CO)_3 (L^{PyMor})]$. Thermal ellipsoids represent 50% probability. H atoms have been omitted for clarity.



Fig. 2. Ellipsoid representation [16] of the molecular structure of $[Re(CO)_3(L^{PyEt})]$. Thermal ellipsoids represent 50% probability. H atoms have been omitted for clarity.

Table 1

Selected bond lengths (Å) and angles (°) in [99 Tc(CO)₃(L^{PyMor})], [Re(CO)₃(L^{PyMor})] and [Re(CO)₃(L^{PyEt})].

	$[^{99}Tc(CO)_3(L^{PyMor})]$	$[Re(CO)_3(L^{PyMor})]$	$[\text{Re}(\text{CO})_3(L^{\text{PyEt}})]$
M-C11	1.933(3)	1.938(4)	1.934(7)
M-C12	1.911(2)	1.909(4)	1.932(8)
M-C13	1.909(3)	1.923(4)	1.932(8)
M-S1	2.4895(7)	2.491(2)	2.500(2)
M-N5	2.141(2)	2.143(3)	2.136(6)
M-N52	2.177(2)	2.176(3)	2.180(6)
S1-C2	1.750(2)	1.754(4)	1.755(8)
C2-N3	1.324(3)	1.322(5)	1.32(1)
C2-N6	1.378(4)	1.384(7)	1.35(1)
N3-C4	1.360(3)	1.351(5)	1.36(1)
C4-N5	1.298(3)	1.307(5)	1.32(1)
N5-C6	1.474(3)	1.469(5)	1.46(1)
C11-M-N5	172.00(9)	171.2(2)	170.5(3)
C11-M-C12	88.4(1)	88.7(2)	89.4(3)
S1-M-N5	81.34(5)	81.0(1)	81.3(2)
N5-M-N52	74.99(7)	74.3(1)	74.5(2)
M-S1-C2	97.77(8)	97.5(1)	96.9(3)
S1-C2-N3	127.9(2)	127.8(3)	126.6(6)
C2-N3-C4	124.1(2)	124.3(3)	124.1(7)
N3-C4-N5	125.4(2)	125.4(3)	125.2(7)
C4-N5-C6	122.6(2)	122.4(3)	121.2(6)
M-N5-C4	127.5(2)	127.4(3)	127.7(5)

dination spheres with facially bonded carbonyl ligands. The remaining three coordination positions are occupied by the singly deprotonated organic ligands. The chelate rings are strongly



Fig. 3. Molecular structure [16] of [$^{99}\text{Tc}(\text{CO})_3(L^{Py\text{COOEt}})$]. H atoms have been omitted for clarity.

Table 2	
HPLC dat	t

Compound	Retention time (min)	Yield (%)
MO_4^{-} (M = Tc, Re)	3.1	-
$[Re(CO)_3Br_3]^{2-}$	6.2	-
$[^{99}Tc(CO)_{3}Cl_{3}]^{2-}$	6.7	-
$[^{99m}Tc(CO)_3(H_2O)_3]^+$	6.7	-
HL ^{PyMor}	19.2	-
[Re(CO) ₃ (L ^{PyMor})]	24.0	-
$[^{99}Tc(CO)_3(L^{PyMor})]$	25.2	-
$[^{99m}Tc(CO)_3(L^{PyMor})]$	23.3	97
HL ^{PyEt}	21.0	-
$[\text{Re}(\text{CO})_3(L^{\text{PyEt}})]$	24.0	-
$[^{99m}Tc(CO)_3(L^{PyEt})]$	24.5	max. 94
HLPycooet	23.7	-
$[\text{Re}(\text{CO})_3(L^{\text{PyCOOEt}})]$	25.8	-
$[^{99}Tc(CO)_3(L^{PyCOOEt})]$	25.5	-
$[^{99m}Tc(CO)_3(L^{PyCOOEt})]$	24.4	max. 96

distorted, with main deviations from planarity of 0.503–0.533 Å for S1 in the six-membered rings and 0.301–0.307 Å for N5 in the fivemembered rings. Bond lengths within the chelate rings indicate only partial double bond character of the C=N bonds. The C4–N5 bond lengths between 1.298(3) and 1.32(1) Å best resemble bond lengths expected for C=N double bonds.

A yellow oil was obtained from the reaction of $(NEt_4)_2$ [Re $(CO)_3Br_3$] with $HL^{PyCOOEt}$. All our efforts to purify the product and to obtain a pure solid sample of $[Re(CO)_3(L^{PyCOOEt})]$ failed. Thus,

only the crude product could be characterized by IR spectroscopy and mass spectrometry. The IR spectrum shows two bands for the CO ligands at 2017 and 1894 cm⁻¹, which equals a mean hypsochromic shift of 25 cm⁻¹ compared to the Re starting complex. The $v_{C=N}$ stretch can be found at 1609 cm⁻¹. Coordination and deprotonation of the ligand is indicated by the absence of an absorption for the v_{NH} stretch (v(N-H): 3371 cm⁻¹ for HL^{PyCOOEt}). Additionally, a band at 1705 cm⁻¹ can be assigned to the ester group of the ligand. The ESI⁺ mass spectrum shows an intense peak corresponding to the expected [M+H]⁺ ion. This confirms the presence of the [Re(CO)₃(L^{PyCOOEt})] in the oily product, which has only been taken for comparison purposes in the HPLC studies on the ^{99m}Tc compounds.

The reaction of (NEt₄)₂[⁹⁹Tc(CO)₃Cl₃] with one equivalent of HL^{PyCOOEt} in a mixture of methanol and water gives the colorless complex $[^{99}Tc(CO)_3(L^{PyCOOEt})]$. It precipitates together with one equivalent of (NEt₄)Cl directly from the reaction mixture and was analysed as co-precipitate. The IR spectrum exhibits the carbonyl bands at 2017, 1909 and 1894 cm^{-1} and the $v_{\text{C=N}}$ stretch at 1605 cm^{-1} . The band at 1717 cm^{-1} can be assigned to the ester group of the ligand. The ¹H NMR spectrum of the complex shows the expected signals. The resonances of the methyl and methylene protons of the ethyl ester appear as triplet at 1.32 ppm and as multiplet between 4.28 and 4.38 ppm. The ⁹⁹Tc NMR spectrum contains one signal at -1216 ppm with a half-width of 815 Hz. A small amount of single crystals of pure $[^{99}Tc(CO)_3(L^{PyCOOEt})]$ was obtained directly from the pre-concentrated reaction solution. They were analysed by ¹H NMR and X-ray diffraction (monoclinic space group $P2_1/n$, unit cell dimensions: a = 15.315 Å; b = 16.398 Å; c = 21.404 Å; $\beta = 90.45^{\circ}$). Unfortunately, the crystals were of low quality and the best data set acquired converged at an R-value of 13.6%. Thus, a detailed discussion of bond lengths and angles, which approximately follow the trends described for the other $[M(CO)_3(L])$ complexes of this communication, will not be included here. All main structural features of the compound. however, can certainly be derived from the calculations. A structural sketch of the complex is shown in Fig. 3. It is obvious, that the ester substituted ligand also coordinates facially as monoanionic, tridentate ligand to the $[^{99}Tc(CO)_3]^+$ core.

The synthesis of the ^{99m}Tc complexes [^{99m}Tc(CO)₃(L)] (L = L^{PyMor} , L^{PyEt} , $L^{PyCOOEt}$) was carried out by adding 1 mM ligand solutions in methanol to equal volumes of aqueous [^{99m}Tc(CO)₃ (H₂O)₃]⁺ solutions. The reactions were optimized by variation of temperature and reaction time. Characterization of the ^{99m}Tc compounds was performed by radio-HPLC and comparison with the



Fig. 4. HPLC data for the reactions of [^{99m}Tc(CO)₃(H₂O)₃]⁺ with HL^{PyEt}.



Fig. 5. HPLC data for the reactions of $[{}^{99m}Tc(CO)_3(H_2O)_3]^+$ with HL^{PyCOOEt}.

HPLC traces (radio- and UV-detector) of the corresponding Re and ⁹⁹Tc compounds. Retention times of all analysed compounds are shown in Table 2.

The reaction of $[^{99m}Tc(CO)_3(H_2O)_3]^+$ with HL^{PyEt} leads to one product with a retention time of 24.5 min, which well resembles that of the corresponding rhenium complex $[Re(CO)_3(L^{PyEt})]$. The reaction is not completed within a time of 30 min at room temperature, but gives almost quantitative yields at 75 °C (Fig. 4). The reaction of $[^{99m}Tc(CO)_3(H_2O)_3]^+$ with HL^{PyMor} was only carried out at 75 °C for 30 min. It was straight forward and gave the desired product $[^{99m}Tc(CO)_3(L^{PyMor})]$ ($t_R = 23.3$ min) in a yield of 97%.

Milder reaction conditions are recommended for the synthesis of $[^{99m}Tc(CO)_3(L^{PyCOOEt})]$ in order to avoid (partial) saponification of the contained ester. Heating of reaction mixtures containing $[^{99m}Tc(CO)_3(H_2O)_3]^+$ and $HL^{PyCOOEt}$ results in the formation of side products as is shown in Fig. 5. The chromatogram of such a reaction mixture at 75 °C for 30 min shows two products with retention times of 23.0 min (19%) and 24.4 min (77%). A comparison

Table	3					
X-ray	structure	data	collection	and	refinement parameter	s.

	$[Tc(CO)_3(L^{PyMor})]$	$[Re(CO)_3(L^{PyMor})]$	$[\text{Re}(\text{CO})_3(L^{\text{PyEt}})]$
Formula	C ₂₁ H ₁₉ N ₄ O ₄ TcS	$C_{21}H_{19}N_4O_4ReS$	C ₂₁ H ₂₁ N ₄ O ₃ ReS
Molecular weight	521.46	609.66	595.68
Crystal system	triclinic	triclinic	monoclinic
a (Å)	6.608(1)	6.606(5)	6.718(1)
b (Å)	8.422(1)	8.386(5)	31.404(2)
c (Å)	20.450(2)	20.405(5)	10.373(1)
α(°)	88.84(1)	88.82(1)	90
β(°)	83.49(1)	83.29(1)	103.55(1)
γ (°)	74.20(1)	74.00(1)	90
V (Å ³)	1088.0(2)	1656.6(3)	2127.3(3)
Space group	ΡĪ	ΡĪ	$P2_1/c$
Ζ	2	2	4
$D_{\text{calc.}}$ (g cm ⁻³)	1.592	1.080(1)	1.860
μ (mm ⁻¹)	0.793	5.763	5.841
Number of	11071	11651	12672
reflections			
Number of	5759	5749	5719
independent			
Number of	269	269	271
parameters			
R_1/wR_2	0.0296/0.0725	0.0297/0.0723	0.0553/0.1302
Goodness-of-fit (GOF) on F ²	1.109	1.177	1.029
CCDC	864853	864854	864855

with the retention times of the Re and ⁹⁹Tc complexes suggests that the main product is the desired complex [^{99m}Tc(CO)₃ (L^{PyCOOEt})] ($t_{\rm R}$ = 24.4 min). The formation of the side-product can readily be explained by a partial cleavage of the ester due to the relatively drastic conditions. This conclusion is supported by the fact that the reaction is accelerated by the presence of trifluoroace-tic acid.

Suitable reaction conditions, which give $[^{99m}Tc(CO)_3(L^{PyCOOEt})]$ in nearly quantitative yields (96%) have been found with a prolonged reaction time (60 min) at room temperature. The observed reactivity under such conditions is also a promising indicator for the suitability for the intended application, the labeling of biomolecules, which require mild conditions anyway.

3. Conclusions

N,*N*-Dialkylamino(thiocarbonyl)-*N*'-picolylbenzamidines are excellent ligands for the stabilization of the $[M(CO)_3]^+$ core. The characterization of the Re and ⁹⁹Tc complexes $[M(CO)_3(L)]$ $(M = Re, {}^{99}Tc; L = L^{PyMor}, L^{PyEt}, L^{PyCOOEt})$ confirm the formation of stable complexes with a facial coordination of the chelating ligands. The corresponding ^{99m}Tc complexes can readily be synthesized from $[{}^{99m}Tc(CO)_3(H_2O)_3]^+$ and characterized by comparative HPLC. Especially the ^{99m}Tc complex $[{}^{99m}Tc(CO)_3(L^{PyCOOEt})]$ has promising properties for further studies since the ester group of the ligand allows linkage between biomolecules and metal core. The observed partial cleavage of the ester bond during the complex formation recommends mild conditions when pre-labelled bioconjugates are used for the synthesis of the technetium complexes.

4. Experimental

4.1. Materials

All reagents used in this study were reagent grade and used without further purification. Na^{99m}TcO₄ was obtained from a commercially available ⁹⁹Mo/^{99m}Tc generator (DRN 4329 Ultra-Technekow FM, Mallinckrodt Medical BV). HL^{PyEt} was synthesized as described in a previous paper [6]. HL^{PyCOOEt} and HL^{PyMor} were synthesized following the same procedure. The syntheses of corresponding *N*,*N*-dialkylamino-*N'*-(thiocarbonyl)benzimidoyl chlorides followed the standard procedures [10]. (NEt₄)₂[Re(CO)₃Br₃] [11], (NEt₄)₂[Tc(CO)₃Cl₃] [12] and [^{99m}Tc(CO)₃(H₂O)₃]⁺ [5a] were prepared by published methods.

4.2. Radiation precautions

 ^{99}Tc is a weak β^- -emitter and $^{99\text{m}}\text{Tc}$ a γ -emitter. All manipulations with these isotopes were performed in a laboratory approved for the handling of radioactive materials. Normal glassware provides adequate protection against the low-energy beta emission of the ^{99}Tc compounds. Secondary X-rays (bremsstrahlung) play an important role only when larger amounts of ^{99}Tc are used. For the $^{99\text{m}}\text{Tc}$ compounds adequate lead shielding was used.

4.3. Physical measurements

Infrared spectra were measured from KBr pellets on a Shimadzu FTIR-spectrometer between 400 and 4000 cm⁻¹. Positive ESI mass spectra were measured with an Agilent 6210 ESI-TOF (Agilent Technologies). All MS results are given in the form: m/z, assignment. Elemental analysis of carbon, hydrogen, nitrogen, and sulphur were determined using a Heraeus Vario EL elemental analyzer. The elemental analyses of the rhenium compounds showed systematically too low values for hydrogen and sometimes carbon (in some cases in a significant extent). This might be caused by an incomplete combustion of the metal compounds and/or hydride formation, and does not refer to impure samples. Similar findings have been observed for analogous oxorhenium(V) complexes with the same type of ligands before [13]. We left these values uncorrected. Additional proof for the identity of the products is given by high-resolution mass spectra for selected representatives. The ⁹⁹Tc values were determined by standard liquid scintillation counting. NMR-spectra were taken with a JEOL 400 MHz multinuclear spectrometer. HPLC analyses were performed on a Merck-Hitachi L6200 system coupled to a Merck Hitachi (1-4250) UV detector (set on 250 nm) and a Beckmann radioactivity detector (171 radioisotope detector). Separations were achieved on a reversed-phase column (Nucleosil 100-5 C18, Knauer) using a gradient of 0.1% CF₃COOH in H₂O (A) and methanol (B) as eluents and flow rates of 0.5 mL/min. Method: 0-3 min 100% A: 3.1-9 min 75% A and 25% B: 9.1-20 min 66% A and 34% B: 20-25 min 100% B: 25-40 min 100% A.

4.4. Syntheses

4.4.1. HL^{PyMor} and HL^{PyCOOEt}

A solution of the morpholine- or ({4-ethylcarboxylyphenyl}methylamine-substituted benzimidoylchloride [10] (1 mmol) in 2 mL of dry acetone was added dropwise to a mixture of 2-methylaminopyridine (109 mg, 1 mmol) and triethylamine (152 mg, 1.5 mmol) in 5 mL of dry acetone over a period of 5 min. The mixture was stirred for 2 h and then cooled to 0 °C. The formed precipitate of (HNEt₃)Cl was filtered off, and the solvent was removed under vacuum. The remaining solid was recrystallized from an acetone/methanol mixture. Yields: 280 mg (82%) for HL^{PyMor} and 240 mg (55%). The identity of the ligands was confirmed by IR, ¹H NMR spectroscopy and elemental analysis.

4.4.2. [Re(CO)₃(L^{PyMor})]

HL^{PyMor} (34 mg, 0.1 mmol) dissolved in 5 mL MeOH was added to a solution of $(NEt_4)_2$ [ReBr₃(CO)₃] (77 mg, 0.1 mmol) in 5 mL MeOH. The colour of the solution immediately turned yellow and a yellow precipitate deposited within 1 h. The yellow powder was filtered off and the product was extracted with acetone. Xray quality single crystals were obtained by slow evaporation of the acetone solution. Yield: 97% (59 mg). Anal. Calc. for Re-C₂₁H₁₉N₄O₄S: C, 41.37; H 3.14; N, 9.19; S, 5.26. Found: C, 41.22; H, 1.68; N, 8.98; S, 4.88%. IR (ν in cm⁻¹): 2997 (w), 2968 (w), 2953 (w), 2841 (w), 2006 (s), 1906 (s), 1865 (s), 1606 (m), 1535 (m), 1468 (s), 1431 (s), 1410 (s), 1387 (m), 1351 (m),

1337 (s), 1287 (m), 1264 (m), 1226 (m), 1207 (m), 1189 (m), 1174 (w), 1154 (w), 1110 (m), 1061 (m), 1025 (m), 984 (w), 965 (w), 929 (w), 892 (m), 847 (w), 788 (w), 734 (w), 710 (m), 690 (w), 675 (w). ¹H NMR (CDCl₃; δ, ppm): 3.61–3.87 (m, 6H, Morpholine), 4.27-4.30 (m, 1H, OCH₂), 4.56-4.59 (m, 1H, OCH₂), 4.88 (d, J = 15.5 Hz, 1H, PyCH₂), 5.20 (d, J = 15.7 Hz, 1H, PyCH₂), 7.11 (d, J = 7 Hz, 1H, Py), 7.20 (m, 1H, Ph), 7.31–7.39 (m, 5H, Py + Ph), 7.70 (t, J = 6 Hz, 1H, Py), 8.74 (d, J = 5 Hz, 1H, Py). ¹³C NMR (CDCl₃; δ, ppm): 197.9 (C_{carbonyl}), 196.4 (C_{carbonyl}), 193.3 (C_{carbonyl}). ESI-TOF-MS 611.08 $[Re(CO)_3(LPyMor)+H]^+$, (m/z): 633.06 [Re(CO)₃(LPyMor)+Na]⁺. High resolution MS of molecular ion [M+H]⁺ Calc.: 611.07627, Found: 611.07635. HPLC (TFA/MeOH, C18rp, min) 24.0.

4.4.3. $[Re(CO)_3(L^{PyEt})]$

HL^{Et} (33 mg, 0.1 mmol) dissolved in 5 mL MeOH was added to a solution of (NEt₄)₂[ReBr₃(CO)₃] (77 mg, 0.1 mmol) in 5 mL MeOH. The color of the solution immediately turned yellow and a yellow precipitate deposited within an hour. The yellow powder was filtered off and the product was extracted with acetone. X-ray quality single crystals were obtained by slow evaporation of the acetone solution or of the original reaction solution. Yield: 85% (51 mg). Anal. Calc. for ReSC₂₁H₂₁N₄O₃: C, 42.34; H 3.55; N, 9.41; S, 5.38. Found: C, 41.69; H, 4.68; N, 8.31; S, 4.42%. IR (v in cm⁻¹): 2981 (w), 2942 (w), 2009 (s), 1899 (s), 1884 (s), 1654 (m), 1605 (w), 1555 (w), 1526 (w), 1482 (s), 1417 (m), 1396 (m), 1341 (m), 1255 (w), 1174 (m), 1066 (w), 1002 (m), 787 (s), 764 (s), 718 (s), 641 (s), 614 (m), 531 (m). ¹H NMR (CDCl₃; δ, ppm): 1.15 (m, 3H, CH₃), 1.29 (t, J = 6 Hz, 3H, CH₃), 3.75 (m, 2H, CH₂), 4.15 (q, J = 7 Hz, 2H, CH₂), 4.96 (m, 1H, PyCH₂), 5.26 (d, J = 14.3 Hz, 1H, PyCH₂), 7.15–7.28 (m, 2H, Py + Ph), 7.40–7.55 (m, 5H, Py + Ph), 7.67–7.75 (m, 1H, Py), 8.76 (d, J = 5 Hz, 1H, Py). ESI-TOF-MS (m/ z): 597.10 $[\text{Re}(\text{CO})_3(\text{L}^{\text{PyEt}})+\text{H}]^+$. High resolution MS of molecular ion [M+H]⁺ Calc.: 597.0970, Found: 597.0975. HPLC (TFA/MeOH, C18rp, min) 24.0.

4.4.4. $[^{99}Tc(CO)_3(L^{PyMor})]$

HL^{PyMor} (34 mg, 0.1 mmol) dissolved in 5 mL MeOH was added to a solution of (NEt₄)₂[TcCl₃(CO)₃] (55 mg, 0.1 mmol) in 5 mL MeOH. The color of the solution immediately turned yellow and a yellow precipitate deposited within an hour. The yellow powder was filtered off and the product was extracted with acetone. X-ray quality single crystals were obtained by slow evaporation of the acetone solution. Yield: 86% (45 mg). Anal. Calc. for TcC₂₁H₁₉N₄O₄S: Tc, 18.8. Found: Tc, 18.3%. IR (v in cm⁻¹): 3001 (w), 2970 (w), 2843 (m), 2017 (s), 1921 (s), 1886 (s), 1609 (m), 1539 (m), 1466 (s), 1408 (s), 1335 (s), 1285 (m), 1261 (m), 1207 (m), 1111 (m), 1057 (m), 1022 (m), 964 (w), 930 (w), 891 (m), 791 (w), 764 (m), 706 (m), 648 (m), 610 (m), 520 (m), 455 (w), 428 (w). ¹H NMR (CDCl₃; δ, ppm): 3.61-3.68 (m, 5H, Morpholine), 3.91 (m, 1H, OCH₂), 4.18 (m, 1H, OCH₂), 4.55 (m, 1H, OCH₂), 4.94 (s, 2H, PyCH₂), 7.05 (d, J = 7.9 Hz, 1H, Py), 7.19 (t, J = 6.2 Hz, 1H, Ph), 7.28–7.35 (m, 5H, Py + Ph), 7.65 (t, J = 7.7 Hz, 1H, Py), 8.64 (d, J = 5 Hz, 1H, Py). ⁹⁹Tc NMR (THF; δ , ppm): -1220 ($\Delta v_{1/2}$ = 596 Hz). HPLC (TFA/MeOH, C18rp, min) 25.2.

4.4.5. [⁹⁹Tc(CO)₃(L^{PyCOOEt})]

 $HL^{PyCOOEt}$ (43 mg, 0.1 mmol) dissolved in 2 mL MeOH was added to a solution of (NEt₄)₂[TcCl₃(CO)₃] (55 mg, 0.1 mmol) in 5 mL MeOH and 5 mL H₂O. A colorless precipitate of [Tc(CO)₃(L^{PyCOOEt})] deposited within an hour. This material consists of [Tc(CO)₃(L^{PyCOOEt})] × (NEt₄)Cl. Yield: 58% (46 mg). *Anal.* Calc. for TcC₂₇H₂₄N₄O₅S+(NEt₄)Cl: Tc, 12.7. Found: Tc, 12.8%. IR (ν in cm⁻¹): 3067 (w), 2966 (w), 2017 (s), 1909 (s), 1894 (s), 1717 (m), 1605 (w), 1512 (w), 1474 (m), 1373 (w), 1273 (m), 1173 (w), 1103 (m), 1061 (w), 1022 (m), 799 (w), 706 (w), 621 (w).¹H NMR (CDCl₃; δ , ppm): 1.23 (t, *J* = 6.5 Hz, 12H, NCH₂*CH*₃), 1.34 (t, *J* = 7.1 Hz, 3H, OCH₂*CH*₃), 3.43 (q, *J* = 6.5 Hz, 8H, NCH₂CH₃), 3.50 (s, 3H, NCH₃), 4.28–4.39 (m, 2H, O*C*H₂CH₃), 7.04 (d, *J* = 8 Hz, 1H, Py), 7.13 (t, *J* = 6.9 Hz, 1H, Ph), 7.32–7.49 (m, 7H, Ph + Py), 7.64 (t, *J* = 7.6 Hz, 1H, Py), 8.01 (d, *H* = 8.3 Hz, 2H, Ph), 8.52 (d, *J* = 4.8 Hz, 1H, Py).⁹⁹Tc NMR (THF; δ , ppm): –1216 ($\Delta v_{1/2}$ = 815 Hz).

An additional small amount of single crystals were obtained by slow evaporation of the reaction solution. They do not contain cocrystallized (NEt₄)Cl and were used for the crystallographic and ¹H NMR studies. ¹H NMR (CDCl₃; δ , ppm): 1.32 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 3.48 (s, 3H, NCH₃), 4.28–4.38 (m, 2H, OCH₂CH₃), 7.04 (d, *J* = 8 Hz, 1H, Py), 7.13 (t, *J* = 6.9 Hz, 1H, Ph), 7.31–7.48 (m, 7H, Ph + Py), 7.63 (t, *J* = 7.6 Hz, 1H, Py), 8.01 (d, *H* = 8.3 Hz, 2H, Ph), 8.52 (d, *J* = 4.8 Hz, 1H, Py). HPLC (TFA/MeOH, C18rp, min) 25.5.

4.4.6. $[^{99m}Tc(CO)_3(L)] (L = L^{PyMor}, L^{PyEt}, L^{PyCOOEt})$

One milliliter of a 10^{-3} M solution of the *N*-picolylbenzamidine (HL^{PyMor}, HL^{PyEt} or HL^{PyCOOEt}) in H₂O was added to 1 mL of a solution of [^{99m}Tc(CO)₃(H₂O)₃]⁺ in H₂O. The reactions were optimized by changing temperature and reaction time.

HPLC (TFA/MeOH, C18rp, min) yields with the following ligands: HL^{PyMor} 23.3 (75 °C, 30 min, 97%). HL^{PyEt} 24.5 (22 °C, 30 min, 76%; 75 °C, 30 min, 94%). HL^{PyCOOEt}24.4 (75 °C, 30 min, 77%; 22 °C, 30 min, 70%; 22 °C, 60 min, 96%).

4.5. X-ray crystallography

The intensities for the X-ray determinations were collected on a STOE IPDS 2T instrument with Mo K α radiation (λ = 0.71073 Å). Standard procedures were applied for data reduction and absorption correction. Structure solution and refinement were performed with SIR 97 [14]. Hydrogen atom positions were calculated for idealized positions and treated with the 'riding model' option of SHELXL [15].

More details on data collections and structure calculations are contained in Table 3. Additional information on the structure determinations has been deposited with the Cambridge Crystallographic Data Centre.

Appendix A. Supplementary data

CCDC 864853, 864854 and 864855 contains the supplementary crystallographic data for $[Tc(CO)_3(L^{PyMor})]$, $[Re(CO)_3(L^{PyMor})]$ and

 $[\text{Re}(\text{CO})_3(L^{\text{PyEt}})]$, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

References

- [1] (a) S. Bhattacharyya, M. Dixit, Dalton Trans. 40 (2011) 6112;
- (b) U. Abram, R. Alberto, J. Braz. Chem. Soc. 17 (2006) 1486.
- [2] R. Alberto, U. Abram, in: A. Vértes, S. Nagy, Z. Klencsár, R.G. Lovas, F. Rösch (Eds.), Handbook of Nuclear Chemistry, vol. 4, Springer, US, 2011, pp. 2073– 2120.
- [3] P.J. Blower, S. Prakash, in: R.W. Hay, H.R. Dilworth, K.B. Nolan (Eds.), Perspectives on Bioinorganic Chemistry, vol. 4, JAI Press Inc., 1999, pp. 91–143.
 [4] (a) S.S. Jurisson, J.D. Lydon, Chem. Rev. 99 (1999) 2205;
- (b) S. Liu, Chem. Soc. Rev. 33 (2004) 445;
- (c) M.D. Bartholomä, A.S. Louie, J.F. Valliant, J. Zubieta, Chem. Rev. 110 (2010) 2903.
- [5] (a) R. Alberto, R. Schibli, A. Egli, P.A. Schubiger, W.A. Herrmann, G. Artus, U. Abram, T.A. Kaden, J. Organomet. Chem. 493 (1995) 119;
 (b) R. Alberto, R. Schibli, A. Egli, A.P. Schubiger, U. Abram, T.A. Kaden, J. Am.
- Chem. Soc. 120 (1998) 7987.
- [6] H.H. Nguyen, J. Grewe, J. Schroer, B. Kuhn, U. Abram, Inorg Chem. 47 (2008) 5136.
- [7] (a) H.H. Nguyen, U. Abram, Polyhedron 28 (2009) 3945;
- (b) J. Schroer, U. Abram, Polyhedron 28 (2009) 2277.
- [8] (a) H.H. Nguyen, K. Hazin, U. Abram, Eur. J. Inorg. Chem. (2011) 78;
 (b) H.H. Nguyen, V.M. Deflon, U. Abram, Eur. J. Inorg. Chem. (2009) 3179;
 (c) H.H. Nguyen, T.N. Trieu, U. Abram, Z. Anorg, Allg. Chem. 637 (2011) 1330.
- [9] (a) U. Abram, S. Abram, R. Alberto, R. Schibli, Inorg. Chim. Acta 248 (1996) 193;
 (b) H. Braband, U. Abram, J. Organomet. Chem. 689 (2004) 2066.
- [10] L. Beyer, R. Widera, Tetrahedron Lett. 23 (1982) 1881.
- [11] R. Alberto, A. Egli, U. Abram, K. Hegetschweiler, V. Gramlich, P.A. Schubiger, J. Chem. Soc., Dalton Trans. (1994) 2815.
- [12] R. Alberto, K. Ortner, N. Wheatley, R. Schibli, A.P. Schubiger, J. Am. Chem. Soc. 123 (2001) 3135.
- [13] H.H. Nguyen, J.J. Jegathesh, P.I.S. Maia, V.M. Deflon, R. Gust, S. Bergemann, U. Abram, Inorg. Chem. 43 (2009) 9356.
- [14] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. Molterni, M. Burla, G. Polidori, M. Carnalli, R. Spagna, SIR 97 program for the solution of crystal structures, Campus Universitario, 1997.
- [15] G.M. Sheldrick, SHELXL-97, program for the refinement of crystal structures, University of Göttingen, Göttingen, Germany, 1997.
- [16] K. Brandenburg, H. Putz, DIAMOND a program for the representation of crystal structures, vers. 3.2, Crystal Impact, Bonn, Germany 2011.