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Synthesis and reactivity of $[ReBr_2(NCCH_3)_2(CO)_2]^-$: A new precursor for bioorganometallic chemistry

Lukas Kromer, Bernhard Spingler, Roger Alberto *

Institute of Inorganic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

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Abstract

We have synthesised $(Et_4N)[ReBr_2(NCCH_3)_2(CO)_2]$ **1** in two steps from $[ReBr_3(CO)_3]^{2-}$. Complex **1** is water and air stable and the two Br^- ligands are easily exchanged for coordinating solvent molecules such as water. The reactivity of **1** with several ligands such as imidazole (imz) and 2-picolinic acid (2-pic) are easily possible with substitution exclusively occurring in *trans*-position to the carbonyl groups. The resulting complexes $[Re(imz)_2(NCCH_3)_2(CO)_2]^+$ and $[Re(2\text{-pic})(NCCH_3)_2(CO)_2]$ have been isolated and structurally characterised. The two acetonitrile ligands are strongly bound and are not substituted under any conditions. Complex **1** represents therefore the new moiety "*trans*,*cis*-$[Re(NCCH_3)_2(CO)_2]^+$" which can be considered as a further building block in organometallic chemistry.

Keywords: Rhenium; Technetium; Bis-carbonyl; Bioorganometallic; Radiopharmacy

1. Introduction

The radionuclide ^{99m}Tc is important for nuclear medicine due to its availability from generators, favourable decay characteristics and low costs, the latter fact becoming more and more important in clinical application [1,2]. Carbonyl-complexes of rhenium and technetium attracted much interest in bioorganometallic and radiopharmaceutical chemistry. Since we reported the direct synthesis of $[M(OH_2)_3(CO)_3]^+$ (M = Re, $^{99,99m}Tc$) in water [3], the $[M(CO)_3]^+$ core is most intensively investigated and represents a simple way of biomolecule labelling especially with the [2+1] mixed ligand concept [4–7]. Organometallic moieties, soluble in water and prone to further substitution-binding reactions are highly interesting in bioorganometallic chemistry. We therefore want to extend the field of stable but reactive cores to bis-carbonyl complexes of the form *cis*-$[Re(CO)_2]^+$. We expect on one hand that such a core would have distinctly different electronic properties from *fac*-$[Re(CO)_3]^+$, and on the other, smaller biomolecule pendant complexes which should affect the biological behaviour to a lesser extent then the larger *fac*-$[Re(CO)_3]^+$ based compounds. Complexes based on the *cis*-$[M(CO)_2]^+$ core would offer four possible binding sites which allow a different labelling pathway or a direct labelling of side chains in peptides. A wide variety of complexes with the *cis*-$[M(CO)_2]^+$ motif are described in literature but most of them are prepared from $[MBr(CO)_5]$ in organic solvents and contain phosphine ligands or Cp derivatives, which is a disadvantage for aqueous chemistry [8,9]. No investigations about their behaviour in water exist. We present the synthesis of $(Et_4N)[ReBr_2(NCCH_3)_2(CO)_2]$ **1**, its fundamental behaviour in water and its reactivity towards biologically relevant ligands such as imidazole (imz) and 2-pyridinecarboxylic acid (2-pic).

2. Results and discussion

2.1. Synthesis

The synthesis of $(Et_4N)[ReBr_2(NCCH_3)_2(CO)_2]$ **1** is not straight forward and includes two steps, an oxidation to Re(III) and a subsequent reduction to **1** (Scheme 1).

* Corresponding author. Tel.: +41 44 645 46 31; fax: +41 44 645 68 03.
E-mail address: ariel@aci.unizh.ch (R. Alberto).

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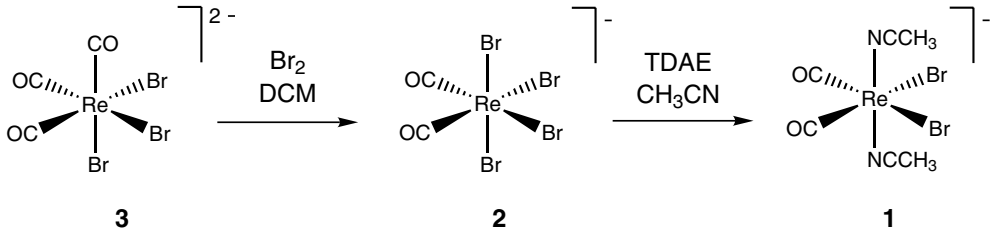

3 2 1

Scheme 1. Synthesis of $[ReBr_2(NCCH_3)_2(CO)_2]^-$ (**1**).

Following a literature procedure, $[ReBr_3(CO)_3]^{2-}$ **3** is oxidised in a first step with Br_2 to the Re(III) compound $[ReBr_4(CO)_2]^-$ **2** in good yield [10]. Compound **2** is unstable in protic solvents and is likely to undergo unexplored disproportion reactions. During oxidation, one CO is released and the cis-arrangement of the remaining two CO ligands retained. In a subsequent step, **2** is reduced to **1** in acetonitrile with the well known reducing agent tetrakis(dimethylamino)ethylene (TDAE) [11]. In the course of the reaction, oxidised TDAE $[C_2(N(CH_3)_2)]^{2+}$ precipitates as its bromide salt and can easily be separated. (Et_4N)-$[ReBr_2(NCCH_3)_2(CO)_2]$ **1**, which is received after stirring in boiling ethanol and filtering in 60% yield, is well soluble in water, methanol and acetonitrile, slightly soluble in ethanol and insoluble in less polar organic solvents.

Other reducing agents such as Mg^0 or Zn^0 which are known to reduce rhenium to low oxidation states in coordinating solvents gave less clear results [12]. With Zn^0 in acetonitrile, we found evidence for the presence of $Re(CO)_2$ species by IR spectroscopy but also many other carbonyl products according to the CO pattern. A clearer product distribution was received with Mg^0 in acetonitrile. Beside the isolation of **1**, the neutral complex $[ReBr(NCCH_3)_3(CO)_2]$ **1a** could also be received in reasonable yield, indicating that **1a** is in equilibrium with **1**.

2.2. Behaviour in coordinating solvents

Versatile complexes for application in bioorganometallic chemistry must be water stable and should comprise ligands such as halides which are easily replaced by water, thus, forming sort of organometallic aqua-ion. As in case of $[Re(OH_2)_3(CO)_3]^+$ these water molecules can be replaced by donors from biomolecules (cisplatin like direct interaction) or from ligands attached to targeting molecules (labelling). Therefore, the behaviour of **1** in water is of crucial importance for potential applicability. Re(I) and Tc(I) are in general considered to be soft metal centres. However, the electron-withdrawing effect of the CO ligands is likely to shift this behaviour towards a preference for more medium-hard ligands such as water. Therefore we expect that the halides are not too strongly bound and could be replaced by solvent molecules. This is confirmed by the reaction of **1** in water in which the halides are readily exchanged by H_2O thereby forming the complex $[Re(NCCH_3)_2(OH_2)_2(CO)_2]^+$ as evident from IR-spectroscopy (Fig. 1). The IR-spectrum of solid **1** in KBr shows two CO stretching frequencies at 1893 and 1794 cm^{-1} (a). An aqueous solution of **1** exhibits the same pattern but substantially blue-shifted to higher wave numbers (1928, 1836 cm^{-1}) (b). The spectra remains unchanged when the bromides are precipitated with 2 equiv. Ag^+ (c) confirming the identity of the two complexes present in aqueous solution prior to and after precipitation of Br^-. The behaviour is the same with other coordinating solvents such as CH_3CN or CH_3OH. The bromides are readily substituted and complexes of the general composition $[Re(NCCH_3)_2(sol)_2(CO)_2]^+$ are formed.

The CO stretching frequencies in **1** (1893, 1794 cm^{-1}) are substantially lower as those in e.g. **3** (2001, 1870 cm^{-1}), taking into account the mono-negative charge of **1** [13]. Strong π-backbonding from Re to the CO carbon renders CO very tightly bound. Very strong π-backbonding is facilitated by one less CO ligand as compared to $[ReBr_3(CO)_3]^{2-}$ for instance. The role of the two acetonitriles is unclear. They act both as π-acceptors or σ-donors. Obviously, the donating effect is strong since, otherwise, we would not observe these very low CO frequencies. Accordingly, the metal centre is electron-rich since the σ-donation effect prevails over the π-acceptor effect. In comparison to the mono-anionic complex **1** the *ν*(CO) are shifted to higher wavenumbers by substitution as expected from the positive or neutral charge change.

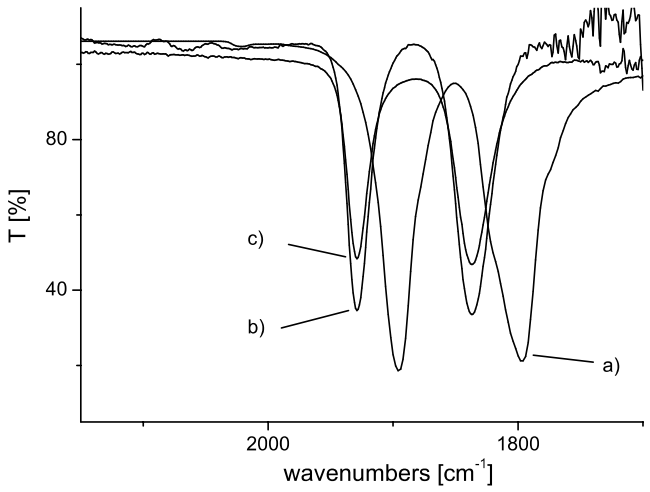

Fig. 1. IR-spectra of $[ReBr_2(NCCH_3)_2(CO)_2]^+$ in H_2O; (a) solid (KBr), (b) aqueous solution and (c) H_2O + 2 equiv. $AgNO_3$.

2.3. Substitution reactions

A small number of compounds containing the *cis*-$[Re(CO)_2]^+$ moiety without phosphine or Cp containing ligands have been described in the literature. In these studies the substitution chemistry of *fac*-$[Re(CO)_3(L)]^+$ was explored under vigorous reaction conditions [14]. In our case we prepared a new precursor with which we investigated several substitution reactions with mono- or bidentate ligands to understand its binding properties and chemical behaviour.

The imidazole (imz) motif is very often encountered in biological molecules, in particular in the side chain of histidine. The model reaction of **1** with imidazole represents therefore a basic entry into further investigations with biomolecules such as histidine or guanine. Starting from **1** in MeOH, the reaction with imz yields $[Re(NCCH_3)_2(CO)_2(imz)_2]Br$ (**4**) and only substitution of the two bromide ligands takes place. The reaction is an equilibrium. In order to shift it to the product side, a twofold excess (4 equiv.) of ligand was applied. Even under strong conditions (excess of imidazole and reflux) there is no further substitution of the acetonitrile ligands. Complex **4** is stable and robust. The coordinated imidazoles are not substituted by e.g. 1-methylimidazol even when present in large excess. This fundamental behaviour towards imidazole implies that the reactive core is not the $[Re(CO)_2]^+$ motif as expected but rather the $[Re(CH_3CN)_2(CO)_2]^+$ moiety with two instead of four available coordination sites prone to ligand exchange. Suitable crystals for X-ray diffraction of **4** were grown by diffusion of hexane into methanol. Complex **4** crystallises in the monoclinic space group $P2_1/c$ as colourless needles. An ORTEP plot of the complex cation is presented in Fig. 2 and selected bond lengths and angles are summarised in Table 1.

The bond lengths (M–L) of the acetonitrile ligands Re(1)–N(10) and Re(1)–N(11) averaged at 2.062(5), are significantly shorter as compared with the bond lengths Re(1)–N(1) and Re(1)–N(3) to the imidazole ligands of 2.199(5). This difference reflects the strong bonding of the acetonitriles. The geometry of the complex is distorted octahedral with an additional interesting feature. The two acetonitrile ligands are bent away from the carbonyls and form an angle of N(10)–Re(1)–N(11) of 172.09(19)°. Regarding the packing of the structure, sterical repulsion of the acetonitrile ligands by imidazoles from neighbouring complexes may be responsible for this unusual feature, however, electronic reasons should not be excluded and theoretical calculation will confirm (or disconfirm) this assumption.

Table 1
Selected bond length and angles of complex **4**

Re(1)–C(1)	1.896(6)
Re(1)–C(2)	1.897(5)
Re(1)–N(11)	2.060(5)
Re(1)–N(10)	2.063(5)
Re(1)–N(3)	2.198(5)
Re(1)–N(1)	2.200(5)
N(11)–Re(1)–N(10)	172.09(19)
N(10)–C(10)–C(11)	178.7(7)
N(11)–C(12)–C(13)	179.3(7)
N(1)–Re(1)–N(3)	83.04(18)

The bidentate ligand 2-pyridinecarboxylic acid (2-pic) is a further important representative of ligands which can be used for labelling [4]. The reaction of **1** with 2-pic yields the neutral complex *trans*,*cis*-$[Re(2\text{-pic})(NCCH_3)_2(CO)_2]$ (**5**). As in the case of the reaction with imidazole, no substitution of the acetonitriles was observed. Substitution occurred exclusively trans to the CO ligands. Exposing **5** to strong ligands such as imidazole or benzylisocyanide in large excess, again, no further substitution of the acetonitrile ligands could be induced, confirming the observations already made with imidazole. Crystals of **5** could be received as yellow plates. An ORTEP plot of **5** is presented in Fig. 3 and selected bond lengths and angles are given in Table 2. The two acetonitriles are again bent away from the carbonyls but even stronger than in **4**. The Re(1)–N(1)/N(2) bond lengths of 2.070(5) in average are comparable

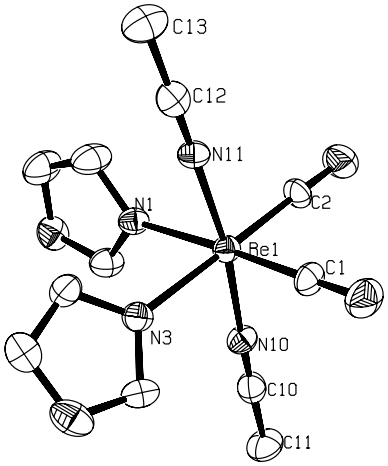

Fig. 2. ORTEP plot of $[Re(NCCH_3)_2(CO)_2(imz)_2]^+$ (**4**).

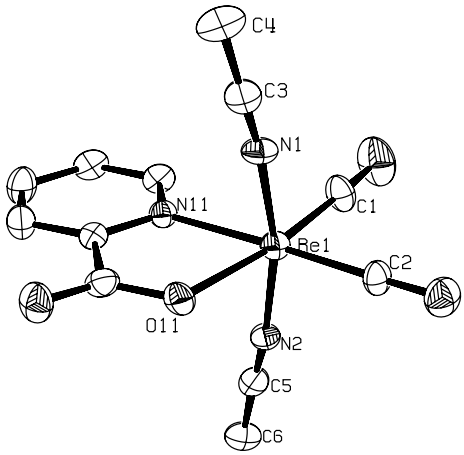

Fig. 3. ORTEP plot of $[Re(2\text{-pic})(NCCH_3)_2(CO)_2]$ (**5**).

Table 2
Selected bond length and angles of complex **5**

Re(1)–C(1)	1.889(7)
Re(1)–C(2)	1.923(6)
Re(1)–N(1)	2.064(5)
Re(1)–N(2)	2.076(5)
Re(1)–N(11)	2.170(5)
Re(1)–O(11)	2.147(5)
N(1)–Re(1)–N(2)	168.3(2)
N(1)–C(3)–C(4)	179.4(8)
N(2)–C(5)–C(6)	177.9(8)

with the corresponding bond lengths in complex **4**. Crystallographic data for both complexes **4** and **5** are presented in Table 3.

Table 3
Crystallographic data and details of data collection and processing

Compound No.	**4**	**5**
Empirical formula	$C_{12}H_{14}BrN_6O_2Re$	$C_{12}H_{10}N_3O_4Re$
Formula weight	540.4	446.43
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$
Unit cell dimensions		
a (Å)	14.8912(9)	7.8212(6)
b (Å)	6.9874(3)	8.2437(7)
c (Å)	16.9133(10)	12.1945(10)
α (°)		99.067(10)
β (°)	106.203(7)	91.834(10)
γ (°)		115.964(9)
Volume (Å^3)	1689.94(16)	693.53(10)
Z	4	2
Density (calculated) (Mg/m^3)	2.124	2.138
Absorption coefficient (mm^{-1})	9.569	8.776
F(000)	1016	420
Crystal size (mm)	0.35 × 0.12 × 0.11	0.31 × 0.17 × 0.03
Crystal description	Colourless needle	Yellow plate
θ Range for data collection (°)	2.85–30.45	2.80–30.48
Index ranges	$-21 \leqslant h \leqslant 21$, $-9 \leqslant k \leqslant 9$, $-23 \leqslant l \leqslant 23$	$-11 \leqslant h \leqslant 11$, $-11 \leqslant k \leqslant 11$, $-17 \leqslant l \leqslant 17$
Reflections collected	24 560	15 124
Independent reflections (R_{int})	5090 (0.1038)	3862 (0.0811)
Reflections observed	3736	3285
Criterion for observation	$>2\sigma(I)$	$>2\sigma(I)$
Completeness to theta = 30.45° (%)	99.30	91.40
Max. and min. transmission	0.5121 and 0.1501	0.6502 and 0.1863
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	5090/0/207	3862/0/183
Goodness-of-fit on F^2	0.975	1.069
Final R indices [$I > 2$sigma(I)]	$R_1 = 0.0401$, $wR_2 = 0.0995$	$R_1 = 0.0475$, $wR_2 = 0.1156$
R indices (all data)	$R_1 = 0.0540$, $wR_2 = 0.1028$	$R_1 = 0.0546$, $wR_2 = 0.1192$
Largest difference in peak and hole (e Å^{-3})	1.854 and −1.075	2.139 and −1.424

3. Conclusion

The new water and air stable complex $[ReBr_2(NCCH_3)_2(CO)_2]^-$ has been synthesised. This complex comprises the *trans*,*cis*-$[Re(CH_3CN)_2(CO)_2]^+$ moiety and is a new building block for bioorganometallic chemistry. The two bromide ligands in *trans* position to the carbonyls can be substituted whereas the two acetonitrile ligands are too strongly bound and not replaced. Substitution of the bromides with model ligands such as imidazole are rapid and well defined implying that reactivity towards real biological ligands such as the nucleobases guanine or adenine or amino acids such as histidine can be expected. Investigations about the behaviour in biological media are under way.

4. Experimental

All reactions were performed under a nitrogen atmosphere and the chemicals were used without further purification. IR spectra were recorded in a PE Spectrum BX FT-IR spectrometer. NMR spectra were recorded on a Varian Mercury 200 MHz spectrometer. ESI-MS were performed on a Merck-Hitachi M-8000 spectrometer; values are reported for the ^{187}Re isotope. Elemental analyses (EA) were performed on a Leco CHNS-932 elemental analyser. For X-ray diffraction studies, suitable crystals were covered with Paratone N oil, mounted on top of a glass fibre and immediately transferred to a Stoe IPDS diffractometer. Data was collected at 183(2) K using graphite-monochromated Mo radiation (0.71073 Å). Data was corrected for Lorentz and polarisation effects as well as for absorption. Melting points were determined on a Mettler FP61. All three compounds decompose between 180 and 200 °C.

4.1. $(Et_4N)[ReBr_2(NCCH_3)_2(CO)_2]$ (**1**)

Compound **3** (2 g, 2.6 mmol) was suspended in CH_2Cl_2 and 0.4 ml (7.8 mmol) Br_2 drop wise added. The solvent and excess Br_2 was removed in vacuo and the residue recrystallised from CH_2Cl_2/Et_2O to get 1.4 g of **2** (78% yield) [10]. Compound **2** (500 mg) was dissolved in CH_3CN and a slight excess (1.5 equiv.) of tetrakis(dimethylamino)-ethylene (TDAE) was added. $TDAEBr_2$ was removed by filtration and the solution dried in vacuo. The residue was washed in boiling ethanol to get **1** in a yield of 77% (340 mg).

Anal. Calc. for $C_{14}H_{26}Br_2N_3O_2Re$: C, 27.37; H, 4.27; N, 6.84. Found: C, 27.18; H, 4.18; N, 6.88. IR (KBr): ν (cm^{-1}) 2274 (CN), 1893 (CO), 1794 (CO). ^1H NMR (D_2O, 200 MHz) δ: 3.13 (q, $J = 7.4$ Hz, 8H), 2.40 (s, 6 H), 1.13 (tt, $J = 7.4$, 2.0 Hz, 12H).

4.2. $[Re(NCCH_3)_2(CO)_2(imz)_2]Br$ (**4**)

Compound **1** (50 mg, 82 μmol) was dissolved in 5 ml MeOH and 22.3 mg (4 equiv.) of imidazole added and stirred at 60°C. After 2 h the solvent was evaporated the

residue washed twice with THF and CH_2Cl_2 and dried to yield 27.7 mg (51 μmol, 63%) **4**.

Anal. Calc. for $C_{12}H_{14}BrN_6O_2Re$: C, 26.67; H, 2.61; N, 15.55. Found: C, 26.71; H, 2.52; N, 15.58. IR (KBr): ν (cm^{-1}) 2262 (CN), 1916 (CO), 1827 (CO). ^1H NMR (CD_3OD, 200 MHz) δ: 7.91 (s, 2H), 7.20 (m, 2H), 7.03 (m, 2H), 2.58 (s, 6H). ESI-MS(+): $m/z = 460$ $[M-Br]^+$, 419 $[M-Br-CH_3CN]^+$.

4.3. [Re(2-pic)(NCCH$_3$)$_2$(CO)$_2$] (5)

Compound **1** (50 mg, 82 μmol) was dissolved in 3 ml H_2O and 11 mg (1.1 equiv.) of 2-pic added and stirred at 40°C. The solution turned immediately to yellow. After a few minutes **5** starts to precipitate. After 4 h the mixture was cooled to r.t. 25 mg (56 μmol, 69%) of **5** was collected by filtration.

Anal. Calc. for $C_{12}H_{10}N_3O_4Re$: C, 32.28; H, 2.26; N, 9.41. Found: C, 32.39; H, 2.41; N, 9.58. IR (KBr): ν (cm^{-1}) 2272 (CN), 1913 (CO), 1835 (CO), 1659 (C=O). ^1H NMR (CD_3OD, 200 MHz) δ: 8.86 (m, 1H), 8.15 (m, 2H), 7.72 (m, 1H), 2.37 (s, 6H). ESI-MS(+): $m/z = 447$ $[M]^+$, 407 $[M-CH_3CN]^+$.

Appendix A. Supplementary material

CCDC 623025 and 623024 contain the supplementary crystallographic data for **4** and **5**. These data can be obtained free of charge via htpp://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. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2006.10.043.

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