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Ethylenediamine- and propylenediaminediacetic acid derivatives as ligands for the "*fac*-$[M(CO)_3]^+$" core ($M = Re$, ^{99m}Tc)

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Abstract

The reaction of $Re(CO)_5Cl$ with *o*- or *p*-*N*-(nitrophenyl)ethylenediaminediacetic acid (H_2L^1, H_2L^2) and *o*- or *p*-*N*-(nitrophenyl)propylenediaminediacetic acid (H_2L^3, H_2L^4) in methanol leads to the formation of stable anionic $[Et_3NH][Re(CO)_3(L)] \cdot H_2O$ complexes **1**–**4**. These compounds have been characterized by means of IR, mass spectrometry, elemental analysis, NMR and conductimetry, as well as X-ray crystallography for **2** and **3**. The $[Re(CO)_3]^+$ moiety is coordinated via the nitrogen of the iminodiacetic acid unit and two oxygens of monodentate carboxylate groups. In each case, the nitro group of the aromatic ring remains uncoordinated. The analogous technetium-99m complexes **1′** and **3′** were also prepared quantitatively by the reaction of H_2L^1 and H_2L^3, respectively, with the *fac*-$[^{99m}Tc(CO)_3(H_2O)_3]^+$ precursor in ethanol. The corresponding Re and ^{99m}Tc compounds were shown to possess the same structure by means of HPLC studies. The high affinity of these ligands for the Tc(I) or Re(I) core, coupled with the easiness of their derivatization (by reduction of the nitro group in amino group), implies that the utilization of this ligand system to develop target-specific radiopharmaceuticals for diagnosis and therapy is promising.

Keywords: Tricarbonylrhenium(I) complexes; Technetium-99m; Organometallic; Crystal structures

1. Introduction

The development of novel radiopharmaceuticals in nuclear medicine based on the $^{99m}Tc(CO)_3$ complexes has attracted growing attention since Alberto and coll. developed a convenient low-pressure synthesis for the preparation of ^{99m}Tc-tricarbonyl complexes from the pertechnetate ion TcO_4^- [1]. The kinetic inertness and chemical robustness of complexes with this core, the high affinity of the Tc(I) ion for a large variety of donor atoms, the organometallic nature of this core which renders chelation more covalent in character, conjugated with the easy production of the *fac*-$[^{99m}Tc(CO)_3(H_2O)_3]^+$ precursor (which is now commercially available as IsoLink kit® from Malinckrodt), could explain this interest. Moreover, the analogous *fac*-$[^{188}Re(CO)_3(H_2O)_3]^+$ core has been developed recently, rhenium-188 being a promising β^- radionuclide for therapeutic applications [2].

Although different new ligand systems have been developed [3–8], recent in vivo and in vitro investigations on the stability of a variety of complexes containing the $[M(CO)_3]^+$ core ($M = {}^{99m}Tc$, ^{188}Re) showed that tridentate chelating systems are preferable, since they form organometallic compounds with more favourable pharmacokinetics [2,9]. A Tc- or Re-tricarbonyl complex with a tridentate ligand is less prone to undergo undesired reactions like

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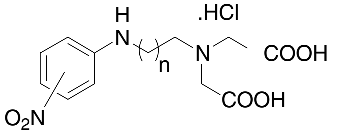


o-NO_2, n = 1: **H_2L^1** ; p-NO_2, n = 1: **H_2L^2**
o-NO_2, n = 2: **H_2L^3** ; p-NO_2, n = 2: **H_2L^4**

Scheme 1. NO_2Ph-EDDA and NO_2Ph-PDDA ligands.

cross-metalation, due to its coordinative saturation and because thermodynamic factors strongly disfavour the dissociation of a donor atom from the tridentate ligand. Among these ligands, those based on amino polycarboxylic acid systems like iminodiacetic acid (IDA) react readily with the *fac*-$[M(CO)_3]^+$ core to form complexes with a stable octahedral coordination sphere, where substitution reaction via a dissociative or an associative mechanism is unlikely [10].

In this regard, as part of our activities on the synthesis of new substitution-inert technetium(I) and rhenium(I) compounds, we recently developed a new range of *N*-substituted iminodiacetic acid derivatives [11]. They comprise an IDA unit for tridentate coordination to the *fac*-$[M(CO)_3]^+$ moiety (M = Re, ^{99m}Tc), an aromatic ring system bearing a nitro group as linking site model, and a tethering moiety (ethylene or propylene bridge) between the linking and coordinating sites. Co-ordination of *N*-(nitrophenyl)ethylenediaminediacetic acid NO_2Ph-EDDA (H_2L^1, H_2L^2) and *N*-(nitrophenyl)propylenediaminediacetic acid NO_2Ph-PDDA (H_2L^3, H_2L^4) ligands (see Scheme 1) to the usual rhenium precursor $Re(CO)_5Cl$ gave straightforwardly complexes of the general formula $[Et_3NH][Re(CO)_3(L)] \cdot H_2O$ under mild conditions. In the present work, we are reporting the synthesis and the physico-chemical characterization of these four novel tricarbonylrhenium(I) complexes, together with X-ray crystal structures of two representative examples. The reactivity of these ligands with the *fac*-$[^{99m}Tc(CO)_3(H_2O)_3]^+$ precursor was also investigated. The corresponding Re and ^{99m}Tc compounds were shown to have the same structure by a comparative HPLC study.

2. Experimental

2.1. General methods

All reagents and organic solvents used in this study were reagent grade and used without further purification. *N*-(nitrophenyl)ethylenediaminediacetic acid (H_2L^1, H_2L^2) and *N*-(nitrophenyl)propylenediaminediacetic acid (H_2L^3, H_2L^4) derivatives were prepared as described previously [11]. $Re(CO)_5Cl$ was purchased from Aldrich Chem. Co. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 300. Chemical shifts are indicated in δ values (ppm) downfield from internal TMS. For aromatic ring NMR assignments, the protons (or carbons) were numbered from 1 to 6 starting from carbon bearing the aromatic amine nitrogen and turning clockwise. Infrared spectra were recorded as KBr pellets with a Bruker Vector 22 spectrometer in the range 4000–400 cm^{-1}. Negative electrospray mass spectra were obtained on a NERMAG R 10–10 mass spectrometer. Carbon, hydrogen and nitrogen analyses were carried out by the microanalytical department of the Ecole Nationale Supérieure de Chimie de Toulouse. HPLC analyses, purifications and comparisons were achieved on a Waters 600E gradient chromatograph with a Waters Lambda Max UV detector, a SAIP radioactivity detector and an ICS dual integrator for effluent monitoring, and a Macherey-Nagel C-18 reversed phase column (10 μm, 125 × 4.6 mm) using MeOH/sodium carbonate buffer 0.1 M pH 8.0 (60/40 v/v) as eluent (flow rate of 1 mL/min). The effluent from the column was monitored by UV absorbance at 220 nm for Re or γ-ray detection for the ^{99m}Tc complexes.

2.2. Synthesis of complexes

The synthetic procedure was very similar for the preparation of the rhenium(I) complexes **1**–**4**. They were prepared by a substitution route from commercial $Re(CO)_5Cl$.

General method. 0.3 mmol of the ligand, 250 mg (0.3 mmol) of commercial $Re(CO)_5Cl$ and 1.26 ml (0.9 mmol) of Et_3N were dissolved in MeOH and stirred at 60 °C for 4 h. After cooling to room temperature, the yellow solution was evaporated to dryness. The crude was washed with ether (3 × 30 mL), then the residue was purified by column chromatography on silica gel (eluent CH_2Cl_2/MeOH: 8/2) to give the complex as the triethylammonium salt.

2.2.1. $[Et_3NH][Re(CO)_3(L^1)] \cdot H_2O$ (**1**)

100 mg of H_2L^1 led to 188 mg of **1** as a yellow powder (Yield 92%).

^{1}H NMR (300 MHz, DMSO-d_6) δ_H (ppm): 1.07 (t, 9H, $J = 7.1$ Hz, $3CH_3$); 3.01 (q, 6H, $J = 7.1$ Hz, $3NCH_2$); 3.39 (m, 2H, $N_{Ar}CH_2$); 3.48 (AB pattern, 2H, $J = 16.0$ Hz, CH_2CO); 3.59 (m, 2H, NCH_2); 3.65 (AB pattern, 2H, $J = 16.0$ Hz, CH_2CO); 6.63 (m, 1H, H-6); 7.17 (d, 1H, $J = 8.5$ Hz, H-4); 7.50 (m, 1H, H-5); 8.00 (dd, 1H, $J = 8.5$ and 1.5 Hz, H-3); 8.13 (t, $J = 6.0$ Hz, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C (ppm): 9.17 ($3CH_3$); 38.5 ($3CH_2$); 46.2 (NCH_2); 63.2 ($2CH_2CO$); 67.2 (NCH_2); 114.9 (C-6); 116.0 (C-4); 126.8 (C-3); 131.8 (C-2); 137.2 (C-5); 145.0 (C-1); 178.9 ($2CO_2$); 199.1, 199.4 (3CO). IR (KBr/cm^{-1}): $\nu_{N-H} = 3370$; $\nu_{C=O}$ (COORe) = 1667, ν(CO) = 1872, 1908, 2013. MS (ES$^-$): 564 (60), 566 (100) [M$^-$]. *Anal.* Calc. for $C_{21}H_{31}N_4O_{10}Re$: C, 36.8; H, 4.6; N, 8.2. Found: C, 37.3; H, 4.4; N, 8.4%.

2.2.2. $[Et_3NH][Re(CO)_3(L^2)] \cdot H_2O$ (**2**)

100 mg of H_2L^2 led to 180 mg of **2** as yellow crystals (Yield 88%).

^{1}H NMR (300 MHz, DMSO-d_6) δ_H (ppm): 1.18 (t, 9H, $J = 7.3$ Hz, 3CH$_3$); 3.08 (q, 6H, $J = 7.3$ Hz, 3NCH$_2$); 3.40 (m, 2H, N$_{Ar}$CH$_2$); 3.45 (m, 2H, NCH$_2$); 3.52 (AB pattern, 2H, $J = 15.6$ Hz, CH$_2$CO); 3.64 (AB pattern, 2H, $J = 15.6$ Hz, CH$_2$CO); 6.74 (d, 2H, $J = 9.3$ Hz, H-2 and H-6); 7.28 (t, 1H, $J = 6.0$ Hz, NH); 8.08 (d, 2H, $J = 9.4$ Hz, H-3 and H-5). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C (ppm): 9.3 (3CH$_3$); 39.2 (3CH$_2$); 46.3 (NCH$_2$); 63.6 (2CH$_2$CO); 67.5 (NCH$_2$); 110.0 (C-2 and C-6); 126.9 (C-3 and C-5); 136.8 (C-4); 154.7 (C-1); 179.0 (2CO$_2$); 199.2, 199.6 (3CO). IR (KBr/cm^{-1}): $\nu_{N-H} = 3388$; $\nu_{C=O}$ (COORe) = 1641; ν(CO) = 1881, 1918, 2024. MS (ES$^-$): 564 (60), 566 (100) [M$^-$]. *Anal.* Calc. for $C_{21}H_{31}N_4O_{10}Re$: C, 36.8; H, 4.6; N, 8.2. Found: C, 36.5; H, 4.6; N, 8.0%.

2.2.3. $[Et_3NH][Re(CO)_3(L^3)] \cdot H_2O$ (3)

105 mg of H$_2$L^3 led to 184 mg of **3** as orange crystals (Yield 88%).

^{1}H NMR (300 MHz, DMSO-d_6) δ_H (ppm): 1.18 (t, 9H, $J = 7.2$ Hz, 3CH$_3$); 1.98 (m, 2H, CH$_2$); 3.08 (q, 6H, $J = 7.2$ Hz, 3NCH$_2$); 3.32 (m, 4H, N$_{Ar}$CH$_2$ + NCH$_2$); 3.41 (AB pattern, 2H, $J = 16.0$ Hz, CH$_2$CO); 3.51 (AB pattern, 2H, $J = 16.0$ Hz, CH$_2$CO); 6.68 (m, 1H, H-6); 7.17 (d, 1H, $J = 8.7$ Hz, H-4); 7.54 (m, 1H, H-5); 8.05 (d, 1H, $J = 8.7$, H-3); 8.15 (m, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C (ppm): 9.1 (3CH$_3$); 24.4 (CH$_2$); 39.4 (3CH$_2$); 46.2 (NCH$_2$); 63.3 (2CH$_2$CO); 67.2 (NCH$_2$); 115.1 (C-6); 115.2 (C-4); 126.7 (C-3); 131.5 (C-2); 137.1 (C-5); 145.5 (C-1); 178.8 (2CO$_2$); 199.3, 199.5 (3CO). IR (KBr/cm^{-1}): $\nu_{N-H} = 3370$; $\nu_{C=O}$ (COORe) = 1637; ν(CO) = 1879, 1917, 2019. MS (ES$^-$): 578 (60), 580 (100) [M$^-$]. *Anal.* Calc. for $C_{22}H_{33}N_4O_{10}Re$: C, 37.8; H, 4.8; N, 8.0. Found: C, 38.0; H, 4.3; N, 7.9%.

2.2.4. $[Et_3NH][Re(CO)_3(L^4)] \cdot H_2O$ (4)

105 mg of H$_2$L^4 led to 194 mg of **4** as yellow crystals (Yield 93%).

^{1}H NMR (300 MHz, DMSO-d_6) δ_H (ppm): 1.15 (t, 9H, $J = 7.2$ Hz, 3CH$_3$); 1.90 (m, 2H, CH$_2$); 3.13 (q, 6H, $J = 7.2$ Hz, 3NCH$_2$); 3.20 (m, 2H, N$_{Ar}$CH$_2$); 3.31 (m, 2H, NCH$_2$); 3.35 (AB pattern, 2H, $J = 15.9$ Hz, CH$_2$CO); 3.52 (AB pattern, 2H, $J = 15.9$ Hz, CH$_2$CO); 6.67 (d, $J = 9$ Hz, 2H, H-2 and H-6); 7.32 (m, 1H, NH); 7.98 (d, 2H, $J = 9$ Hz, H-3 and H-5). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C (ppm): 9.2 (3CH$_3$); 24.1 (CH$_2$); 40.2 (3CH$_2$); 46.3 (NCH$_2$); 63.3 (CH$_2$CO); 67.4 (NCH$_2$); 111.2 (C-2 and C-6); 126.7 (C-3 and C-5); 136.2 (C-4); 155.0 (C-1); 178.7 (2CO$_2$), 199.3, 199.5 (3CO). IR (KBr/cm^{-1}): $\nu_{N-H} = 3316$; $\nu_{C=O}$ (COORe) = 1651; ν(CO) = 1878, 1915, 2024; MS (ES$^-$): 578 (60), 580 (100) [M$^-$]. *Anal.* Calc. for $C_{22}H_{33}N_4O_{10}Re$: C, 37.8; H, 4.8; N, 8.0. Found: C, 38.2; H, 4.4; N, 8.0%.

2.3. Radiolabelling of H$_2$L^1 and H$_2$L^3

To a solution of the chelator H$_2$L^1 or H$_2$L^3 (10^{-3} M in ethanol, 200 μL) in a 10 mL glass vial under nitrogen, were added successively 200 μL of an aqueous acetic acid/sodium carbonate buffer 0.1 M pH 3.4 and 40 mL of a freshly prepared $[^{99m}Tc(CO)_3(H_2O)_3]^+$ solution. The vial was sealed with a Teflon-lined cap and the mixture was heated at 80 °C for 30 min. After cooling, the resulting complex was analyzed and purified with the HPLC system described above.

2.4. X-ray crystal structure determination of complexes **2** and **3**

$[Et_3NH][Re(CO)_3(L^2)] \cdot H_2O$ (**2**) and $[Et_3NH][Re(CO)_3(L^3)] \cdot H_2O$ (**3**) were crystallized by slow evaporation of a methanol solution. The data were collected on a Bruker P4 diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Automatic search in the reciprocal sphere yielded the reduced cell. The Niggli parameters indicated monoclinic unit cells, primitive for **2** and C-centred for **3**. A whole sphere of data was collected, which were corrected for the Lorentz effect, polarization and absorption (psi-scan). These data confirmed the $2/m$ Laue symmetry and they were averaged to provide the basic two-octant set. Space group $P2_1/n$ was uniquely defined for **2** from the systematic absences ($h0l$, $h + l \neq 2n$; $0k0$, $k \neq 2n$). For **3**, space groups Cc and $C2/c$ were consistent with the systematic absences (hkl, $h + k \neq 2n$; $h0l$, $l \neq 2n$). The structure solved and refined normally in the centric $C2/c$ group.

All calculations were done with the SHELXTL-97 package [12]. The structures were solved by direct methods with SHELXS-97 [13] and refined on F_o^2 using all reflections with SHELXL-97 [14]. The coordinates of the Re atom were obtained first, and the remaining non-hydrogen atoms were located from ΔF maps. These atoms were refined anisotropically by full-matrix least squares. The hydrogen atoms were generally placed at idealized positions (N–H = 0.86 Å; C–H = 0.97 Å) and allowed to ride on the supporting atom. They were assigned fixed isotropic displacement parameters $U_{iso} = 1.2 \times U_{eq}$ of the atom to which they were bonded ($1.5 \times U_{eq}$ for methyl groups). The hydrogen atoms of the water molecule were refined, but they were constrained to have equal O–H distances and equal displacement parameters. In both structures, the $[Et_3NH]^+$ cation was disordered over two orientations and constraints on the distances and angles were applied during the refinement. Occupancy factors for the two groups were refined in the first place, then rounded off to 0.50/0.50 for **3** and 0.80/0.20 for **2**, and finally fixed for the rest of the refinement. The relevant crystal data are summarized in Table 1.

3. Results and discussion

3.1. Ligand syntheses

The four ligands (o-; p-NO$_2$Ph-EDDA and o-; p-NO$_2$Ph-PDDA) (see Scheme 1) used as chelating agents in the present work were synthesized in good yield via multistep reac-

Table 1
Crystal data for $[Et_3NH][Re(CO)_3(L^2)] \cdot H_2O$ (**2**) and $[Et_3NH][Re(CO)_3(L^3)]$ H_2O (**3**)

	Complex **2**	Complex **3**
Formula	$C_{21}H_{31}N_4O_{10}Re$	$C_{22}H_{33}N_4O_{10}Re$
M	685.70	699.72
Crystal system	monoclinic	monoclinic
Color/shape	yellow/block	yellow/platelet
Crystal size (mm^3)	0.50 × 0.46 × 0.30	0.52 × 0.46 × 0.16
Space group	$P2_1/n$	$C2/c$
a (Å)	7.7210(10)	31.117(6)
b (Å)	11.315(2)	11.648(2)
c (Å)	29.643(4)	16.335(3)
α (°)	90	90
β (°)	91.240(10)	113.65(2)
γ (°)	90	90
V (Å^3)	2589.1(7)	5423(2)
Z	4	8
T (K)	293(2)	293(2)
d (g/cm^3)	1.759	1.714
$F(000)$	1360	2784
Total reflections	19793	22085
Independent reflections	5087	5333
Observed reflections [$I > 2\sigma(I)$]	4391	4276
Data/restraints/parameters	5087/71/372	5333/20/383
Final R indices [$I > 2\sigma(I)$]^a	$R_1 = 0.0270$, $wR_2 = 0.0626$	$R_1 = 0.0312$, $wR_2 = 0.0639$
R indices (all data)^a	$R_1 = 0.0350$, $wR_2 = 0.0661$	$R_1 = 0.0469$, $wR_2 = 0.0690$
S^a	1.118	1.050

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum w(F_o^2)^2\}^{1/2}$, $S = \{\sum[w(F_o^2 - F_c^2)^2]/(N_{obs} - N_{param})\}^{1/2}$.

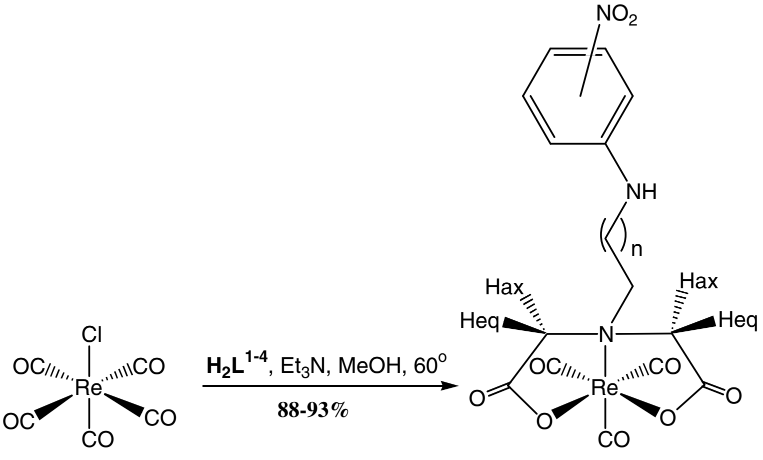
tions as previously described [11]. The coordinating iminodiacetic acid unit acts as a tridentate dianionic ligand by coordination via the two negatively charged monodentate carboxylate functions and the tertiary nitrogen bearing these two carboxylate groups.

3.2. Syntheses and characterization of the rhenium/technetium complexes

The rhenium complexes **1**–**4** were prepared in excellent yields (88–93%) by reacting equivalent amounts of ligands H_2L^1 to H_2L^4 and $Re(CO)_5Cl$ in methanol in the presence of triethylamine as deprotonating agent (see Scheme 2). Co-ordination took place in 4 h under reflux and led for each ligand, after purification by column chromatography, to a single tricarbonylrhenium complex isolated as a triethylammonium salt of general formula $[Et_3NH][Re(CO)_3(L)] \cdot H_2O$, as evidenced from the elemental analyses. All complexes exhibited a good solubility in polar solvents and in water/alcohol mixtures, which was a prerequisite for biological studies. The low-spin d^6 nature of the metal centre renders the complexes very robust and no decomposition was observed in the solid state as well as in organic polar solvents for a period of weeks, as shown by HPLC and NMR.

The four tricarbonylrhenium complexes were characterized by the usual analytical techniques, including X-ray diffraction analysis for complexes **2** and **3**. The facial arrangement of the carbonyl groups in all complexes is evidenced from the CO-stretching absorptions in the IR spectra. The three strong $\nu(CO)$ stretching bands appear in the region of 2025–1880 cm^{-1} (see Table 2), indicating the presence of the *fac*-$[Re(CO)_3]^+$ core [15]. In addition, a single, strong absorption of the carboxylate functionalities with a significant blue shift due to metal coordination could be observed at ca. 1650 cm^{-1} in the four complexes. Tridentate coordination of the IDA ligand to the metal core was confirmed by the NMR experiments.

The resonances were assigned on the basis of 1D ($^1H/^{13}C$) as well as 2D (^1H–^1H COSY and ^1H–^{13}C HMQC) NMR experiments. For the free ligands H_2L^1–H_2L^4, the signals of the NCH_2COO protons of the IDA moiety are singlets in the 3.51–3.59 ppm range [11]. After the ligands have been coordinated to rhenium, these proton signals split into two doublets corresponding to an AB-spin system in the region 3.35–3.52 and 3.52–3.65 ppm with coupling constants consistent with geminal coupling (15.6–16.0 Hz) (see Table 2). The coordination to the metal centre results in a rigid environment which produces non-equivalence of the protons in the methylene groups close to the rhenium site. These results are in accordance with the proposed



Scheme 2.

Table 2
Selected ^{1}H, ^{13}C NMR and IR data of rhenium(I) complexes **1**–**4**

	NMR		IR
	CH_2CO δ_H H_{eq}/H_{ax} (ppm);J_{H-H} (Hz)	*COO*/*CO* δ_C (ppm)	$Re(CO)_3$ ν (cm^{-1})
Complex **1**	3.48/3.65; $J = 16.0$	178.9/199.1; 199.4	1872; 1908; 2013
Complex **2**	3.52/3.64; $J = 15.6$	179.0/199.2; 199.6	1881; 1918; 2024
Complex **3**	3.41/3.51; $J = 16.0$	178.8/193.3; 199.5	1879; 1917; 2019
Complex **4**	3.35/3.52; $J = 15.9$	178.7/193.3; 199.5	1878; 1918; 2024

tridentate coordination via the tertiary amine and the two carboxylate groups. Moreover, in each complex, the hydrogen resonances of the nitrophenyl moiety were either unchanged or exhibited very minor shifts compared to those of the free ligand. The lack of appreciable shifts confirms the pendant nature of the nitrophenyl ring. Therefore, coordination or interaction of the metal centre with the nitro group (linking site model) can largely be excluded.

The ^{13}C NMR spectra show only two peaks near 199–200 ppm for the three CO ligands of the *fac*-$[Re(CO)_3]^+$ moiety (see Table 2). The characteristic 2:1 peak height ratio for these carbonyl resonances indicates that two CO groups are magnetically equivalent. This result implies that the coordination sphere exhibits mirror symmetry including one of the three facial carbonyl groups and the coordinated amino group, as confirmed by the X-ray structures of complexes **2** and **3**. The same spectroscopic feature has been recently reported for rhenium-tricarbonyl complexes of IDA derivatives [16] or SAAC (Single Amino ACid) ligands [6]. Similarly, the carbon atoms of the two carboxylate groups are magnetically equivalent and downfield shifted by 6–7 ppm upon co-ordination. All these NMR results indicate that the coordination sphere of complexes **1**–**4** retains its solid-state structure in solution.

Negative-ion ESI-MS spectra of each Re-complex showed the parent peak with the correct isotope distribution pattern consistent with the monomeric anion $[Re(CO)_3(L)]^-$, without significant fragmentation. The conductivity of 105–115 Ω^{-1} cm^2 mol^{-1} for all complexes in methanol corresponds to a 1:1 electrolyte [17], as expected.

3.3. Crystallographic studies

The X-ray diffraction analyses confirm that the metal centre is in a distorted octahedral environment. ORTEP views of the anionic units of complexes **2** and **3** are shown in Figs. 1 and 2, respectively. Selected bond distances and angles are given in Table 3.

Both complexes crystallize as triethylammonium salt and contain one lattice water molecule. In the monomeric complex anion, the three CO ligands are coordinated to one face of the octahedron, whereas the other face is occupied by a tridentate IDA dianion, bonded via two carboxylate oxygens and the adjacent tertiary amino group, forming two five-membered chelate rings. As suggested by the spectroscopic data, the environment of the metal exhibits in both cases an approximate mirror plane containing the O(21)–C(21)–Re–N(1) bonds.

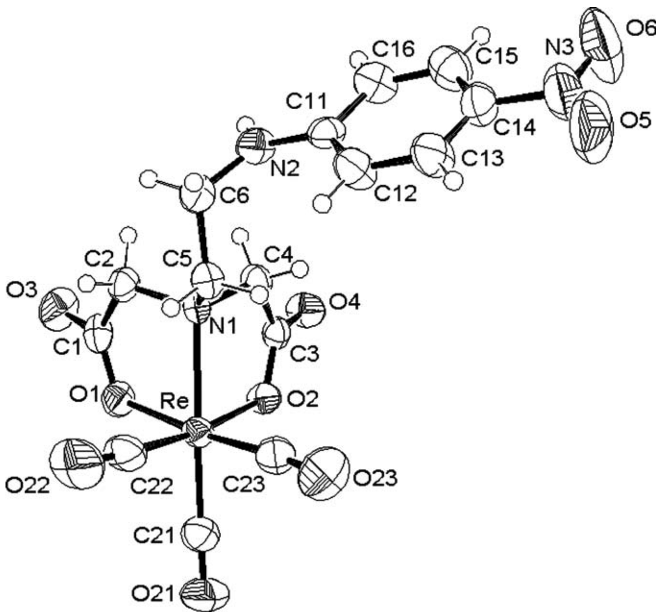


Fig. 1. ORTEP drawing of the $[Re(CO)_3(L^2)]^-$ complex anion (**2**) with numbering scheme. Thermal ellipsoids are drawn at 30% probability level.

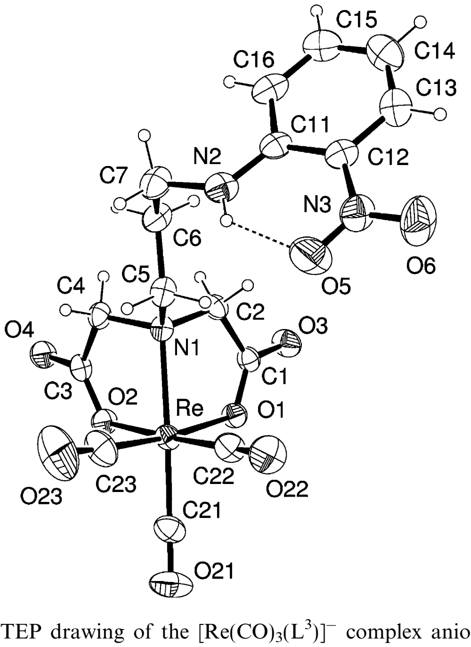


Fig. 2. ORTEP drawing of the $[Re(CO)_3(L^3)]^-$ complex anion (**3**) with numbering scheme. Thermal ellipsoids are drawn at the 30% probability level.

Table 3
Selected bonds lengths (Å) and angles (°) in $[Re(CO)_3(L^2)]^-$ (**2**) and $[Re(CO)_3(L^3)]^-$ (**3**)

	$[Re(CO)_3(L^2)]^-$	$[Re(CO)_3(L^3)]^-$
Bond lengths (Å)		
Re–C(21)	1.908(5)	1.903(6)
Re–C(22)	1.886(5)	1.896(5)
Re–C(23)	1.895(5)	1.883(6)
Re–O(1)	2.136(3)	2.126(3)
Re–O(2)	2.121(3)	2.148(3)
Re–N(1)	2.249(3)	2.258(4)
C(1)–O(1)	1.277(6)	1.260(5)
C(1)–O(3)	1.227(6)	1.239(5)
C(3)–O(2)	1.270(5)	1.270(5)
C(3)–O(4)	1.237(5)	1.232(5)
C(21)–O(21)	1.147(6)	1.151(6)
C(22)–O(22)	1.152(6)	1.156(6)
C(23)–O(23)	1.156(6)	1.151(7)
Bond angles (°)		
C(21)–Re–N(1)	172.5(2)	171.7(2)
C(22)–Re–N(1)	96.2(2)	100.3(2)
C(23)–Re–N(1)	98.6(2)	96.6(2)
O(1)–Re–N(1)	77.18(11)	77.55(12)
O(2)–Re–N(1)	77.98(11)	77.20(12)
C(21)–Re–C(22)	90.0(2)	86.9(2)
C(21)–Re–C(23)	85.8(2)	87.9(3)
C(21)–Re–O(1)	98.2(2)	97.7(2)
C(21)–Re–O(2)	95.4(2)	95.4(2)
C(22)–Re–C(23)	88.4(2)	86.0(3)
C(22)–Re–O(1)	93.7(2)	96.8(2)
C(22)–Re–O(2)	172.0(2)	176.8(2)
C(23)–Re–O(1)	175.5(2)	173.8(2)
C(23)–Re–O(2)	97.9(2)	96.3(2)
O(1)–Re–O(2)	79.67(12)	80.69(12)
Re–O(1)–C(1)	118.7(3)	119.7(3)
Re–O(2)–C(3)	118.9(2)	117.9(3)
O(1)–C(1)–O(3)	125.2(4)	124.9(4)
O(2)–C(3)–O(4)	123.6(4)	124.8(4)
Re–C(21)–O(21)	177.4(5)	179.1(5)
Re–C(22)–O(22)	177.3(5)	177.6(5)
Re–C(23)–O(23)	176.5(4)	177.4(7)

Corresponding bond lengths and angles in **2** and **3** are very similar (see Table 3) and compare well to those observed for related complexes [5,6,15c,18–20]. The Re–carbonyl bond lengths (mean 1.895 Å) lie on the short side of the range (1.89–2.03 Å) found for other tricarbonyl-rhenium compounds [18–20]. Conversely, the Re–N1 distances (mean 2.254 Å) are greater than the one reported for the similar complex $Re(CO)_3$(N-(3-aminopropyl)iminodiacetate) (2.239(3) Å) [2]. As to the Re–O distances (2.121–2.148 Å), they are close to those found in related compounds where a carboxylate oxygen is coordinated *trans* to a carbonyl ligand. The rather large deviations from the idealized octahedral geometry (bond angle ranges: *cis* 77.2–100.3°; *trans*, 171.7–176.8°) can be ascribed to the constraints imposed by ring closure, the O–Re–N bite angle being ~77.5°.

The ligand side-chains keep the nitrophenyl group at a large distance from the core of the molecule and precludes any coordinative or hydrogen-bonding interactions with components near the coordination sphere. In compound **3** containing an *o*-nitrophenyl group, intramolecular hydrogen bonding between the nitro O(5) atom and the free amino group (N(2)···O(5) = 2.593(6) Å, N(2)–H···O(5) = 131°) contributes to keeping the aromatic ring coplanar with the C(7)–N(2) bond (C(7)–N(2)–C(11)–C(16) torsion angle = −5.5(7)°). However, this hydrogen bond does not seem to be a determining factor, since the *p*-nitrophenyl ring in **2** adopts the same orientation (C(6)–N(2)–C(11)–C(12) torsion angle = 4.0(7)°), even though the nitro group does not participate in inter- or intramolecular hydrogen bonding. In both cases, crystal packing leads to π–π interactions of 3.8 Å between aromatic moieties of adjacent complexes. Since the nitro group is essentially free, it should offer, after conversion into an amino group, an ideal site for functionalization or coupling with a biomolecule.

In both structures, the lattice water molecule forms O(7)–H···O bonds with free carboxylate oxygens O(3) and O(4) of different molecules (O···O = 2.78–2.83 Å,O–H···O = 165–172°). At the same time, it acts as the acceptor in N–H···O hydrogen bonds from the free amino group N(2) or the $[Et_3NH]^+$ cation. In **3**, where the amino group is already hydrogen-bonded to the *ortho* nitro group, the hydrogen

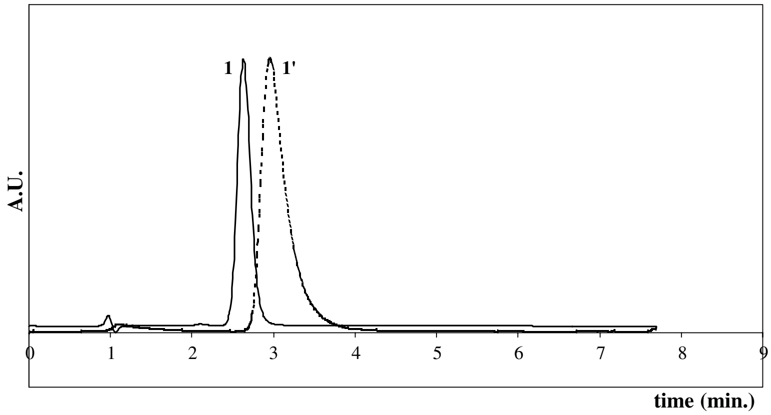


Fig. 3. HPLC traces and retention times of the tricarbonyl complexes **1** (rhenium complex, UV, 220 nm, $T_r = 2.64$ min) and **1′** (^{99m}Tc complex, radiometric detection, $T_r = 2.97$ min). Similar results (not shown) were obtained for **3** ($T_r = 2.51$ min) and **3′** ($T_r = 2.87$ min).

bond to water is formed by the $[Et_3NH]^+$ cation ($N(4)\cdots O(7) = 2.771(6)$ Å, $N(4)–H\cdots O(7) = 168°$). In **2**, this role is played by the free amino group ($N(2)\cdots O(7) = 3.041(5)$ Å , $N(2)–H\cdots O(7) = 155°$), while the $[Et_3NH]^+$ ion is linked to the carboxylate O(4) atom ($N(4)\cdots O(4) = 2.785(5)$ Å, $N(4)–H\cdots O(7) = 170°$).

3.4. ^{99m}Tc-labeling studies

Considering our interest in potential medical applications, we prepared the analogous ^{99m}Tc-complexes **1′** and **3′**. Ligands H_2L^1 and H_2L^3 were radiolabelled with the precursor *fac*-$[^{99m}Tc(CO)_3(H_2O)_3]^+$. After 30 min at 80 °C $[^{99m}Tc(CO)_3(H_2O)_3]^+$ had disappeared completely and the presence of a single new peak could be noticed in the radiochromatogram. Complexes **1′** and **3′** were both obtained in an excellent radiolabelling yield (>95%). Since the retention time of the ^{99m}Tc-complex **1′** (and **3′**) is similar to that of the “cold” Re-complex **1** (and **3**) (see Fig. 3), it may be assumed that identical structures are adopted by the species generated at the tracer level and the complex produced and characterized on the macroscopic scale. The differences between the $Re(CO)_3$ and the $^{99m}Tc(CO)_3$ species are explained by the distance separating the UV/Vis and the radiodetector in the instrument [21].

4. Conclusion

Our tridentate chelating systems NO_2Ph-EDDA and NO_2Ph-PDDA stabilize the *fac*-$[Re(CO)_3]^+$ moiety, forming well-defined complexes with a 1:l metal-to-ligand ratio. These ligands act as tridentate species by coordination via the nitrogen of the iminodiacetic acid unit and two oxygens of monodentate carboxylate groups. The structures of the complexes consist of mononuclear anions with a distorted octahedral geometry, the nitro group of the aromatic ring (linking site model) remaining uncoordinated. Studies at the n.c.a level have shown that it is possible to prepare the analogous ^{99m}Tc compounds. Therefore, the high affinity of these ligands for the *fac*-$[M(CO)_3]^+$ core ($M = {}^{99m}Tc$, Re), coupled with the easiness of their derivatization (by reduction of the nitro group into amino group), implies that utilization of these ligand systems are promising model compounds for the development of target-specific radiopharmaceuticals for diagnosis and therapy.

5. Supplementary material

Crystallographic data for $[Et_3NH][Re(CO)_3(L^2)]\cdot H_2O$ (**2**) and $[Et_3NH][Re(CO)_3(L^3)]\cdot H_2O$ (**3**) have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 286365 and 286366, respectively. Copies of these information may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk or http://www.cam.ac.uk.

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