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FULL PAPER

Coordination capabilities of pyrazolyl containing ligands towards the *fac*-$[Re(CO)_3]^+$ moiety †

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The coordination capabilities of the pyrazolyl containing ligands pz*$(CH_2)_2NH(CH_2)_2$pz*, pz*$(CH_2)_2NH(CH_2)_2NH_2$, pz*$(CH_2)_2S(CH_2)_2$pz* and pz*$(CH_2)_2S(CH_2)_2NH_2$ (pz* = 3,5-Me_2pz) towards the synthon $(NEt_4)_2[ReBr_3(CO)_3]$ (**1**) were studied. Depending on the reaction conditions, neutral or cationic Re(I) tricarbonyl complexes have been isolated: $[ReBr(CO)_3(\kappa^2$-pz*$(CH_2)_2NH(CH_2)_2$pz*$)]$ (**2**), $[ReBr(CO)_3(\kappa^2$-pz*$(CH_2)_2S(CH_2)_2$pz*$)]$ (**3**) $[Re(CO)_3(\kappa^3$-pz*$(CH_2)_2NH(CH_2)_2$pz*$)]$Br (**4**), $[Re(CO)_3(\kappa^2$-pz*$(CH_2)_2S(CH_2)_2$pz*$)$MeOH]Br (**5**), $[Re(CO)_3(\kappa^3$-pz*$(CH_2)_2NH(CH_2)_2NH_2)]$Br (**6**) and $[Re(CO)_3(\kappa^3$-pz*$(CH_2)_2S(CH_2)_2NH_2)]$Br (**7**). Complexes **2**–**7** have been characterized by the normal techniques, including X-ray crystallographic analysis in the case of **3**, **4**, **6** and **7**. In these complexes the Re atom adopts a distorted octahedral coordination, being one of the triangular faces defined by the three carbonyl groups and the other three remaining coordination positions by the bidentate and the bromide ligands (**3**), or by the tridentate and neutral pyrazolyl containing ligands (**4**, **6**, **7**). Complexes **2**–**4**, **6** and **7** are static in solution and the ^{1}H NMR data indicate clearly a κ^2-coordination mode of the ligand in **2** and **3** and a κ^3-coordination in **4**, **6** and **7**, which agrees with the coordination mode found in the solid state. Compound **5** displays a fluxional behaviour in solution as shown by variable temperature ^{1}H NMR studies. No X-ray data exists for this complex but the pattern obtained for the NMR spectrum at 215 K indicates a κ^2-coordination mode for the pyrazolyl containing ligand.

Introduction

The importance of technetium in nuclear medicine has been well established.[1] Whereas in the past, the ^{99m}Tc compounds were preferentially applied as perfusion agents, nowadays the great challenge is to find ^{99m}Tc specific radiopharmaceuticals.[2,3] More recently, the introduction of the precursors $[M(CO)_3(H_2O)_3]^+$ (M = Re, Tc),[4,5] which are easily obtained from $[MO_4]^-$, led to an increasing interest in the use of Tc(I) and Re(I) tricarbonyl compounds for the development of receptor-specific targeting molecules, potentially useful in nuclear medicine.[6] The coordination chemistry developed, so far, has shown a high substitution stability of the CO ligands and a substitution lability of the water molecules. Different (bi)tridentate ligand systems have already been explored for the stabilization of this low valence core, namely isonitriles,[7] thiourea and its derivatives,[8] thiophosphoryl amides,[9] thioethers,[10,11] P-containing ligands,[12–14] N-containing ligands combining aromatic and aliphatic amines and/or carboxylic acids,[15–17] mercaptoimidazolylborates[18,19] and cyclopentadienyls.[20] Some of these chelating ligands allowed simultaneously the stabilization of the $[M(CO)_3]^+$ core and linking to biomolecules, such as central nervous system receptor ligands or peptides.[14–16]

Advances in this field still depend on the availability of chelating systems well-suited to be combined with different biomolecules. In this sense, the chelates should distinguish themselves by high stability, small size, adoptable lipophilicity and absence of isomers. As part of our ongoing research work to access a general labeling protocol for biomolecules, namely peptides, we decided to study the chemistry of Re(I)- and ^{99m}Tc(I)-tricarbonyl complexes with the almost unexplored ligands pz*$(CH_2)_2NH(CH_2)_2$pz* (**L**^{1}), pz*$(CH_2)_2S(CH_2)_2$pz* (**L**^{3}), pz*$(CH_2)_2S(CH_2)_2NH_2$ (**L**^{4})[21–23] and with the novel pz*$(CH_2)_2NH(CH_2)_2NH_2$ (**L**^{2}) (pz* = 3,5-Me_2pz). This family of compounds present a range of features, namely stability, solubility, coordination possibilities and easy functionalization, through the pyrazolyl, the amine groups and the methylenic backbone, which make them quite promising for biomedical applications, specifically for labeling peptides with the *fac*-$[M(CO)_3]^+$ moiety. Herein, we report on the synthesis and characterization of the new ligand pz*$(CH_2)_2NH(CH_2)_2NH_2$ (**L**^{2}). We also report on the synthesis and characterization of the novel Re(I) tricarbonyl complexes $[ReBr(CO)_3(\kappa^2$-pz*$(CH_2)_2NH(CH_2)_2$pz*$)]$ (**2**), $[ReBr(CO)_3(\kappa^2$-pz*$(CH_2)_2S(CH_2)_2$pz*$)]$ (**3**,) $[Re(CO)_3(\kappa^3$-pz*$(CH_2)_2NH(CH_2)_2$pz*$)]$Br (**4**), $[Re(CO)_3(\kappa^2$-pz*$(CH_2)_2S(CH_2)_2$pz*$)$MeOH]Br (**5**), $[Re(CO)_3(\kappa^3$-pz*$(CH_2)_2NH(CH_2)_2NH_2)]$Br (**6**), and $[Re(CO)_3(\kappa^3$-pz*$(CH_2)_2S(CH_2)_2NH_2)]$Br (**7**), which have been obtained by reacting $(NEt_4)_2[ReBr_3(CO)_3]$ (**1**) with the corresponding ligands in different reaction conditions.

Experimental

General procedures

Chemicals and solvents were of reagent grade and were used without further purification. The compounds pz*$(CH_2)_2NH(CH_2)_2$pz* (**L**^{1}), pz*$(CH_2)_2S(CH_2)_2$pz* (**L**^{3}), pz*$(CH_2)_2S(CH_2)_2NH_2$ (**L**^{4}), *N*-(2-*p*-toluenesulfonylethyl)-3,5-dimethylpyrazole and the Re precursor $(NEt_4)_2[ReBr_3(CO)_3]$ (**1**) were prepared according to published methods.[21–25]

^{1}H spectra were recorded on a Varian Unity 300 MHz spectrometer; ^{1}H chemical shifts were referenced with the residual solvent resonances relative to tetramethylsilane. NMR spectra were run in $CDCl_3$ and IR spectra were recorded as KBr pellets on a Perkin-Elmer 577 spectrometer. C, H and N analysis were performed on an EA110 CE Instruments automatic analyser. It was not possible to obtain accurate C, H, N analysis for the ligand **L**^{2} and for compound **4**, although the ^{13}C and ^{1}H NMR indicated that the compounds were pure.

† Electronic supplementary information (ESI) available: experimental mass spectrum for **5**; simulated isotope distribution patterns for mono- and di-meric **5**. See http://www.rsc.org/suppdata/dt/b2/b207164a/

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Synthesis of pz*$(CH_2)_2NH(CH_2)_2NH_2$ (L^2)

Ethylenediamine (16 mL, 240 mmol) was dissolved in an aqueous solution of NaOH (0.50 g, 12.5 mmol in 20 mL H_2O) and a solution of *N*-(2-*p*-toluenesulfonylethyl)-3,5-dimethylpyrazole in THF (3.50 g, 12 mmol in 10 mL THF) was added dropwise. After refluxing for 4 hours, THF was removed from the solution under reduced pressure and the remaining aqueous phase was extracted with dichloromethane (3 × 15 mL). The organic phase was dried with magnesium sulfate, filtered and the solvent evaporated to dryness. The crude residue was purified by chromatography (silica gel column, 5% NH_4OH–MeOH), giving compound $\mathbf{L^2}$ as a yellow oil which gives a solid on standing. Yield: 81% (1.76 g). ^{1}H NMR ($CDCl_3$): δ (ppm) 5.74 (s, 1H, *H*(4)-pz), 4.03 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 2.75 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 2.20 (s, 3H, CH_3-pz), 2.17 (s, 3H, CH_3-pz). ^{13}C NMR ($CDCl_3$): δ (ppm) 147.5 (pz), 139.1 (pz), 104.9 (pz), 51.6 (CH_2), 49.0 (CH_2), 48.3 (CH_2), 41.3 (CH_2), 13.44 (CH_3-pz), 11.1 (CH_3-pz).

General synthesis of compounds 2 and 3

Compounds **2** and **3** were obtained by reacting **1** (0.130 mmol) with equimolar amounts of $\mathbf{L^1}$ and $\mathbf{L^3}$, respectively, in methanol. After one hour at room temperature, concentration of the reaction mixture allowed the isolation of **2** and **3**, which precipitated as white solids. These solids were separated, washed with water and/or methanol and vacuum dried.

[ReBr(CO)$_3$(κ^2-pz*(CH$_2$)$_2$N(H)(CH$_2$)$_2$pz*)] (2). Compound **2**: 40% yield. Anal. calc. (found) for $C_{17}H_{23}N_5O_3ReBr$: C, 33.39 (33.35); H, 3.79 (3.55); N, 11.45 (11.06)%. IR (KBr, ν/cm^{-1}): 2000, 1920, 1880 (CO str). ^{1}H NMR ($CDCl_3$): δ (ppm) 5.96 (s, 1H, *H*(4)-pz), 5.85 (s, 1H, *H*(4)-pz), 4.70 (m, 2H, CH_2), 4.26 (m, 2H, CH_2), 4.05 (m, 1H, N–*H*), 3.84 (m, 1H, CH_2), 3.71 (m, 1H, CH_2), 3.32 (m, 1H, CH_2), 2.90 (m, 1H, CH_2), 2.52 (s, 3H, CH_3-pz), 2.26 (6H, CH_3-pz), 2.17 (s, 3H, CH_3-pz).

[ReBr(CO)$_3$(κ^2-pz*(CH$_2$)$_2$S(CH$_2$)$_2$pz*)] (3). Compound **3**: 90% yield. Anal. calc. (found) for $C_{17}H_{22}N_4O_3SReBr$: C, 32.49 (33.12); H, 3.53 (4.10); N, 8.91 (9.14); S, 5.10 (5.04)%. IR (KBr, ν/cm^{-1}): 2020, 1915, 1880 (CO str). ^{1}H NMR ($CDCl_3$): δ (ppm) 5.98 (s, 1H, *H*(4)-pz), 5.82 (s, 1H, *H*(4)-pz), 4.98 (m, 1H, CH_2), 4.21 (m, 1H, CH_2), 3.83 (m, 1H, CH_2,), 3.50 (m, 1H, CH_2,), 4.32 (m, 2H, CH_2), 2.69 (m, 2H, CH_2), 2.56 (s, 3H, CH_3-pz), 2.30 (s, 3H, CH_3-pz), 2.25 (s, 3H, CH_3-pz), 2.21 (s, 3H, CH_3-pz). ^{1}H NMR (CD_3OD): δ (ppm) 6.10 (s, 1H, *H*(4)-pz), 5.87 (s, 1H, *H*(4)-pz), 4.99 (m, 1H, CH_2), 4.39–4.31 (m, 2 + 1H, CH_2), 3.65 (m, 1H, CH_2), 3.51 (m, 1H, CH_2), 2.87 (m, 2H, CH_2), 2.54 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.17 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 155.0 (pz), 148.5 (pz), 142.1 (pz), 139.9 (pz), 108.3 (pz), 105.7 (pz), 46.9 (CH_2), 45.6 (CH_2), 39.2 (CH_2), 32.42 (CH_2), 17.43 (CH_3-pz), 13.4 (CH_3-pz), 12.1 (CH_3-pz), 11.1 (CH_3-pz).

General synthesis of compounds 4–7

Compounds **4**–**7** were obtained by refluxing **1** (100 mg, 0.130 mmol) with the corresponding pyrazolyl containing ligands (0.130 mmol), in methanol. After three hours, the reaction mixtures were vacuum dried leading to crude residues, which were purified differently depending on the solubility of the complexes.

[Re(CO)$_3$(κ^3-pz*(CH$_2$)$_2$NH(CH$_2$)$_2$pz*)]Br (4). The crude residue was washed with water and vacuum dried leading to a white solid which was formulated as **4**. Yield: 44% (35 mg). IR (KBr, ν/cm^{-1}): 2020, 1890 (v br) (CO str). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.53 (s, br, 1H, N*H*), 5.97 (s, 2H, *H*(4)-pz), 4.36 (m, 2H, CH_2), 3.63 (m, 4H, CH_2), 3.33 (m, 2H, CH_2), 2.33 (s, 6H, CH_3-pz), 2.13 (s, 6H, CH_3-pz). ^{13}C NMR ($CDCl_3$): δ (ppm) 193.3 (CO), 192.8 (CO), 153.7 (pz), 143.5 (pz), 108.2 (pz), 54.1 (CH_2), 49.2 (CH_2), 15.44 (CH_3-pz), 14.63 (CH_3-pz).

[Re(CO)$_3$(κ^2-pz*(CH$_2$)$_2$S(CH$_2$)$_2$pz*)MeOH]Br (5). Extraction of the crude residue with THF, followed by removal of the solvent and recrystallization from CH_2Cl_2–hexane yielded a white solid formulated as **5**. Yield: 60% (51 mg). Anal. calc. (found) for $C_{18}H_{26}N_4O_4SReBr$: C, 32.73 (32.21); H, 3.97 (3.52); N, 8.48 (8.79); S, 4.85 (5.06)%. IR (KBr, ν/cm^{-1}): 2040, 1940, 1920 (CO str). ^{1}H NMR ($CDCl_3$), T = 323 K: δ (ppm) 6.08 (s, 2H, *H*(4)-pz), 4.66 (br, 4H, CH_2), 2.49 (br, 6H, CH_3-pz), 2.17 (br, 6H, CH_3-pz); T = 215 K: 6.85 (1H, br), 6.06 (s, 1H, *H*(4)-pz), 6.05 (s, 1H, *H*(4)-pz), 4.91 (br, 1H, CH_2), 4.67 (d, 1H, CH_2), 4.36 (1 + 2H, br, CH_2), 3.66 (br, 1H, CH_2), 2.32 (br, 2H, CH_2), 2.65 (s, 3H, CH_3-pz), 2.59 (s, 3H, CH_3-pz), 2.20 (s, 3H, CH_3-pz), 1.57 (s, 3H, CH_3-pz). FAB/MS (referenced to the species with ^{187}Re and ^{79}Br; relative abundance in parentheses): MS (+): *m*/*z* 549 $[Re(CO)_3L^3]^+$ (100%), 465 $[ReL^3]^+$ (80%). MS (−): *m*/*z* 79 $[Br]^-$ (100%).

[Re(CO)$_3$(κ^3-pz*(CH$_2$)$_2$NH(CH$_2$)$_2$NH$_2$)]Br (6). The crude product was washed several times with chloroform. The remaining insoluble white solid was formulated as **6**. Yield: 80% (55 mg). Anal. calc. (found) for $C_{12}H_{18}N_4O_3ReBr$: C, 27.07 (26.39); H, 3.41 (3.34); N, 10.52 (9.81)%. IR (KBr, ν/cm^{-1}): 2020 (str), 1920 (sh), 1900 (str, br) (CO str). ^{1}H NMR (CD_3OD): δ (ppm) 6.95 (s, br, 1H, N–*H*), 6.20 (s, 1H, *H*(4)-pz) 5.43 (s, br, 1H, N–*H*), 4.5 (m, 1H, CH_2), 3.92 (m, 1H, CH_2), 3.91 (s, br, 1H, N–*H*), 3.50 (m, 1H, CH_2), 2.90 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 2.43 (s, 3H, CH_3-pz), 2.39 (m, 1H, CH_2), 2.35 (s, 3H, CH_3-pz).

[Re(CO)$_3$(κ^3-pz*(CH$_2$)$_2$S(CH$_2$)$_2$NH$_2$)]Br (7). The residue was washed several times with chloroform and vacuum dried, yielding a white solid formulated as **7**. Yield: 60% (42 mg). Anal. calc. (found) for $C_{12}H_{17}N_3O_3SReBr$): C, 26.23 (26.48); H, 3.12 (2.74); N, 7.64 (7.97); S, 5.83 (5.68)%. IR (KBr, ν/cm^{-1}): 2020, 1910, 1900, 1880 (CO str). ^{1}H NMR (CD_3OD): δ (ppm) 6.25 (s, 1H, *H*(4)-pz), 5.65 (br, 1H, N–*H*), 4.74 (m, 1H, CH_2), 4.10 (m, 1H, CH_2), 4.00 (br, 1H, N–*H*), 3.72 (m, 1H, CH_2), 2.98 (m, 1H, CH_2), 2.85 (m, 1H, CH_2), 2.68 (m, 1H, CH_2), 2.55 (m, 1H, CH_2), 2.46 (s, 3H, CH_3-pz), 2.43 (1H, CH_2), 2.38 (s, 3H, CH_3-pz).

X-Ray crystallographic analysis

The crystals were obtained by slow evaporation of concentrated solutions of the compounds in acetonitrile (**4**) or in methanol (**3**, **6** and **7**) and were mounted in thin-walled glass capillaries. Data were collected at room temperature on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Mo-Kα radiation, using a ω–2θ scan mode. For **4**, **6** and **7** crystal data are summarized in Table 1. For **3** the crystal structure was not of good quality (see Results and discussion).

The data were corrected[26] for Lorentz and polarization effects, and empirically for absorption by Ψ scans. The heavy atom positions were located by Patterson methods using SHELX-97.[27] The remaining atoms were located in successive Fourier-difference maps and refined by least-squares refinements on F^2 using SHELX-97.[27] All the non-hydrogen atoms were refined anisotropically and the contributions of the hydrogen atoms were included in calculated positions. Atomic scattering factors and anomalous dispersion terms were as in SHELX-97.[27] The drawings were made with ORTEP-3,[28] all the calculations were performed on a 3000 Dec α computer.

CCDC reference numbers 190654–190656.

See http://www.rsc.org/suppdata/dt/b2/b207164a/ for crystallographic data in CIF or other electronic format.

Table 1 Crystallographic data for complexes **4**, **6** and **7**

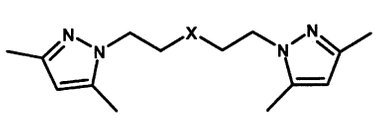
	4	**6**	**7**
Formula	$C_{17}H_{23}BrN_5O_3Re$	$C_{12}H_{18}BrN_4O_3Re$	$C_{12}H_{17}BrN_3O_3ReS$
M/g mol^{-1}	611.51	532.41	549.46
Crystal system	Triclinic	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a/Å	8.6142(11)	8.6270(11)	12.7828(15)
b/Å	15.622(3)	9.0940(15)	9.3652(9)
c/Å	17.244(4)	10.7625(16)	14.9315(19)
α/°	114.52(2)	88.582(18)	90
β/°	92.647(15)	85.696(13)	111.212(10)
γ/°	95.593(12)	74.688(14)	90
V/Å^3	2091.6(7)	812.1(2)	1666.4(3)
Z	4	2	4
μ(Mo-Kα)/mm^{-1}	7.746	9.956	9.826
Reflections collected	8701	3747	3743
Independent reflections	8410 [R_{int} = 0.0297]	3507 [R_{int} = 0.0140]	3607 [R_{int} = 0.0438]
Parameters	487	190	191
R^a	0.0458 (0.0795)[b]	0.0305 (0.0366)[b]	0.0467 (0.0734)[b]
$wR_2{}^a$	0.0790 (0.0943)[b]	0.0693 (0.0734)[b]	0.0938 (0.1109)[b]

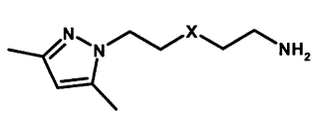
[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma(w(F_o^2 - F_c^2)^2)/[\Sigma(w(F_o^2)^2)]^{1/2}$; $[F_o > 4\sigma(F_o)]$. [b] Based on all data.

Results and discussion

Synthesis

Since the labelling of biomolecules with the organometallic $[M(CO)_3]^+$ moieties (M = ^{99m}Tc, $^{186/188}$Re) is a relatively new research field, it is important to explore different bifunctional chelating ligands suitable for the stabilization of the metal and adequate to the biomolecule under study. We investigated the feasibility of using the pyrazolyl containing ligands **L**^{1}–**L**^{4} (Scheme 1) for the synthesis of novel and stable building blocks for labeling biomolecules, namely peptides.





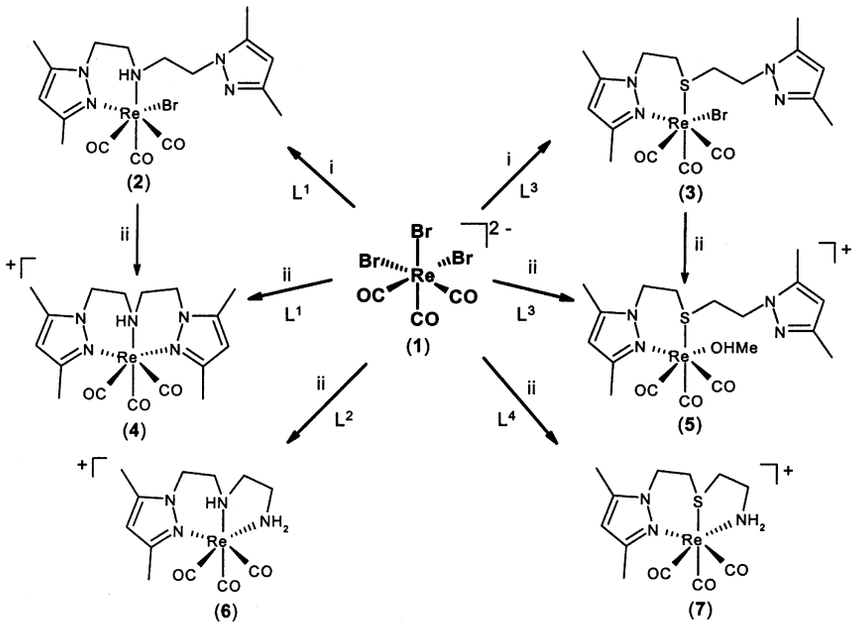
Scheme 1 Pyrazolyl containing ligands.

Compounds **L**^{1}, **L**^{3} and **L**^{4} have been synthesized as previously described.[22–25] The novel compound **L**^{2} was obtained by refluxing 1,2-ethylenediamine with *N*-(2-*p*-toluenesulfonylethyl)-3,5-dimethylpyrazole in THF. Bearing in mind the use of Re complexes as surrogates for the analogous ^{99m}Tc species, we reacted the mixed halide-carbonyl $(NEt_4)_2[ReBr_3(CO)_3]$ (**1**) with **L**^{1}–**L**^{4}, using methanol as solvent at different reaction conditions. We found that **L**^{1}–**L**^{4} react with **1** forming complexes with a metal-to-ligand ratio 1 : 1 (Scheme 2). The neutral complexes **2** and **3** are formed when **1** reacts with **L**^{1} or **L**^{3} at room temperature. These compounds precipitate from the reaction mixture as white powders and after washing with methanol and/or water provide pure compounds. By refluxing compounds **2** or **3** in methanol, or by reacting **1** with **L**^{1} or **L**^{3} under reflux, new species, soluble in methanol, were obtained, which were formulated as **4** and **5**, respectively. Complex **5** also formes when compound **3** is dissolved in methanol and left for some days at room temperature.

The follow-up of all reactions by ^{1}H NMR spectroscopy has demonstrated that compounds **2** and **3** are always intermediates in the synthesis of **4** and **5**, respectively. However, reactions of **1** with **L**^{2} or **L**^{4} are very fast and the only species detected, at room temperature or under reflux, are compounds **6** and **7**. Compounds **2**–**7** have been characterized by elemental analysis, IR, ^{1}H NMR spectroscopy and by X-ray crystallographic analysis in the case of **3**, **4**, **6** and **7**. Additionaly, the characterization of **5** also includes FAB/MS. Complexes **2**–**5** are very or slightly soluble in chlorinated solvents, while **6** and **7** are insoluble in these solvents. Compounds **4**–**7** are also soluble in polar solvents, such as methanol, tetrahydrofuran, acetonitrile and water.

The ^{1}H NMR spectra of **2**, **3** and **4** indicate clearly that these complexes have a static behaviour in solution, maintaining the structure found in the solid state (*vide infra*). This assignment is mainly based on the splitting of the protons H(4) and Me groups of the pyrazolyl rings. Clearly, in compounds **2** and **3** the **L**^{1} and **L**^{3} ligands are bidentate (two resonances for H(4) and four for the Me groups) while in compound **4** the ligand **L**^{1} is tridentate (one resonance for the protons H(4) and two for the Me groups). Consistent with this denticity is the splitting observed for the methylenic protons of **L**^{1} and **L**^{3}: six multiplets in the ratio 1 : 1 : 1 : 1 : 2 : 2 (**2** and **3**) or three resonances in the ratio 2 : 4 : 2 (**4**), due to the occasional overlapping of two resonances. Compounds **6** and **7**, although stabilized by asymmetric pyrazolyl containing ligands, also present a ^{1}H NMR spectra relatively simple consistent with the presence of neutral and tridentate ligands, with a facial array of the donor atoms, as found in the solid state structures. This coordination mode also accounts for the presence in the ^{1}H NMR spectra of **6** and **7** of two broad resonances assigned to the NH_2 protons, which become diastereotopic after coordination of the amine group to the Re center. Compound **5** is fluxional in solution, as indicated by ^{1}H NMR data. The spectrum obtained at room temperature exhibited three very broad peaks for the methyl protons of the pyrazolyl ring and for the methylenic protons of the chain, while only one resonance appears, at 6.05 ppm, for H(4). By increasing the temperature the dynamic process becomes faster on the NMR time scale, and at 323 K the pattern obtained indicates the magnetic equivalence of the two pyrazolyl rings, as only one resonance, at 6.08 ppm, was observed for the H(4) protons and two resonances, at 2.49 and 2.17 ppm, for the Me groups (relative areas: 2 : 6 : 6).

Cooling **5** resulted in progressive broadening, coalescence and splitting of the resonances associated with **L**^{3}. By 215 K, the dynamic process was slowed down, and the spectrum displays a pattern consistent with a κ^2-coordination mode for **L**^{3}: two resonances for the H(4) protons (6.06, 6.05 ppm), four resonances for the Me groups (2.65, 2.59, 2.20, 1.57 ppm), as



Scheme 2 Synthesis of Re complexes: i) MeOH, rt; ii) MeOH, reflux.

well as five multiplets in the ratio 1 : 1 : 1 + 2 : 1 : 2 for the methylenic protons (see Experimental section). In this spectrum also a very broad resonance, integrating for one proton, appears at 6.85 ppm. At 215 K, two-dimensional NMR experiments (^{1}H/^{1}H COSY) revealed coupling between the two methylenic protons which appear at 2.30 ppm and the other two which appear at 4.36 ppm. These resonances are due to the methylenic protons of the non-coordinated arm of the $\mathbf{L}^3$ ligand. As indicated in the Experimental section, the two protons at 4.36 ppm occasionally overlap with one methylenic proton from the coordinated arm.

In summary, the pattern of the methylenic protons is also in accordance with the splitting observed for the protons of the pyrazolyl rings, confirming a κ^2-coordination mode for $\mathbf{L}^3$. Based on these results and considering an octahedral coordination geometry for complex **5**, as found for **2**–**4**, **6** and **7**, one of the triangular faces of the octahedron will be defined by the nitrogen and sulfur atoms of $\mathbf{L}^3$ and the third position has to be occupied by a monodentate ligand. Taking into account our results and previously published work, the monodentate ligand can be either a halogen or a solvent molecule. For instance, reactions of *fac*-$(NEt_4)_2[MBr_3(CO)_3]$ with bidentate ligands, such as 2-picolinic acid or histamine, allowed the X-ray characterization of *fac*-$[Re(OH_2)(\kappa^2\text{-picolinic})(CO)_3]$ and *fac*-$[ReBr(\kappa^2\text{-hist})(CO)_3]$.[17,16] Comparing the properties of complexes **3** and **5** (solubility, NMR and IR spectroscopic data) it is clear that these are different species. For complex **3**, the X-ray structural analysis confirmed that Br^- together with the sulfur and one of the nitrogen atoms of $\mathbf{L}^3$ define one of the triangular faces of the octahedron. As the values of the carbonyl stretching frequencies in **5** (2040, 1940, 1920 cm^{-1}) are higher than the values found for **3** (2020, 1915, 1880 cm^{-1}), in complex **5** the third coordination position must be occupied by a weaker σ-donor than the bromide ligand found in **3**. Based on the spectroscopic data, on elemental analysis, as well as on the slow transformation of **3** into **5**, when left in methanol solution, we formulate **5** as $[Re(CO)_3(\kappa^2\text{-pz*}(CH_2)_2S(CH_2)_2pz^*)MeOH]Br$. Nevertheless, in the NMR spectrum of **5** at 215 K the resonance due to the methanol could not be assigned. It is possible that at this temperature the Me group of the methanol is still broad and can not be distinguished from the baseline.

One possible mechanism for the fluxional behaviour of **5** could be the exchange between the uncoordinated and the coordinated pyrazolyl rings. This is certainly a twist mechanism involving the breaking/making of the two Re–N bonds.[29] At high temperature, this process is fast, being responsible for the magnetic equivalence of the two aromatic rings which are non-equivalent when the process is slow on the NMR time scale. The existence of an interaction between one proton of the coordinated methanol and the lone pair of the nitrogen atom of the uncoordinated pyrazolyl ring could explain the presence of the very broad resonance at 6.08 ppm observed at 215 K, and also the high activation energy for this process. In order to clarify this point, **5** was also analysed by FAB/MS. The FAB/MS positive spectrum of **5** presents two prominent ion peaks with an isotope distribution pattern consistent with a monomeric species: *m*/*z* 547/549 ($[Re(CO)_3(pz^*(CH_2)_2S(CH_2)_2pz^*)]^+$, 100%); *m*/*z* 463/465 $[Re(pz^*(CH_2)_2S(CH_2)_2pz^*)]^+$, 80%). In the negative FAB/MS only one intense peak appears at *m*/*z* 79/81 ([Br], 100%). This fragmentation also seems to indicate that complex **5** is a cation, but still in the FAB/MS (+) coordinated methanol could not be found. To gain a better insight into this issue, it is essential to obtain the solid state structure of **5**, a target that we are currently pursuing.

Molecular structures

The structures of the complexes $[Re(CO)_3(\kappa^3\text{-pz*}(CH_2)_2NH(CH_2)_2pz^*)]Br$ (**4**), $[Re(CO)_3(\kappa^3\text{-pz*}(CH_2)_2NH(CH_2)_2NH_2)]Br$ (**6**), and $[Re(CO)_3(\kappa^3\text{-pz*}(CH_2)_2S(CH_2)_2NH_2)]Br$ (**7**) consist of ion-pair units in which the Re atom in the cation is in a distorted octahedral environment. For compound $[ReBr(CO)_3(\kappa^2\text{-pz*}(CH_2)_2S(CH_2)_2pz^*)]$ (**3**) monocrystals of poor quality have been obtained from a saturated solution of the compound in methanol: triclinic space group $P\bar{1}$ with cell parameters a = 8.221(3), b = 10.817(4), c = 13.022(3) Å, α = 80.06(3), β = 81.15(2), γ = 68.47(3)°, V = 1056(1) Å^3 and Z = 2. The X-ray crystallographic analysis did not provide an adequate data set for an accurate determination of the structure, but the data collected allowed to define unambiguously the connectivities of the atoms around Re. For this neutral compound the Re is six-coordinated, being one of the triangular faces of the octahedron defined by three carbonyl ligands and another one by the bromide and by the nitrogen and sulfur atoms of the bidentate ligand. In the cations of **4**, **6** and **7** the carbonyl ligands occupy one triangular face of the coordination polyhedron, and the other three remaining positions are occupied by the tridentate pyrazolyl containing ligands. In compounds **4**, **6** and **7** the bromide anion forms hydrogen bonds with the amines, being the N ··· Br distances in the range 3.282

(5)–3.428(8) Å. In **4** the N ··· Br distances and the N–H–Br angles are 3.308, 3.324 Å and 158.6, 177.9° for molecules 1 and 2, respectively; in **6**, the N(2) ··· Br distance and the N(2)–H(2)–Br angle are 3.282 Å and 154.2°; and in **7** the N(1) ··· Br distance and the N(1)–H(1A)–Br angle are 3.428 Å and 158.4°. Weaker intermolecular hydrogen bonds can be considered in compounds **6** and **7**.

Complex **4** crystallizes with two crystallographically independent but chemically similar molecules in the asymmetric unit. ORTEP views of the neutral compound **3**, of the cations **6** and **7** and of the cation of one of the molecules of **4** are shown in Figs. 1–4. Selected bond distances and angles for compounds **4**, **6** and **7** are given in Tables 2 and 3.

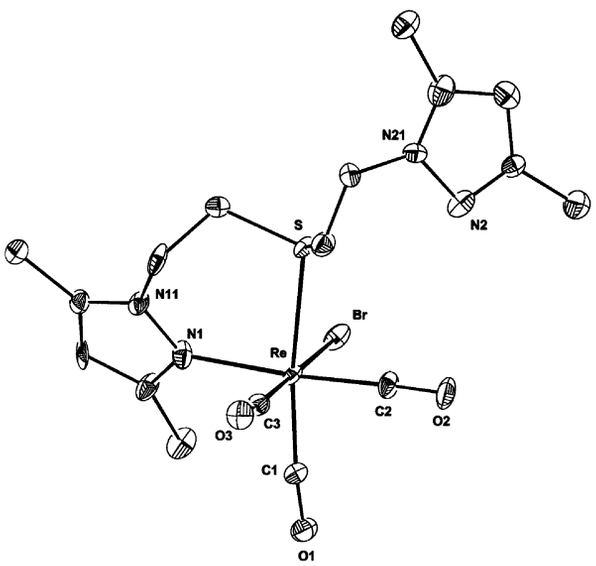


Fig. 1 ORTEP view of **3**. Vibrational ellipsoids are drawn at the 20% probability level.

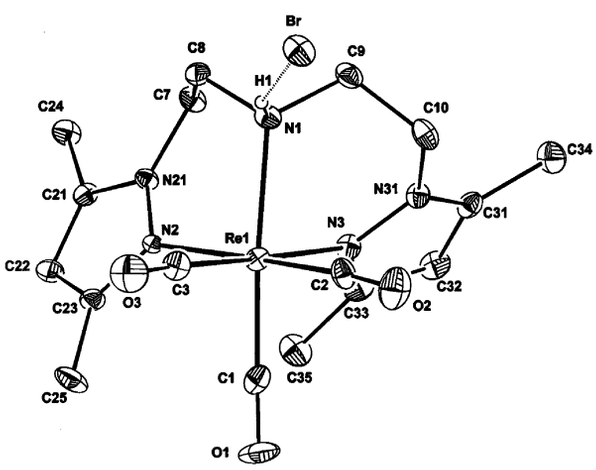


Fig. 2 ORTEP view of one of the molecules of **4**. Vibrational ellipsoids are drawn at the 40% probability level.

Deviations from the idealized octahedral geometry can be seen on the bond angles around the Re atom (Tables 2 and 3). The *cis* and *trans* bond angles range between 82.3–95.9 and 175.5–178.2, 77.5–98.9 and 174.6–176.5, 80.2–99.2 and 173.8–179.4°, in **4**, **6** and **7**, respectively. The tridentate coordination mode of the ligands defines two six-membered chelate rings in **4** but in compounds **6** and **7** there are one six- and one five-membered chelate ring. Cation **4** presents two different types of boat conformation: one with the Re atom at an apex of the boat (apexes Re(1), C(10) and Re(2), C(14)), the other one with the Re atom at the boat base (apexes N(2), C(8) and N(6), C(11)),

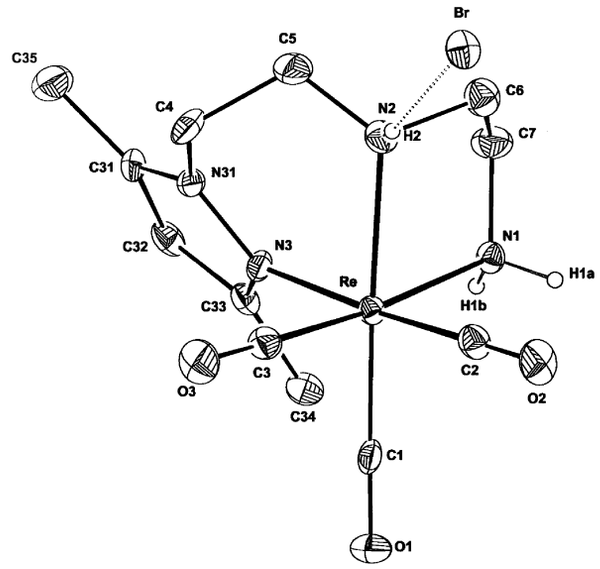


Fig. 3 ORTEP view of **6**. Vibrational ellipsoids are drawn at the 40% probability level.

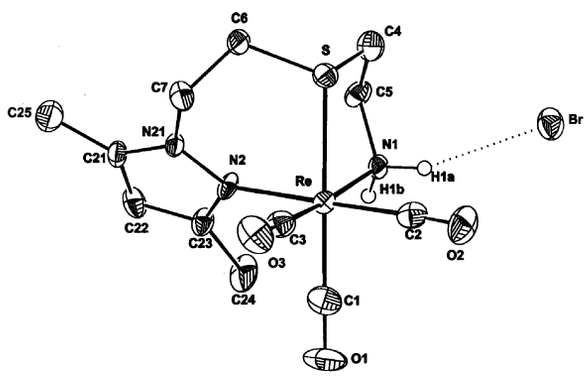


Fig. 4 ORTEP view of **7**. Vibrational ellipsoids are drawn at the 40% probability level.

Table 2 Selected bond lengths (Å) and angles (°) for [$Re(CO)_3$-(κ^3-pz*$(CH_2)_2NH(CH_2)_2$pz)]Br (**4**)

Molecule 1			
Re(1)–C(1)	1.896(10)	Re(1)–N(1)	2.242(7)
Re(1)–C(2)	1.880(9)	Re(1)–N(2)	2.211(6)
Re(1)–C(3)	1.931(10)	Re(1)–N(3)	2.190(7)
C(1)–Re(1)–C(2)	84.4(4)	C(1)–Re(1)–C(3)	88.2(4)
C(2)–Re(1)–C(3)	87.9(4)	C(2)–Re(1)–N(3)	92.5(3)
C(1)–Re(1)–N(3)	93.6(3)	C(3)–Re(1)–N(3)	178.2(3)
C(2)–Re(1)–N(2)	177.9(3)	C(1)–Re(1)–N(2)	95.0(3)
C(3)–Re(1)–N(2)	90.1(3)	N(3)–Re(1)–N(2)	89.5(2)
N(1)–Re(1)–N(2)	86.9(2)	N(3)–Re(1)–N(1)	82.3(3)
C(1)–Re(1)–N(1)	175.5(3)	C(2)–Re(1)–N(1)	93.9(4)
C(3)–Re(1)–N(1)	95.9(3)		
Molecule 2			
Re(2)–C(4)	1.913(9)	Re(2)–N(4)	2.240(7)
Re(2)–C(5)	1.908(10)	Re(2)–N(5)	2.170(7)
Re(2)–C(6)	1.885(10)	Re(2)–N(6)	2.219(7)
C(6)–Re(2)–C(5)	89.6(4)	C(5)–Re(2)–C(4)	86.7(4)
C(6)–Re(2)–C(4)	83.6(4)	C(6)–Re(2)–N(5)	93.9(3)
C(5)–Re(2)–N(5)	176.4(4)	C(5)–Re(2)–N(4)	94.9(3)
C(6)–Re(2)–N(6)	178.9(3)	C(5)–Re(2)–N(6)	91.1(4)
C(4)–Re(2)–N(6)	97.3(4)	N(5)–Re(2)–N(6)	85.4(2)
N(4)–Re(2)–N(6)	86.8(3)	N(4)–Re(2)–N(5)	83.8(2)
C(4)–Re(2)–N(5)	94.8(3)	C(6)–Re(2)–N(4)	92.4(3)
C(4)–Re(2)–N(4)	175.6(3)	C(6)–Re(2)–N(6)	178.9(3)

the latter type being the more distorted. This last type of boat conformation corresponds to the greatest N_{amine}–Re–N_{pz} angle (av. 86.9° compared with 83.1° for the first type).

Table 3 Selected bond lengths (Å) and angles (°) for $[Re(CO)_3(\kappa^3\text{-pz*}(CH_2)_2NH(CH_2)_2NH_2)]Br$ (**6**) and $[Re(CO)_3(\kappa^3\text{-pz*}(CH_2)_2S(CH_2)_2NH_2)]Br$ (**7**)

	6	**7**
Re(1)–C(1)	1.909(6)	1.904(12)
Re(1)–C(2)	1.918(6)	1.931(11)
Re(1)–C(3)	1.893(7)	1.903(11)
Re(1)–N(1)	2.208(5)	2.215(8)
Re(1)–N(2)	2.227(5)	2.212(8)
Re(1)–N(3)	2.198(5)	
Re(1)–S(1)		2.479(3)
C(1)–Re(1)–C(2)	87.6(3)	87.2(5)
C(1)–Re(1)–C(3)	86.3(3)	86.7(5)
C(2)–Re(1)–C(3)	88.7(3)	87.6(5)
C(2)–Re(1)–N(3)	176.1(2)	—
C(1)–Re(1)–N(3)	95.2(2)	—
C(3)–Re(1)–N(3)	94.2(2)	—
C(2)–Re(1)–N(2)	92.5(2)	176.5(4)
C(1)–Re(1)–N(2)	176.5(2)	92.5(4)
C(3)–Re(1)–N(2)	97.3(2)	95.8(4)
N(3)–Re(1)–N(2)	84.5(2)	—
N(1)–Re(1)–N(2)	77.5(2)	85.7(3)
N(3)–Re(1)–N(1)	83.9(2)	—
C(1)–Re(1)–N(1)	98.9(2)	99.2(4)
C(2)–Re(1)–N(1)	93.1(2)	90.9(4)
C(3)–Re(1)–N(1)	174.6(2)	173.8(4)
S(1)–Re(1)–N(1)		80.2(2)
S(1)–Re(1)–N(2)		87.4(2)
C(1)–Re(1)–S(1)		179.4(4)
C(2)–Re(1)–S(1)		92.8(3)
C(3)–Re(1)–S(1)		93.9(3)

In **6** the six-membered chelate ring, [ReN(3)N(31)C(4)C(5)-N(2)], adopts a boat conformation and the five-membered ring, [ReN(2)C(6)C(7)N(1)], presents a twist conformation, placing atoms C(6) and C(7) 0.40 and 0.32 Å, respectively, above and below the N(2)–Re–N(1) plane. In **7** the five-membered ring, [ReSC(4)C(5)N(1)], presents an envelope conformation, N(1)–C(4)–S(1)–Re being co-planar within 0.01 Å, while C(5) is displaced 0.67 Å out of this plane. The six-membered ring adopts a boat conformation more distorted than in compound **6**, probably due to the longer Re–S bond distance compared with the Re–Npz* distance in **6**, and to the wider S–Re–N(2) angle of 87.4° (N(2)–Re–N(3), 84.5° in **6**).

The average Re–C bond distances of 1.90(2), 1.907(13), and 1.913(16) Å for **4**, **6** and **7**, respectively, are comparable and are in the range (1.89–2.03 Å) found for other tricarbonyl complexes containing mono-, bi- or tri-dentate ligands.[7–20] For **6** and **7** the longer Re–C bond distance is *trans* to the pyrazolyl ring. The Re–S bond distance (2.479(3) Å) is comparable with other thioether containing rhenium(I) complexes (range, 2.46–2.47 Å).[11] The Re–Npz* bond distances in **4** (av. molecule 1, 2.20(2); molecule 2, 2.19(3) Å), **6** (2.198(5) Å) and **7** (2.212(8) Å) are comparable. The Re–N1 bond distance in **6** (2.208(5) Å) and in **7** (2.215(8) Å) are also comparable and, as expected, are slightly shorter than the distance between the metal and the nitrogen atom of the secondary amine in **6** (Re–N(2), 2.227(5) Å).

Concluding remarks

The pyrazolyl containing ligands $\mathbf{L^1}$–$\mathbf{L^4}$ stabilize the *fac*-$[Re(CO)_3]^+$ moiety forming well defined complexes with a metal-to-ligand ratio of 1 : 1. We have shown that the asymmetric ligands always coordinate as tridentate, while the coordination behaviour of the symmetric ones, $\mathbf{L^1}$ and $\mathbf{L^3}$, depends on the nature of the donating atoms involved. Higher temperature forces the tridentate coordination of $\mathbf{L^1}$ with replacement of the bromide ligand, leading to complex **4**, while the presence of the sulfur atom in $\mathbf{L^3}$ prevents the coordination of the second pyrazolyl ring. These complexes are stable towards hydrolysis and aerial oxidation and are good surrogates for the analogous ^{99m}Tc and $^{186/188}$Re complexes, their physicochemical properties being promising for labeling peptides. The nature of the $\mathbf{L^1}$–$\mathbf{L^4}$ ligands allows an easy control of the size and lipophilicity of the complexes and different possibilities of functionalization with biomolecules, which are currently in progress. Studies at the *n.c.a* level have shown that it is possible to prepare analogous ^{99m}Tc compounds with very high specific activity,[30] an important issue for the development of specific radiopharmaceuticals.

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