Available online at www.sciencedirect.com

SCIENCE DIRECT®

Journal of Organometallic Chemistry 689 (2004) 4833–4836

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

Exploring the nitrosyl-approach: “$Re(CO)_2(NO)$”- and “$Tc(CO)_2(NO)$”-complexes provide new pathways for bioorganometallic chemistry

D. Rattat [a,*], A. Verbruggen [a], H. Berke [b], R. Alberto [b]

[a] *Laboratory of Radiopharmaceutical Chemistry, Catholic University of Leuven, Herestraat 49, B-3000 Leuven, Belgium*
[b] *Institute of Inorganic Chemistry, University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland*

Received 22 July 2004; accepted 27 September 2004
Available online 6 November 2004

Abstract

Nitrosylation reactions are rare in the context of low valent Re(I)- and Tc(I)-tricarbonyl complexes so far. We herein describe a method for the conversion of a “$M(CO)_3$-moiety” (M = Re, Tc) into a dicarbonyl-nitrosyl moiety “$M(CO)_2NO$”, the synthesis of important precursor complexes and intermediates and possible applications for this new kind of Re- and Tc-chemistry.

The behavior of the complex $[ReCl_3(CO)_2(NO)]^-$ in water was studied in detail and compared to that of $[ReCl_3(CO)_3]^{2-}$. Contrary to the conversion of $[ReCl_3(CO)_3]^{2-}$ to the mixed aquo-carbonyl complex $[Re(OH_2)_3(CO)_3]^+$ in water, one chloride remains initially bound to the metal center in the dicarbonyl-nitrosyl complex, making $[ReCl(OH_2)_2(CO)_2(NO)]^+$ the main species for further reactions. In this context, we isolated and characterized the complex $[Re(\mu_3\text{-}O)(CO)_2(NO)]_4$. Examples of complexes with different bi- and tridentate ligands based on $ReCl_3(CO)_2(NO)]^-$ are discussed.

For the development of potential new radiopharmaceuticals we also adapted the nitrosylation technique to the n.c.a. level with ^{99m}Tc. $[^{99m}Tc(OH_2)_3(CO)_3]^+$ served as starting material to form a $^{99m}Tc(CO)_2(NO)$-core. Labelling reactions with ligands such as iminodiacetic acid (IDA), nitrilotriacetic acid (NTA) and diethylenetriamine pentaacetic acid (DTPA) were performed, resulting in the complexes $[^{99m}Tc(IDA)(CO)_2(NO)]$, $[^{99m}Tc(NTA)(CO)_2(NO)]$ and $[^{99m}Tc(DTPA)(CO)_2(NO)]$. In this way, the “nitrosyl-approach” adds a new and challenging synthetic tool to the already established organometallic chemistry of Re- and Tc-tricarbonyl complexes.

Keywords: Rhenium; Technetium; Carbonyl; Nitrosyl; Cluster; Labelling

1. Introduction

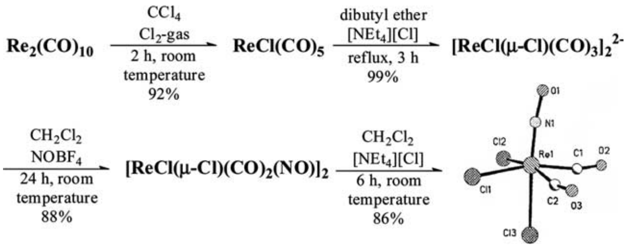
Nitrosylation reactions are well known in organometallic chemistry, but rare in the context of low valent Re(I)- and Tc(I)-tricarbonyl complexes so far [1]. On the other hand, a variety of Re- and Tc-comlexes with a “$M(CO)_3$-moiety” (M = Re, Tc) has been developed during the last years [2–4]. Such Re- and Tc-tricarbonyl complexes are useful as starting material for a conversion of the $M(CO)_3$-core into a $M(CO)_2(NO)$-core [5]. The introduction of a charged NO^+ group instead of a neutral CO group changes the charge of the formed dicarbonyl-nitrosyl complexes by +1 as compared to the original tricarbonyl compounds, while the *fac*-geometry of the three groups (CO, CO, NO) in the complex is retained. Also the electronic properties of the $M(CO)_2(NO)$-complexes differ, as NO^+ is a stronger π-acceptor, but a weaker σ-donor as compared to the isoelectronic CO [6].

A possible starting material for the $Re(CO)_2(NO)$-chemistry is the complex $[ReCl(\mu\text{-}Cl)(CO)_2(NO)]_2$,

---

[*] Corresponding author. Tel.: +3216343892; fax: +3216343891.
E-mail address: dirk.rattat@uz.kuleuven.ac.be (D. Rattat).

0022-328X/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2004.09.074



Scheme 1. Synthesis of $[NEt_4][ReCl_3(CO)_2(NO)]$ starting from $Re_2(CO)_{10}$.

already described by Uguagliaty and co-workers in the 1970s [7]. We developed an optimized synthesis of this complex starting from $[Re_2(CO)_{10}]$ in CCl_4. After flushing a solution of this precursor with Cl_2-gas, $[ReCl(CO)_5]$ was obtained, which was converted with NEt_4Cl to $[NEt_4]_2$ $[ReCl(\mu\text{-}Cl)(CO)_3]_2$ [8]. Subsequent nitrosylation with $NOBF_4$ gave the dinuclear complex $[ReCl(\mu\text{-}Cl)(CO)_2(NO)]_2$. Reaction with an excess of NEt_4Cl resulted in the mononuclear complex $[NEt_4][ReCl_3(CO)_2(NO)]$ [6]. Scheme 1 shows a graphical summary of the process, which can easily be monitored by IR-spectroscopy. The complexes *fac*-$[ReCl_3(CO)_2(NO)]^-$ and *fac*-$[ReBr_3(CO)_2(NO)]^-$ served as precursors for most of the experiments with the new $M(CO)_2(NO)$-core. The main focus of this paper is the behavior of these precursors in water and the reaction with different ligands.

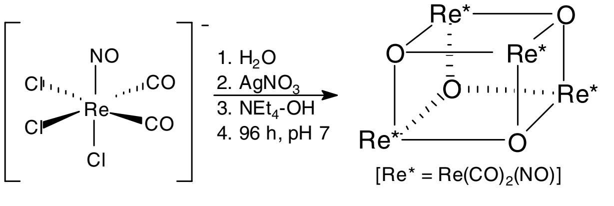
2. Results and discussion

The behavior of the complex $[ReCl_3(CO)_2(NO)]^-$ in water was studied in detail and compared to that of $[ReCl_3(CO)_3]^{2-}$ as continuation of previous research [6]. The Re-tricarbonyl complex $[ReCl_3(CO)_3]^{2-}$ replaces three halides by water, resulting in the "tris-aquo" complex $[Re(H_2O)_3(CO)_3]^+$. $[ReCl_3(CO)_2(NO)]^-$ showed a different behavior. In a first step only two of the chlorides were replaced by water molecules. This was monitored by addition of one or two equivalents of a silver salt, which did not change at all the ATR-IR spectrum with bands at 2112 (CO), 2044 (CO) and 1800 (NO) cm^{-1}. Consequently, two of the chlorides cannot have been located at the Re-center after dissolution and therefore these bands can be attributed to the complex $[ReCl(H_2O)_2(CO)_2(NO)]^+$. With the addition of the third equivalent of Ag^+ (and precipitation of AgCl) the bands shifted to 2106, 2036 and 1789 cm^{-1}, indicating that the third chloride was initially still bound in the complex (Scheme 2).

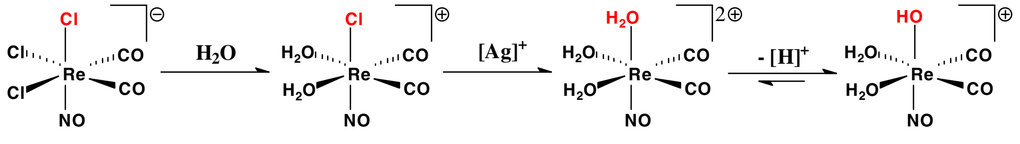
The dissolution behaviour of $[NEt_4][ReCl_3(CO)_2(NO)]$ in water was also studied by potentiometric analysis using a chloride selective electrode. According to this analysis also the third chloride ion was released from the complex in a slow process (up to 24 h). The pH of the hydrolyzed solution (1.06 mM) was 3.18 (calculated pK_a of 2.96). $Re(H_2O)_3(CO)_2(NO)]^{2+}$ therefore represents an acid of medium strength. Titration of $[Re(H_2O)_3(CO)_2(NO)]^{2+}$ with NaOH showed a first deprotonation step at one equivalent of base. Subsequent deprotonation steps were kinetically slow (long equilibration times to achieve constant pH). We assume that the formation of aggregates might be an explanation for this behavior and succeeded in isolating the yellow cubane-type cluster $[Re(\mu_3\text{-}O)(CO)_2(NO)]_4$, which precipitated from solution at a pH of 7 (Scheme 3).

The complex was characterized by IR (2082, 2005 and 1752 cm^{-1}) and mass spectroscopy. Starting from the molecular peak at 1154 Da every fragmentation of the eight CO- and four NO-groups was detected as well defined peak in the spectrum, with a distance of 28 Da (-CO) or 30 Da (-NO), respectively (Fig. 1). The basic structure was a Re_4O_4-unit (Scheme 3). Although thermodynamically favored, the very slow cluster formation was not observed, if the pH was raised faster.

To further study the behavior of the "aquo-complex" $[Re(H_2O)_3(CO)_2(NO)]^{2+}$, $[NEt_4][ReCl_3(CO)_2(NO)]$ was dissolved in water and the three chlorides were precipitated with $AgNO_3$. Fig. 2 shows the ATR-IR spectrum of the solution at different pH values. In acidic solution the known pattern of bands at 2106, 2036 and 1789 cm^{-1} was observed (see above). Starting from pH 5–6 a unique CO-band developed at 1976 cm^{-1}, which



Scheme 3. Formation of the cluster-type complex $[Re(\mu_3\text{-}O)(CO)_2(NO)]_4$.



Scheme 2. ATR-IR experiments show that one chloride remains bound to the Re-center, when $[ReCl_3(CO)_2(NO)]^-$ is dissolved in water. After removal of the chloride with a silver salt, the "aquo-complex" represents an acid of medium strength.

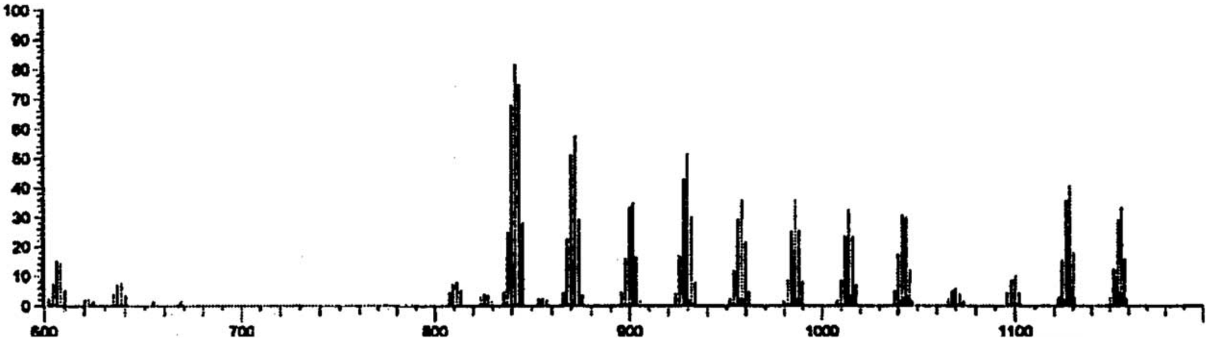


Fig. 1. Mass spectrum of $[Re(\mu_3\text{-}O)(CO)_2(NO)]_4$.

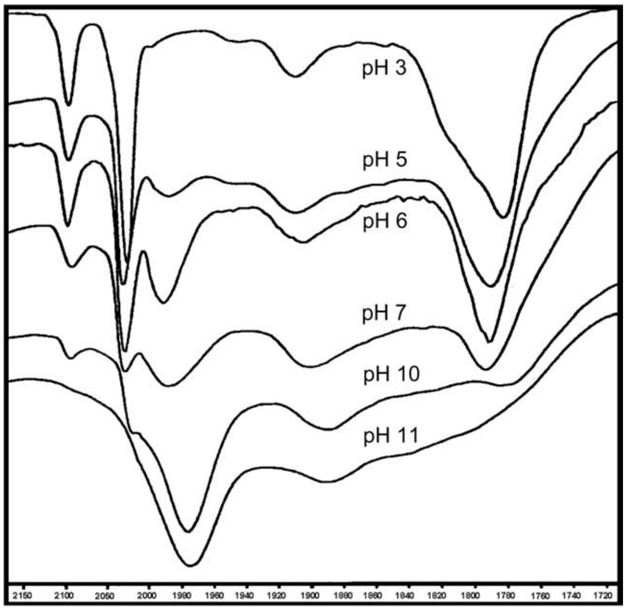


Fig. 2. ATR-IR spectra of the “aquo-complex” $[Re(H_2O)_3\text{-}(CO)_2(NO)]^{2+}$ at pH 3, 5, 6, 7, 10 and 11.

became dominant and shifted to 1966 cm^{-1} at basic pH values of 10–11. However, a loss of CO was not detected during this process. This band was therefore attributed to a monocarbonyl species bearing a rhenacarboxylic acid group formed via nucleophilic attack of a OH^- ion on a CO ligand instead of the Re-center. Acidification showed that this process is reversible.

These findings raised the question which ligands are suitable for the $Re(CO)_2(NO)$-core. As only one CO-group was replaced by an isoelectronic NO^+, ligands suitable for complexation with $[Re(CO)_3]^+$ are in principle also possible targets for $[Re(CO)_2(NO)]^{2+}$. Experience with the bidentate ligand picolinic acid (PIC) demonstrated that the NO^+ can be introduced before or after complexation with a ligand and therefore in different stages of an ongoing process [5]. Histidine (HIS), an example of a tridentate ligand, was used to prepare the complex $[Re(HIS)(CO)_2(NO)][BF_4]$ in the same way [6].

Based on these results, the nitrosylation technique was adapted to the n.c.a. level with ^{99m}Tc. $[^{99m}Tc(CO)_3(H_2O)]^+$ was the starting material, which was synthesized from $^{99m}TcO_4^-$ (in saline solution) using an IsoLink™ kit (Tyco-Mallinckrodt, Petten, The Netherlands). As a conversion of the $Tc(CO)_3$-core with $NOBF_4$ in water was not successful, we first made the $^{99m}Tc(CO)_3$-ligand complexes, evaporated the solutions to dryness and reacted the residue with $NOBF_4$ in CH_2Cl_2 or acetonitrile to form the appropriate $^{99m}Tc(CO)_2(NO)$-ligand complexes. The conversion was most successful when the Tc-tricarbonyl complex was negatively charged (or neutral). In this way, we synthesized the complexes with iminodiacetic acid $[^{99m}Tc(IDA)(CO)_2(NO)]$, nitrilotriacetic acid $[^{99m}Tc(NTA)(CO)_2(NO)]$ and diethylenetriamine pentaacetic acid $[^{99m}Tc(DTPA)(CO)_2(NO)]$. They showed different retention times on HPLC as compared to the corresponding $Tc(CO)_3$-complexes. Results of analyses by LC–MS supported the supposed formulas. Biodistribution studies in mice for the three compounds are currently in progress. Preliminary results for the complex $[^{99m}Tc(DTPA)(CO)_2(NO)]$ showed a high blood level and enhanced liver and kidney values (even after 1 h), which is clearly different from the behavior of the corresponding Tc-tricarbonyl complex $[^{99m}Tc(DTPA)\text{-}(CO)_3]^-$.

3. Conclusion

We explored a new class of compounds, i.e. Re- and Tc-dicarbonyl-nitrosyl complexes. The conversion of the “$Re(CO)_3$ “ core to the “$Re(CO)_2(NO)$” core is described as well as model complexes with bidentate or tridentate ligands like picolinic acid and histidine. The behavior of the complex $[ReCl_3(CO)_2(NO)]^-$ in water was studied at different pH values and the cubane-type cluster $[Re(\mu_3\text{-}O)(CO)_2(NO)]_4$ was isolated as product of a condensation process.

The nitrosylation technique was also adapted to the n.c.a. level with ^{99m}Tc and three model complexes were synthesized, namely $[^{99m}Tc(IDA)(CO)_2(NO)]$,

[^{99m}Tc(NTA)(CO)$_2$(NO)] and [^{99m}Tc(DTPA)(CO)$_2$-(NO)]. The new Re- and Tc-dicarbonyl-nitrosyl compounds showed clearly different characteristics (e.g. behavior in water, polarity, for the Re-complexes also the color) as compared to their corresponding tricarbonyl complexes. In this way, the "nitrosyl-approach" introduces a new synthetic tool, extends the already established Tc-tricarbonyl chemistry and increases the number of potentially useful ^{99m}Tc-tracer agents.

4. Experimental

4.1. General

Most reactions with organometallic rhenium compounds were carried out under argon or nitrogen using standard Schlenk techniques. Organic solvents were dried prior to use. The prepared Re-complexes were characterized by elemental analysis (LECO CHNS-923, LECO Corporation, St. Joseph, USA) and spectroscopic methods. IR spectra were recorded with a Bio-Rad FTS-45 (Bio-Rad Laboratories, Hercules, USA) or FT-IR-16PC spectrometer (Perkin-Elmer, Wellesley, USA), in aqueous solutions according to the HATR-method (horizontal attenuated total reflectance) with a ZnSe-crystal. Mass spectrometry was performed on a Finnigan MAT-8320 (FAB; Thermo Finnigan, San Jose, USA) or a Fisons VG Trio (electrospray; Fisons, UK, now Fisher Scientific, Loughborough,Leicestershire, UK) spectrometer, X-ray-structure analysis on a Siemens Nicolet R3m/V2000 diffractometer (Siemens, Munich, Germany). Routine ^{1}H NMR spectra were recorded using a Varian Gemini 2000 instrument (300 MHz) (Varian, Paolo Alto, USA). The spectra were referenced internally to residual solvent resonance.

^{99m}Tc-complexes were analysed by reversed phase HPLC (X-Terra RP-18 column 4.6 mm × 250 mm, Waters; gradient elution from 0.1% trifluoroacetic acid in water to 0.1% trifluoroacetic acid in acetonitrile in 20 min; flow rate 1 ml/min) and LC–MS (Waters separation module, XTerra MS C18 column 50 mm × 2.1 mm, 3-inch NaI(Tl) radiation detector, Micromass LCT mass spectrometer and MassLynx software, Waters-Micromass, Manchester, UK).

4.2. Synthesis

4.2.1. Preparation of [Re(μ_3-O)(CO)$_2$(NO)]$_4$

Typical procedure: [NEt$_4$][Re(NO$_3$)$_3$(CO)$_2$(NO)] (92 mg, 0.156 mmol) was dissolved in 3 ml water and 0.118 ml (2.1 equivalents) of an aqueous solution of [NEt$_4$][OH]$^-$ (2.7 M) was added. After vigorous stirring for 10 min, the solution was kept without stirring for 4 days. Microcrystalline precipitation of the yellow complex started overnight. The precipitate was filtered off and dried, yielding 29 mg (0.025 mmol, 65%) of [Re(μ_3-O)(CO)$_2$(NO)]$_4$.

IR (KBr): ν (cm^{-1}) = 2082 (CO), 2005 (CO), 1752 (NO)

MS (EI): 1154 (M), 1126, 1098, 1070, 1042, 1014, 986, 958, 930, 900, 870, 840, 810

4.2.2. Preparation of ^{99m}Tc-dicarbonyl-nitrosyl-compounds

General procedure: The tricarbonyl precursor [^{99m}Tc(H$_2$ O)$_3$(CO)$_3$]$^+$ was synthesized by adding 370–1000 MBq of ^{99m}TcO$_4^-$ in 1 ml 0.9% saline solution to an IsoLink™ kit and heating for 20 min at 100 °C. After cooling to room temperature 0.1 ml 1 M HCl was added and 0.3 ml of this solution was mixed with 0.1 ml of an aqueous solution of the ligand (approx. 5 μmol). The mixture was heated for 15 min at 70 °C and analysed by HPLC to determine the relative amount of the formed Tc(CO)$_3$-complex.

The ^{99m}Tc-tricarbonyl complexes [^{99m}Tc(IDA)-(CO)$_3$]$^-$ (HPLC retention time = 7.2 min), [^{99m}Tc-(NTA)(CO)$_3$]$^-$ (R_t = 12.1 min) and [^{99m}Tc(DTPA) (CO)$_3$]$^-$ (R_t = 11.3 min) were formed with yields >97% at pH 8–9. After neutralization and removal of the solvent, the conversion to the corresponding ^{99m}Tc-dicarbonyl-nitrosyl complexes was carried out by adding an excess of NOBF$_4$ (3–5 mg) in 2 ml dichloromethane and incubating the mixture at room temperature (completed after 4–5 h). [^{99m}Tc(IDA)(CO)$_2$(NO)] (R_t = 14.5 min), [^{99m}Tc(NTA)(CO)$_2$(NO)] (R_t = 14.2 min) and [^{99m}Tc(DTPA)(CO)$_2$(NO)] (R_t = 14.3 min) were formed with yields of 50–70%. Results of the analyses by LC–MS support the supposed structures of the Tc-dicarbonyl-nitrosyl complexes.

Acknowledgment

Tyco-Mallinckrodt (Petten, The Netherlands) is gratefully acknowledged for their support with IsoLink™ kits.

References

[1] G.B. Richter-Addo, P. Legzdins, Metal Nitrosyls, Oxford University Press, New York, Oxford, 1992.

[2] R. Waibel, R. Alberto, J. Willuda, Nat. Biotechnol. 17 (1999) 897–901.

[3] B. Johannsen, H.J. Pietzsch, Eur. J. Nucl. Med. Mol. I 29 (2002) 263–275.

[4] R. Schibli, A.P. Schubiger, Eur. J. Nucl. Med. Mol. I 29 (2002) 1529–1542.

[5] D. Rattat, P.A. Schubiger, H.G. Berke, H. Schmalle, R. Alberto, Cancer Biother. Radiopharmaceut. 16 (2001) 339–343.

[6] D. Rattat, A. Verbruggen, H. Schmalle, H.G. Berke, R. Alberto, Tetrahedron Lett. 45 (2004) 4089–4092.

[7] F. Zingales, A. Trovati, P. Cariati, P. Uguagliati, Inorg. Chem. 10 (1971) 507.

[8] H.-U. Hund, U. Ruppli, H. Berke, Helv. Chim. Acta 76 (1993) 963.