Inorganica Chimica Acta 400 (2013) 2–6

Contents lists available at SciVerse ScienceDirect

Inorganica Chimica Acta

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

A new bifunctional tridentate NSN ligand leading to cationic tricarbonyl *fac*-[M(NSN)(CO)$_3$]$^+$ (M = Re, ^{99m}Tc) complexes

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ARTICLE INFO

Article history:
Received 3 October 2012
Received in revised form 31 January 2013
Accepted 1 February 2013
Available online 10 February 2013

Keywords:
Rhenium
Technetium
Tricarbonyl complexes
Bifunctional

ABSTRACT

The synthesis and characterization of the new NSN tridentate bifunctional chelating agent 3-[2-(2′-pyridin-2-yl-ethylsulfanyl)ethylamino] propionic acid (as its hydrochloric salt, **1**) and of its corresponding rhenium complex *fac*-[Re(NSN)(CO)$_3$]$^+$, **2**, is described. Both compounds were characterized by elemental analysis, IR and NMR spectroscopies and X-ray crystallography. In complex **2** the coordination geometry around rhenium is distorted octahedral with the NSN atoms participating in the coordination sphere while the carboxylate group remains free. At tracer level, the analogous complex *fac*-[^{99m}Tc(NSN)(CO)$_3$]$^+$, **3**, was obtained in high yield by reacting ligand **1** with the *fac*-[^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ precursor at pH 6.5. The structure of **3** was established by HPLC comparison to the prototype rhenium complex **2.** Complex **3** is stable in solution as well as in the presence of strongly coordinating agents like histidine or cysteine. Our data indicate that ligand **1** can be used as a bifunctional NSN chelating agent in the design of potential ^{99m}Tc-radiopharmaceuticals.

1. Introduction

The coordination chemistry of technetium (Tc) and its surrogate rhenium (Re) has been studied extensively as a result of the importance of these radiometals in the development of radiopharmaceuticals for imaging (^{99m}Tc) and/or radiotherapy (^{186}Re, ^{188}Re) in Nuclear Medicine. ^{99m}Tc ($t_{1/2}$ = 6 h; E_γ = 140 keV) is the radionuclide of choice for imaging, due to its ideal nuclear properties, its low cost, and widespread availability. Furthermore, the introduction of the high-energy beta-emitters ^{186}Re ($t_{1/2}$ = 90 h; E_{max} = 1.07 MeV) and ^{188}Re ($t_{1/2}$ = 17 h; E_{max} = 2.12 MeV) in the development of therapeutic radiopharmaceuticals has made coordination studies on technetium and rhenium even more attractive. In fact, ^{99m}Tc and $^{186/188}$Re can be considered to be a matched pair for imaging and therapy [1].

The bifunctional strategy for the development of technetium and rhenium radiopharmaceuticals has become the most widely used method for producing well-defined technetium and rhenium labeled receptor ligands capable of highly specific in vivo localization in target tissues [2]. This strategy involves the development of a suitable bifunctional chelating agent (BFCA) for the chelation of the radionuclide and the conjugation of the target specific moiety. An ideal BFCA is that which is able to form stable and inert ^{99m}Tc or $^{186/188}$Re complexes in high yield, at low concentration. The introduction of the air-stable *fac*-[M(H$_2$O)$_3$(CO)$_3$]$^+$ (M = ^{99m}Tc or Re) precursor produced by the gentle reduction of M(VII) to M(I) under 1 atm of CO, established the *fac*-[M(CO)$_3$]$^+$ core as an easily accessible platform towards the synthesis of new radiopharmaceuticals [3,4]. In the *fac*-[M(H$_2$O)$_3$(CO)$_3$]$^+$ synthon three coordination sites are occupied by CO groups in the stable *facial* configuration while the remaining three coordination sites are occupied by water molecules that can be easily replaced by suitable bidentate or tridentate ligands in aqueous solution. Both bidentate and tridentate ligands give complexes of high kinetic and thermodynamic stability, with tridentate ligands exhibiting faster reaction rates and better stabilizing the complex against trans-chelation reactions [4,5]. A series of suitable tridentate chelating agents which may combine an amine or aromatic N, a thioether S, and a carboxylate O as donor atoms, has been applied to produce stable hexacoordinated complexes [6].

In the present work, we describe the synthesis and characterization of the new BFCA 3-[2-(2-pyridin-2-yl-ethylsulfanyl)

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http://dx.doi.org/10.1016/j.ica.2013.02.001

ethylamino]propionic acid (NSN, **1**) and of the corresponding tricarbonyl rhenium and technetium complexes. The new ligand **1** and the cationic *fac*-$[Re(NSN)(CO)_3]^+$ complex, **2** were synthesized and fully characterized by X-ray crystallography and other spectroscopic methods (Scheme 1). Chemistry was successfully transferred at the ^{99m}Tc tracer level to obtain the analogous radioactive complex **3**.

2. Experimental

2.1. Materials and methods

All reagents and organic solvents used in this study were purchased from Aldrich and used without further purification. Solvents for high-performance liquid chromatography (HPLC) were HPLC-grade. They were filtered through membrane filters (0.22 μm, Millipore, Milford, MA) and degassed by a helium flux before and during use. $[NEt_4]_2[ReBr_3(CO_3]$ was prepared according to published procedure [3]. For labeling with ^{99m}Tc a kit containing 5.5 mg $NaBH_4$, 4 mg Na_2CO_3 and 10 mg Na–K tartrate was purged with CO gas prior to addition of $Na^{99m}TcO_4$, as described in the literature [4]. 2-(2-Pyridin-2-yl-ethylsulfanyl)ethylamine was synthesized following a reported method [7].

IR spectra were recorded as KBr pellets on a Perkin–Elmer 1600 FT-IR spectrophotometer in the region 4000–500 cm^{-1}. The NMR spectra were recorded in DMSO-d_6 at 25 °C on a Bruker 500 MHz Avance DRX spectrometer using $(CH_3)_4Si$ as the internal reference. Elemental analysis for C, H and N was conducted on a Perkin–Elmer 2400 automatic elemental analyzer. HPLC analysis was performed on a Waters 600 chromatography system coupled to both a Waters 2487 Dual λ Absorbance detector and a Gabi gamma detector from Raytest. Separations were achieved on a C-18 RP column (10 μm, 250 × 4 mm) eluted with a binary gradient system at a 1 mL/min flow rate. Mobile phase A was methanol containing 0.1% trifluoroacetic acid, while mobile phase B was water containing 0.1% trifluoroacetic acid. The elution gradient was 0–1 min 100% B (0% A), followed by a linear gradient to 70% A (30% B) in 9 min; this composition was held for another 10 min. After a column wash with 95% A for 5 min, the column was re-equilibrated by applying the initial conditions (100% B) for 15 min prior to the next injection.

2.2. Synthesis of *1*

To a solution of 2-(2-pyridin-2-yl-ethylsulfanyl)ethylamine (1.82 g, 10 mmol) in 15 mL ethanol, a solution of ethyl acrylate (1 g, 10 mmol) in 15 mL ethanol was slowly added at 0 °C. The solution was stirred for 3 h at 0 °C and for an additional 24 h at room temperature. The solvent was subsequently removed under reduced pressure and the residue was dissolved in dichloromethane and washed with water. The organic layer was collected and evaporated to dryness. The residue was dissolved in 20 mL NaOH 1 N, stirred for 24 h and washed with dichloromethane. The pH of the aqueous layer was adjusted to 3 using HCl 1 N and the solvent was evaporated. The resulting white solid was recrystallized from tetrahydrofuran/methanol and crystals of **1** suitable for X-ray analysis were obtained. Yield: 2.36 g (81%), t_R: 9.7 min, IR (cm^{-1}, KBr): 1713. *Anal.* Calc. for $C_{12}H_{19}ClN_2O_2S$: C, 49.56; H, 6.59; N, 9.63. Found: C, 49.31; H, 6.40; N, 9.58%. ^{1}H and ^{13}C NMR data are given in Table 1.

2.3. Synthesis of *2*

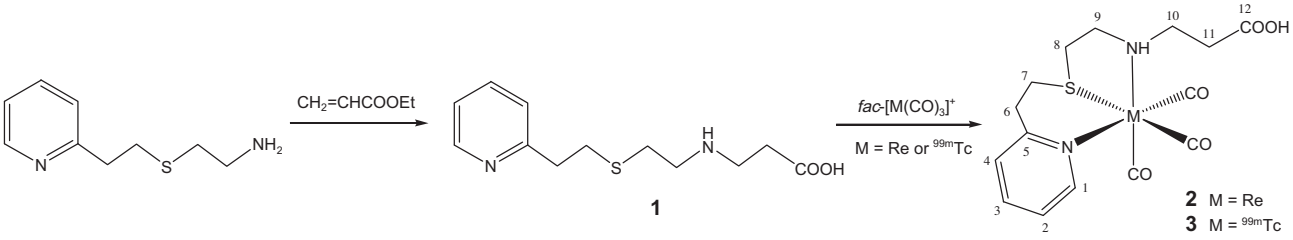
To a stirred solution of $[NEt_4]_2[ReBr_3(CO)_3]$ (77 mg, 0.1 mmol) in 7 mL methanol, a solution of **1** (29.1 mg, 0.1 mmol) in 8 mL methanol and 0.1 mL NaOH 1 N (0.1 mmol) was added. The solution was refluxed and the reaction progress was monitored by HPLC. After 5 h the solvent was removed under reduced pressure the residue was washed with dichloromethane and crystallized by slow evaporation from methanol. Yield: 56.2 mg (93%), t_R: 16.7 min, IR (cm^{-1}, KBr): 2021, 1938, 1896, 1730. *Anal.* Calc. for $C_{15}H_{18}BrN_2O_5ReS$: C, 29.80; H, 3.00; N, 4.63. Found: C, 29.69; H, 2.92; N, 4.55%. ^{1}H and ^{13}C NMR data are given in Table 1. Crystals suitable for X-ray analysis were obtained from recrystallization from methanol/THF.

2.4. Synthesis of *3*

900 μL of a solution of the *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ precursor (pH 6.5) were added to a vial containing 100 μL of a 10^{-3} M solution of **1** in water. The vial was sealed, flushed with N_2 and heated for 20 min at 80 °C. HPLC analysis demonstrated the formation of a single complex eluting at 16.8 min. The yield of the reaction was quantitative (>98%). The identity of the ^{99m}Tc-complex was established by comparative HPLC studies using samples of the well characterized **2** as reference. The radioactivity recovery of the HPLC column after the injections was monitored and found to be quantitative.

2.5. X-ray crystallography

Crystals of **1** and **2** suitable for X-ray analysis were mounted in air on a Crystal Logic Dual Goniometer diffractometer using graphite monochromated Mo Kα radiation. Unit cell dimensions were determined by using the angular settings of 25 automatically centered reflections in the range $11 < 2\theta < 23°$ and they appear in Table 2. Intensity data were recorded using a θ–2θ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization and psi-scan absorption corrections (for **2** only) were applied using Crystal Logic software. The structures were solved by direct methods using SHELXS-97 [8] and refined by full-matrix least squares techniques on F^2 using SHELXL-97 [9]. Further crystallographic details of **1**: $2\theta_{max} = 48°$, reflections collected/unique/used 2541/2387 [$R_{int} = 0.0115$]/2387, 239 parameters refined, $[\Delta\rho]_{max}/[\Delta\rho]_{min} = 0.255/-0.248$ e/Å^3, $[\Delta/\sigma]_{max} = 0.001$, R_1/wR_2 (for all data) = 0.0630/0.1066. Hydrogen atoms were located by difference maps and were refined



Scheme 1. Synthesis of ligand **1** and of complexes **2** and **3.**