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Communication

Isolation of *fac*-$[Re(CO)_3(HMPA)_3][BF_4]$. Structural characterization of a key cationic intermediate in the exchange reaction between $[Re(CO)_6][BF_4]$ and acetylferrocene. Implications in radiopharmaceutical chemistry

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Abstract

$[Re(CO)_6][BF_4]$ reacts with HMPA to form $[Re(CO)_3(HMPA)_3][BF_4]$ (**4**), whose structure was determined by X-ray crystallography and proves to be a key intermediate in the ligand exchange reaction between three CO and Cp; and may be related to other cations such as $[Re(CO)_3(H_2O)_3]^+$, $[Re(CO)_3(CH_3CN)_3]^+$, $[Re(CO)_3(DMSO)_3]^+$, obtained by different ways, and important in the field of organometallic radiopharmaceuticals.

Keywords: Rhenium; Carbonyl(cyclopentadienyl)rhenium; Hexacarbonylrhenium; Ferrocene; HMPA; Ligand transfer; Cationic crystal model

1. Introduction

The synthesis of radiopharmaceuticals oriented towards selected targets, namely involving radionucléides ^{99m}Tc, ^{186}Re or ^{188}Re, requires the development of new strategies adapted to these outcomes. The true experimental challenge for the synthesis of such compounds is the ability to efficiently incorporate the radioactive metal in the last step of a multistage synthesis. Recently, numerous attempts have been made to prepare [R-(η^5-C_5H_4)$Re(CO)_3$] complexes (R = steroid hormone [1], neurostransmittor [2], etc.) because the organometallic group (η^5-C_5H_4)$Re(CO)_3$ is particularly attractive. This neutral and lipophile group is stable in biological environment and of relatively small size compared to the chelate groups commonly used in the synthesis of target radiopharmaceuticals [3].

The only currently available sources for radionucleides ^{99m}Tc and ^{188}Re are the pertechnetate et perrhenate salts, thus any radiopharmaceutical synthesis depends upon these compounds. The first attempt of preparation of an hormone molecule containing the (η^5-C_5H_4)$^{99m}Tc(CO)_3$ group was performed by Wenzel in 1992 using a ligand exchange reaction known as a double ligand transfer reaction between a hormone ferrocene derivative and pertechnetate in the presence of $SnCl_2$ acting as a reducing agent and $BrMn(CO)_5$ being the source of CO [4]. Katzenellenbogen has since revised this method [5]. Alberto was able to transform the MO_4^- salt (M = Tc, Re) into $[MX_3(CO)_3]^{2-}$, which is a key reagent for the synthesis of rheniumtricarbonyl radiopharmaceuticals [6]. More recently, he has compellingly prepared the $[M(CO)_3(H_2O)_3]^+$ aqua-ion by reducing MO_4^- with $K_2H_3BCO_2/BH_3{*}NH_3$, which also acts as a source of CO [7]. While these methods represent important and useful advances in the synthesis of (η^5-C_5H_4)$Re(CO)_3$ derivatives, they do not apply to general reactions of this type since the success of these synthesis relies on the presence of an activated Cp by the presence of an

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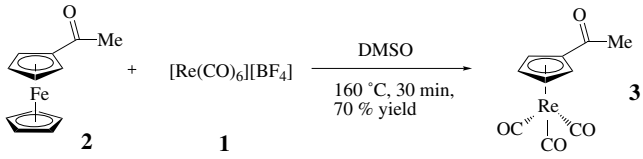


Scheme 1. Ligand transfer reaction between acetylferrocene and rhenium hexacarbonyl cation.

electron-attracting substituent such as a carbonyl group. While exploring alternative synthetic approaches, we recently reported the double ligand transfer reaction between $[Re(CO)_6]^+$ and cyclopentadienyl derivatives [8]. This choice appeared appropriate to us since $[Re(CO)_6]^+$ can be obtained in a radioactive form due to $^{188}W(CO)_6$ disintegration [9]. For instance, we found that $[Re(CO)_6][BF_4]$ reacts with acetylferrocene at 160 °C in DMSO or in a DMSO/H_2O mixture or only in water (Scheme 1). This reaction proceeds via loss of three CO ligands to yield the final product [8].

At the time, on the basis of IR data, we postulated the formation of a putative $[M(CO)_3(solvent)_3]^+$ intermediate in this reaction. We here report direct evidence of the formation of such an intermediate by the isolation and solid state structure determination of $[Re(CO)_3(HMPA)_3][BF_4]$. This note describes the synthesis and the structural study of $[Re(CO)_3(HMPA)_3][BF_4]$ as well as its reaction with acetylferrocene which establishes its key role as a reaction intermediate.

2. Results and discussion

2.1. Synthesis of $[Re(CO)_3(HMPA)_3][BF_4]$

A yellow solution of $[Re(CO)_6][BF_4]$ in HMPA was heated to 160 °C for 15 min. (Scheme 2) which resulted in an orange-colored reaction mixture. The IR spectrum of the crude mixture showed the complete disappearance of the ν_{CO} band corresponding to $[Re(CO)_6][BF_4]$ (2085 cm^{-1}) and the presence of two new bands at 2019 and 1885 cm^{-1} characteristic of a ponctual C_{3V} symmetry structure. The salt compound $[Re(CO)_3(HMPA)_3][BF_4]$ (**4**) was isolated in a pure form by precipitation with Et_2O in a 48% yield. The formation of compound **4** was confirmed by mass spectroscopy and elemental analysis.

2.2. X-ray structure of $[Re(CO)_3(HMPA)_3][BF_4]$

X-ray quality single crystals of $[Re(CO)_3(HMPA)_3][BF_4]$ (**4**) were obtained from a THF solution (plus a few drops of $CHCl_3$) of **4** stored at −25 °C and its molecular structure was determined by X-ray crystallography analysis (Fig. 1). Selected bond distances and angles are summarized in Fig. 1.

The Re salt $[Re(CO)_3(HMPA)_3][BF_4]$ crystallizes with a molecule of $CHCl_3$ as discrete $[Re(CO)_3(HMPA)_3]^+$ cations and BF_4^- anions with no unsual non-bonded contacts. The molecular structure of the cation $[Re(CO)_3(HMPA)_3]^+$ is illustrated in Fig. 1. The Re center in **4** adopts a slightly distorted octahedral *fac*-structure by coordination of three HMPA and three CO molecules. The O–Re–O and C–Re–C bond angles (79.61(9)° and 88.0 (6)° in average, respectively, Fig. 1) slightly deviate from 90°, the ideal angle for such a structure. The Re–C and C–O bond distances (1.89(1) and 1.16(1) Å in average, respec-

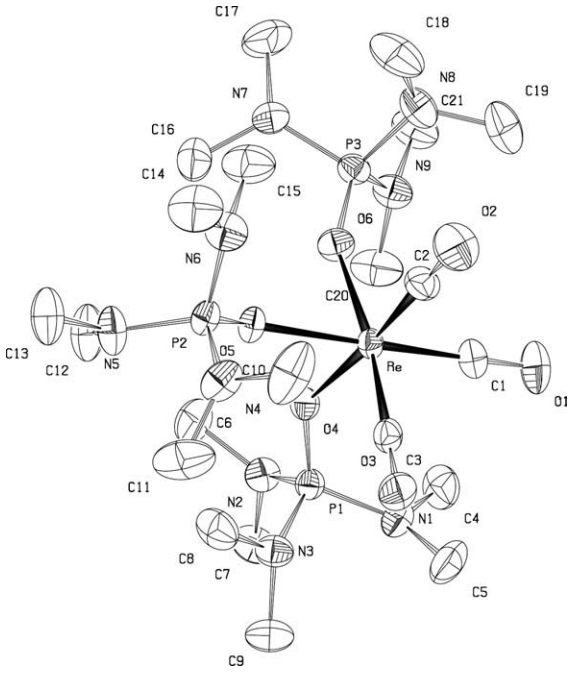
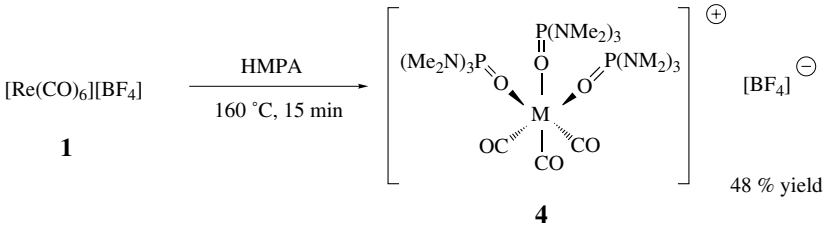


Fig. 1. Molecular structure of the $Re(CO)_3(HMPA)_3^+$ cation. Selected bond distances (Å) and angles (°): Re–C(1) = 1.904(4), Re–C(2) = 1.878(4), Re–C(3) = 1.897(3), Re–O(4) = 2.144(2), Re–O(5) = 2.132(2), Re–O(6) = 2.133(2), C(2)–Re–C(3) = 88.23(16), C(2)–Re–C(1) = 86.84 (17), O(5)–Re–O(4) = 79.84(9), O(6)–Re–O(4) = 79.59(9).



Scheme 2. Thermal reaction of $[Re(CO)_6][BF_4]$ with HMPA.

tively) are nearly identical to those in the related Re complex $[Re(CO)_3(CH_3CN)_3]^+$ (1.91(1) and 1.16(1) Å in average, respectively) [10] and the neutral dinuclear species $Re(CO)_3\{CpCo[PO(OR)_2]_3\}$ (Re–C : 1.890(8) Å in average) [11]. It is worth noticing that $[Re(CO)_3(CH_3CN)_3]^+$ is a very stable complex and can be obtained by reaction of the cluster $[Re_4(CO)_{16}]^{2-}$ in CH_3CN [10].

2.3. Reaction of 4 with acetylferrocene

The reaction of $[Re(CO)_3(HMPA)_3][BF_4]$ (**4**) with acetylferrocene was carried out using two different pathways in order to clearly identify compound **4** as an intermediate in the double ligand transfer reaction.

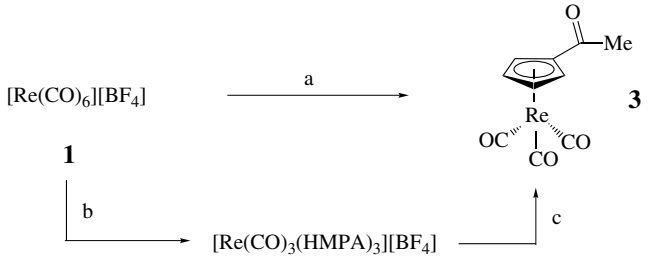
Pathway (a): a HMPA solution of $[Re(CO)_6][BF_4]$ was heated to 160 °C for 15 min yielding the formation of $[Re(CO)_3(HMPA)_3][BF_4]$ as observed by IR spectroscopy. Subsequent addition of three equivalents of acetylferrocene afforded the formation of the acetylcyclopentadienyl tricarbonyl Re complex **3**, which was isolated in a pure form in 37% yield.

Pathway (b): a HMPA solution of pure $[Re(CO)_3(HMPA)_3][BF_4]$ and acetylferrocene was heated to 160 °C for 20 min. The IR spectrum of the crude mixture shows the complete disappearance of **4** and the presence of three new bands (2031, 1936 and 1688 cm^{-1}) assigned to the acetylcyclopentadienyl Re complex **3**, which was isolated in a pure form in 19% yield.

The low yields of both pathways (a) and (b) may be due to the poor stability of compound **4** in the reaction conditions. However, these two experiments clearly show that $[Re(CO)_6][BF_4]$ reacts in HMPA to yield the acetylferrocene compound **3** via the formation of $[Re(CO)_3(HMPA)_3][BF_4]$, a perfectly characterized intermediate (Scheme 3).

The above ligand transfer reaction was also performed in other solvents such as DMSO and DMF and the results are summarized in Table 1 [8]. In both solvents, the formation of the $[Re(CO)_3(solvent)_3]^+$ intermediate was evidenced by IR spectroscopy. In particular, the IR spectra of the crude mixtures both contain two new IR bands (for DMSO, 2021 and 1893 cm^{-1}; for DMF, 2027 and 1901 cm^{-1}) characteristic of $[Re(CO)_3(solvent)_3]^+$ species. The reaction in DMSO occurs in good yield either with acetylferrocene (70%) or with propionylferrocene **5** (entry 4).

It is noteworthy that the reaction does not proceed when performed in CH_3CN which suggests that $[Re(CO)_3(CH_3CN)_3]^+$, formed in such conditions, is not reactive enough for the Cp transfer reaction.

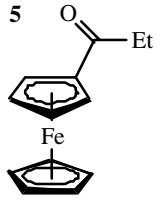
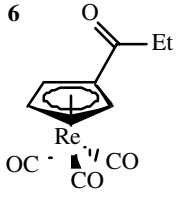


Scheme 3. Synthesis of **3** from $[Re(CO)_6][BF_4]$. (a) **2**, HMPA, 160 °C, 25 min, 37% yield; (b) HMPA, 160 °C, 15 min, 48% yield; (c) **2**, HMPA, 160 °C, 20 min, 19% yield.

3. Conclusion

In conclusion, we first synthesized the Re salt *fac*-$[Re(CO)_3(HMPA)_3][BF_4]$, which was characterized by X-ray crystallography. Its preparation and characterization clearly establish that the reaction of $[Re(CO)_6][BF_4]$ with HMPA proceeds via substitution of three CO ligands by three HMPA ligands. In fact, $[Re(CO)_3(HMPA)_3]^+$ is a key reactant in the Cp transfer ligand reaction, which contrasts with the lack of reactivity of $[Re(CO)_3(CH_3CN)_3]^+$ in this reaction. As such, the synthesis and the reactivity study of $[Re(CO)_3(HMPA)_3]^+$ as a ligand transfer agent are potentially interesting to access radiopharmaceuticals.

Table 1
Reaction of $[Re(CO)_6][BF_4]$ with ketoferrocene in different solvents

Entry	Ketoferrocene	Product	Solvent	Heating time (min)	Yield (%)
1	**2**	**3**	DMSO[a]	30	70
2	**2**	**3**	DMF[a]	30	64
3	**2**	**3**	HMPA[b]	25	37
4	**5** 	**6** 	DMSO[a]	30	74

[a] Reference [8].
[b] This work.

4. Experimental section

$[Re(CO)_6][BF_4]$ was prepared according to the procedure described in the literature [12].

4: A solution of $[Re(CO)_6][BF_4]$ (0.150 g, 0.340 mmol) in HMPA (2 ml) was heated for 15 min at 160 °C. The mixture was cooled to room temperature and 20 ml of diethylether were added to provoke a formation of white precipitate. The precipitate was washed twice with 30 ml of diethylether to give **4** as a pale yellow powder. Yield: 0.146 g (48%); m.p. 231 °C; elemental analysis calcd (%) for $[Re(CO)_3(HMPA)_3][BF_4]$; $C_{21}H_{54}BF_4N_9O_6P_3Re$: C 28.19, H 6.08, N 14.08; found: C 28.06, H 5.91, N 13.99. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.70$ (d, 27 H, $J = 9.5$ Hz), 2.73 (s, 27H). IR (KBr, cm^{-1}) ν_{CO}: 2014 s, 1884 vs. ESI(+)MS (two mass are reported to indicate the significant isotopic abundance of both ^{185}Re and ^{187}Re): m/z 806.5/808.5 $[Re(CO)_3(HMPA)_3]^+$. $[Re(CO)_3(HMPA)_3][BF_4]$ crystallized from THF/chloroform solution at −25 °C in pale yellow crystals suitable for X-ray analysis.

Crystal data for $[Re(CO)_3(HMPA)_3][BF_4]$: $C_{21}H_{54}N_9O_6P_3Re, CHCl_3, BF_4$, $M = 1014.02$, triclinic, space group $P-1$ (No 2), $a = 8.8650(1)$, $b = 14.8680(2)$, $c = 16.5440(2)$ Å, $\alpha = 96.5720(10)$, $\beta = 102.0990(8)$, $\gamma = 90.7780(8)°$, $V = 2116.55(5)$ Å^3, $Z = 2$, $D_c = 1.591$ g cm^{-3}, $\mu(Mo\,K\alpha) = 3.235\,mm^{-1}$, $F(000) = 1020$, $T = 173$ K; $0.08 \times 0.10 \times 0.13$ mm, Kappa CCD diffractometer, ϕ-scans, 12,324 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full matrix based on F^2 to give $R_1 = 0.0352$, $wR_2 = 0.0939$ for 10,838 independent observed reflections and 451 parameters.

3 or **6**: $[Re(CO)_6][BF_4]$ (0.073 g, 0.166 mmol) was dissolved in solvent (see Table 1) in a 5 ml round-bottom flask equipped with a magnetic stir bar. Three equivalents of ketoferrocene **2** (**2**: 0.118 g, **5**: 0.126 g, 0.519 mmol) were added and the solution was heated for 30 min at 160 °C. The mixture was allowed to cool to room temperature and then 10 ml of water was added. The product was extracted with dichloromethane (2×50 ml). The organic phase was washed, dried over $MgSO_4$, filtered and concentrated. The mixture was purified by chromatography on silica gel plate (petroleum ether:ethyl acetate 7:1) to give the product. Yield: see Table 1. Product **3**: m.p. 79 °C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.34$ (s, 3H, CH_3), 5.40 (t, 2H, C_5H_4), 5.98 (t, 2H, C_5H_4). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 26.5$ (CH_3), 85.2 (2C, C_5H_4), 88.1 (2C, C_5H_4), 96.1 (1C, C_5H_4), 191.7 and 192.4 (CO). IR (CH_2Cl_2, cm^{-1}) ν_{CO}: 2032 s, 1939 s, 1688 w ($COCH_3$). Anal. calc. for $C_{10}H_7O_4$ Re: C, 31.83; H, 1.87. Found: C, 31.83; H, 1.84. Product **6**: m.p. 64 °C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.18$ (s, 3H, CH_3), 2.65 (s, 2H, CH_2), 5.40 (t, 2H, C_5H_4), 6.00 (t, 2H, C_5H_4). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 8.3$ (CH_3), 32.1 (CH_2), 85.1 (2C, C_5H_4), 87.7 (2C, C_5H_4), 95.9 (1C, C_5H_4), 191.9 and 195.8 (CO). IR (CH_2Cl_2, cm^{-1}) ν_{CO}: 2031 s, 1939 s, 1683 w ($COCH_3$). Anal. calc. for $C_{11}H_9O_4$ Re: C, 33.77; H, 2.32. Found: C, 33.87; H, 2.35.

5. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data CCDC No. 212629 for compound **4**.

Acknowledgements

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References

[1] (a) F. Le Bideau, M. Salmain, S. Top, G. Jaouen, Chem. Eur. J. 7 (2001) 2289;
(b) G. Jaouen, S. Top, A. Vessières, R. Alberto, J. Organomet. Chem. 600 (2000) 23;
(c) F. Minutolo, J.A. Katzenellenbogen, Organometallics 18 (1999) 2519;
(d) P. Morel, S. Top, A. Vessières, E. Stéphan, I. Laïos, G. Leclercq, G. Jaouen, C. R. Acad. Sci. Paris, Chemistry 4 (2001) 201;
(e) F. Le Bideau, A. Pérez-Luna, J. Marrot, M.-N. Rager, E. Stéphan, S. Top, G. Jaouen, Tetrahedron 57 (2001) 3939.
[2] R.R. Cesati, G. Tamagnan, R.M. Baldwin, S.S. Zoghbi, R.B. Innis, N.S. Kula, R.J. Baldessarini, J.A. Katzenellenbogen, Bioconjugate Chem. 13 (2002) 29.
[3] (a) H.-J. Pietzsch, A. Gupta, M. Reisgys, A. Drews, S. Seifert, R. Syhre, H. Spies, R. Alberto, U. Abram, P.A. Schubiger, B. Johannsen, Bioconjugate Chem. 11 (2000) 414;
(b) J.R. Dilworth, S.J. Parrott, Chem. Soc. Rev. 27 (1998) 43;
(c) N. Metzler-Nolte, Angew. Chem. Int. Ed. 40 (2001) 1040.
[4] M. Wenzel, J. Labelled Compd. Radiopharm. 31 (1992) 641.
[5] T.W. Spradau, J.A. Katzenellenbogen, Organometallics 17 (1998) 2009.
[6] (a) R. Alberto, R. Schibli, W.A. Hermann, G. Artus, V. Abram, P.A. Schubiger, T.A. Kaden, J. Organomet. Chem. 493 (1995) 119;
(b) R. Alberto, R. Schibli, A. Egli, V. Abram, S. Abram, T.A. Kaden, P.A. Schubiger, Polyhedron 17 (1998) 1133;
(c) R. Alberto, R. Schibli, P.A. Schubiger, V. Abram, R. Hübener, H. Berke, T.A. Kaden, Chem. Commun. (1996) 1291.
[7] (a) R. Schibli, R. Schwarzbach, R. Alberto, K. Ortner, H. Schmalle, C. Dumas, A. Egli, P.A. Schubiger, Bioconjugate Chem. 13 (2002) 750;
(b) J. Wald, R. Alberto, K. Ortner, L. Candreia, Angew. Chem. Int. Ed. 40 (2001) 3062.
[8] (a) S. Top, S. Masi, G. Jaouen, Eur. J. Inorg. Chem. (2002) 1848;
(b) S. Masi, S. Top, G. Jaouen, Inorg. Chim. Acta 350 (2003) 665.
[9] (a) V.D. Nefedov, A. Toropova, Zhur. Neorg. Kim. 2 (1957) 1667;
(b) S.R. Naryan, D.R. Wiles, Can. J. Chem. 47 (1969) 1019;
(c) V.D. Nefedov, V. Mikulai, Soviet. Radiochem. 15 (1973) 855.
[10] L.Y.Y. Chan, E.E. Isaacs, W.A.G. Graham, Can. J. Chem. 55 (1977) 111.
[11] D.J. Kramer, A. Davison, A.G. Jones, Inorg. Chim. Acta 312 (2001) 215.
[12] D.J. Darensbourg, J.A. Froelich, J. Am. Chem. Soc. 99 (1977) 4726.