Novel Carbohydrate-Appended Metal Complexes for Potential Use in Molecular Imaging

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Abstract: Seven discrete sugar-pendant diamines were complexed to the $\{M(CO)_3\}^+$ (^{99m}Tc/Re) core: 1,3-diamino-2-propyl β-D-glucopyranoside (**L^1**), 1,3-diamino-2-propyl β-D-xylopyranoside (**L^2**), 1,3-diamino-2-propyl α-D-mannopyranoside (**L^3**), 1,3-diamino-2-propyl α-D-galactopyranoside (**L^4**), 1,3-diamino-2-propyl β-D-galactopyranoside (**L^5**), 1,3-diamino-2-propyl β-(α-D-glucopyranosyl-(1,4)-D-glucopyranoside) (**L^6**), and bis(aminomethyl)bis[(β-D-glucopyranosyloxy)methyl]methane (**L^7**). The Re complexes [Re(**L^1**–**L^7**)(Br)$(CO)_3$] were characterized by ^{1}H and ^{13}C 1D/2D NMR spectroscopy which confirmed the pendant nature of the carbohydrate moieties in solution. Additional characterization was provided by IR spectroscopy, elemental analysis, and mass spectrometry. Two analogues, [Re(**L^2**)$(CO)_3$Br] and [Re(**L^3**)$(CO)_3$Br], were characterized in the solid state by X-ray crystallography and represent the first reported structures of Re organometallic carbohydrate compounds. Conductivity measurements in H_2O established that the complexes exist as [Re(**L^1**–**L^7**)$(H_2O)(CO)_3$]Br in aqueous conditions. Radiolabelling of **L^1**–**L^7** with $[^{99m}Tc(H_2O)_3(CO)_3]^+$ afforded in high yield compounds of identical character to the Re analogues. The radiolabelled compounds were determined to exhibit high in vitro stability towards ligand exchange in the presence of an excess of either cysteine or histidine over a 24 h period.

Keywords: carbohydrates · molecular imaging · radiopharmaceuticals · rhenium · technetium

Introduction

Carbohydrates are of primary importance as energy sources for living organisms. Due to the properties inherent to this class of molecules, carbohydrates have been utilized to prepare bioactive materials,[1] better targeted drugs,[2] as well as for the functionalization of hydrophobic materials.[3] Metal–carbohydrate interactions are also of significant interest in bioinorganic chemistry.[4–6] However, direct metal ion–carbohydrate interactions are difficult to study due to the multifunctionality, complicated stereochemistry, and weak coordinating ability typical of carbohydrates. Carbohydrate ligands with well-tailored binding groups for metal ions such as iminodiacetic acid,[7,8] tris(2-aminoethyl)amine,[9] 1,4,7-triazacyclononane,[6] imino-[10] and amino-[11] phenols, ethylenediamine,[12] 1,3-propanediamine,[12,13] and ethylenedicysteine,[14] have been attached to carbohydrates to generate a well-defined binding environment as well as increase the stability of the resultant metal complexes. A potential benefit of utilizing this approach is that the carbohydrate can remain pendant, thereby being freely available to interact with carbohydrate transport and metabolic pathways in the body. Exam-

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

 DOI: 10.1002/chem.200400719

ples of this approach in medicinal inorganic chemistry include carbohydrate-appended cisplatin analogues as potent antitumour agents,[13,15] antifungal Ni^{II} complexes derived from amino sugars,[16] as well as carbohydrate-appended metal complexes of the radioisotopes ^{99m}Tc and ^{186}Re for potential use in nuclear imaging and therapy.[8,11,14] In many cases however the resultant metal complexes exhibit binding of the carbohydrate moiety to the metal center which limits the targeting potential of these compounds.

Radiolabelled carbohydrates have found widespread utility in the field of nuclear medicine.[17] Currently 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) (Figure 1) is the most

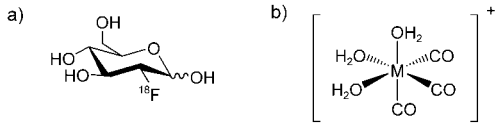


Figure 1. a) 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG); b) the organometallic precursor $[M(H_2O)_3(CO)_3]^+$ (M = ^{99m}Tc, Re).

widely used carbohydrate-based diagnostic imaging agent. FDG, imaged by positron emission tomography (PET), has proven to be very useful for the detection of tumours and metastatic tissue and also for the assessment of tissue viability in cardiac patients.[17] The high cost of PET and the relatively short half-lives of PET emitters have, however, limited their utility and hence led to the search for alternatives to FDG utilizing radionuclides that decay by a process that can be imaged by single photon emission computed tomography (SPECT). SPECT is much more prevalent and allows for the use of ^{99m}Tc which has ideal nuclear properties ($t_{1/2}$ = 6.01 h, γ = 142.7 keV) and is the most widely used isotope in nuclear medicine.[18] In addition, Re, a third row analogue of Tc, can be used in development chemistry and itself has particle emitting radioisotopes ($^{186/188}$Re) with physical properties applicable to therapeutic nuclear medicine. We have thus endeavoured to design a series of carbohydrate-appended Re and Tc complexes for potential use in nuclear medicine. Tc–carbohydrate conjugates have not been extensively studied in the literature, with early work, typical of metal–carbohydrate chemistry, plagued by poor characterization as well as potential interactions/chelation of the carbohydrate itself with the metal center.[19] In order to mimic the in vivo properties of the carbohydrate it is evident that the effect of the radionuclide must be minimized. Factors that most likely effect recognition include the size of the metal chelate as well as the distance between the chelate and the pendant glucose moiety. Recent studies utilizing 1,3-*N*,*N*-di-β-D-glucopyranosyldiethylenetriamine (DGTA) and ethylenedicysteine-deoxyglucose (ECDG) as chelates for ^{99m}Tc displayed tumour uptake.[14,20] Further studies with ^{99m}Tc–ECDG have shown that this compound is active in the hexosamine biosynthetic pathway and has significant in vivo tumour imaging potential.[21] Both studies highlight the potential of carbohydrate-labelled ^{99m}Tc compounds for tumour imaging.

Stable core structures have found utility in the chemistry of Tc due to the wide range of accessible oxidation states (Tc^{-I} to Tc^{VII}). Organometallic metal cores offer advantages in terms of stability, kinetic inertness, and size. In particular, the $\{M(CO)_3\}^+$ (M = Tc/Re) core exists in a low-spin d^6-electron configuration. The added stability of the CO ligands to substitution further protects the metal center from ligand substitution and/or oxidation, contributing to the overall kinetic inertness. The organometallic approach, first developed by Jaouen et al.,[22] and Alberto and co-workers[23] has led to widespread interest in the development of target-specific radiopharmaceuticals utilizing the $\{M(CO)_3\}^+$ (Tc/Re) cores.[24,25]

The labelling precursor $[^{99m}Tc(H_2O)_3(CO)_3]^+$ (Figure 1) is easily prepared from a kit formulation in aqueous conditions utilizing a boranocarbonate as a dual-function reducing agent and in situ CO source.[26] The three labile water molecules are easily exchanged for suitable chelating ligands.

In an effort to develop carbohydrate-appended imaging agents we have investigated the utility of 1,3-diaminocarbohydrates (Figure 2) as ligands for the $\{M(CO)_3\}^+$ (^{99m}Tc/Re) core. The 1,3-diaminocarbohydrates have been developed by Yano and co-workers[12] for potential use in bioinorganic chemistry. In all cases the carbohydrate moiety is connected to the chelating unit via the C-1 position. Prior work has shown that amines, such as those of the 1,3-diaminopropyl chelating group, are very well-suited for the $\{M(CO)_3\}^+$ (Tc/Re) core.[27–29] Utilizing the five distinct carbohydrate ligands shown in Figure 2 we were able to examine the solution and solid state properties of a number of different carbohydrates with the $\{M(CO)_3\}^+$ (Tc/Re) core.

Structural investigations were initially carried out on the "cold" Re derivatives utilizing the starting material $[NEt_4]_2[ReBr_3(CO)_3]$[30] to ascertain solution and solid state configuration. In solution the compounds were analyzed by 1D (^{1}H/^{13}C) and 2D (^{1}H,^{1}H COSY, ^{1}H,^{13}C HMQC, and ^{1}H,^{15}N HSQC) NMR experiments, as well as mass spectrometry and conductivity. Two analogues, $[Re(\mathbf{L^2})Br(CO)_3]$ and $[Re(\mathbf{L^3})Br(CO)_3]$, were analyzed by X-ray crystallography and represent the first reported structures of Re organometallic carbohydrate compounds. Labelling studies and preliminary in vitro stability measurements for the analogous ^{99m}Tc derivatives are also presented.

Results and Discussion

The synthesis of the Re complexes proceeded in a straightforward manner from $[NEt_4]_2[ReBr_3(CO)_3]$ and one of $\mathbf{L^1}$–$\mathbf{L^7}$ in refluxing methanol to afford neutral $[Re(\mathbf{L^1}$–$\mathbf{L^7})(CO)_3Br]$ in moderate yield after chromatography (Schemes 1 and 2). ^{1}H NMR analysis of the crude product was consistent in each case with the formation of the proposed structures as well as the presence of the by-product NEt_4Br. This salt was then removed by column chromatography to afford the complexes as white powders. The compounds were found to be stable in the solid state, but to de-

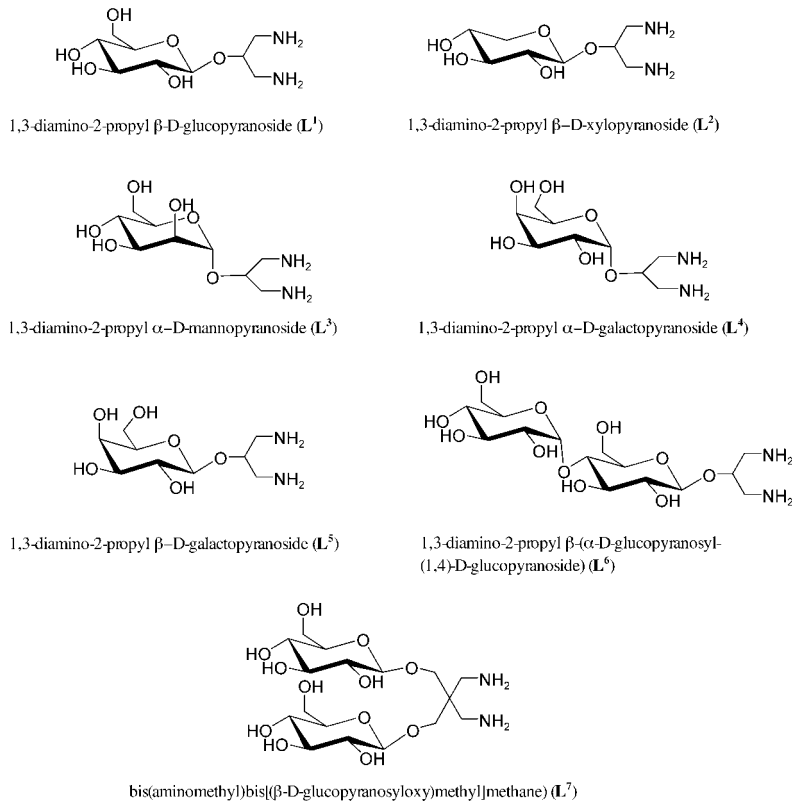


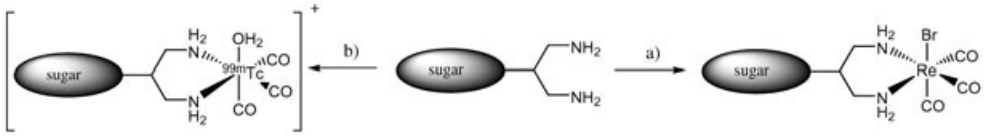
Figure 2. 1,3-Diaminocarbohydrate ligands.

compose slowly over a period of months in aqueous solution.

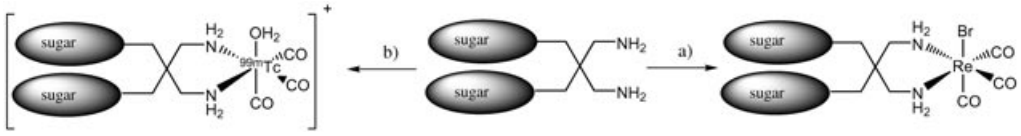
NMR analysis: NMR analysis of the Re compounds in $[D_6]$DMSO/D_2O was indicative of the mode of ligand binding (N atoms) and illustrated the lowered symmetry of the ligands once bound to the $\{Re(CO)_3\}^+$ core. The largest changes in chemical shift induced by ligand binding were for the hydrogens within the six-membered chelate ring formed between the 1,3-propanediamine moiety and the Re-metal center (Figure 3). In all cases (except **L**^{7}) the CH-propyl hydrogen signal shifted downfield by ~0.6 ppm. As a further consequence of metal binding the signals for the geminal CH_2-propyl hydrogens were split into two separate resonances (Ha/Ha′ and Hb/Hb′) due to the asymmetric environment produced upon chelation to the metal. A certain amount of asymmetry is already present in the ligands due to the many chiral centers of the sugar ring. This asymmetry extends to the CH_2-propyl carbon atoms of the binding moiety as two separate ^{13}C NMR signals are visible for these carbon atoms in the ligand[12] and the associated Re complexes (see below).

Interestingly, the NH protons were also visible in the ^{1}H NMR experiments (assigned unequivocally by ^{1}H,^{15}N HSQC). The NH protons of the free ligand are readily exchangeable in protic solvents and thus are not visible in the ^{1}H NMR spectra. This is not the case with the Re complexes; as a result of N-binding to the Re center the NH exchange process becomes slow on the NMR time-scale and these resonances are visible. The four separate NH resonances are indicative of the asymmetry at the metal center.

The hydrogen and carbon resonances of the sugar moieties in the complexes were unchanged as compared with these in the free ligands (values similar in $[D_6]$DMSO, $[D_4]$MeOH, and D_2O).[12] The lack of coordination induced shifts[5] (CIS) due to carbohydrate ligation to the metal center confirms the pendant nature of the carbohydrate



Scheme 1. Reaction scheme for Re and ^{99m}Tc complexes of the 1,3-diaminocarbohydrate ligands **L**^{1}–**L**^{6}: a) $[NEt_4]_2[ReBr_3(CO)_3]$, MeOH, reflux, 6 h, 44–68% yield; b) $[^{99m}Tc(H_2O)_3(CO)_3]^+$, 70°C, 40 min, PBS buffer.



Scheme 2. Reaction scheme for Re and ^{99m}Tc complexes of the bis-sugar analogue **L**^{7}: a) $[NEt_4]_2[ReBr_3(CO)_3]$, MeOH, reflux, 6 h, 45% yield; b) $[^{99m}Tc(H_2O)_3(CO)_3]^+$, 70°C, 40 min, PBS buffer.

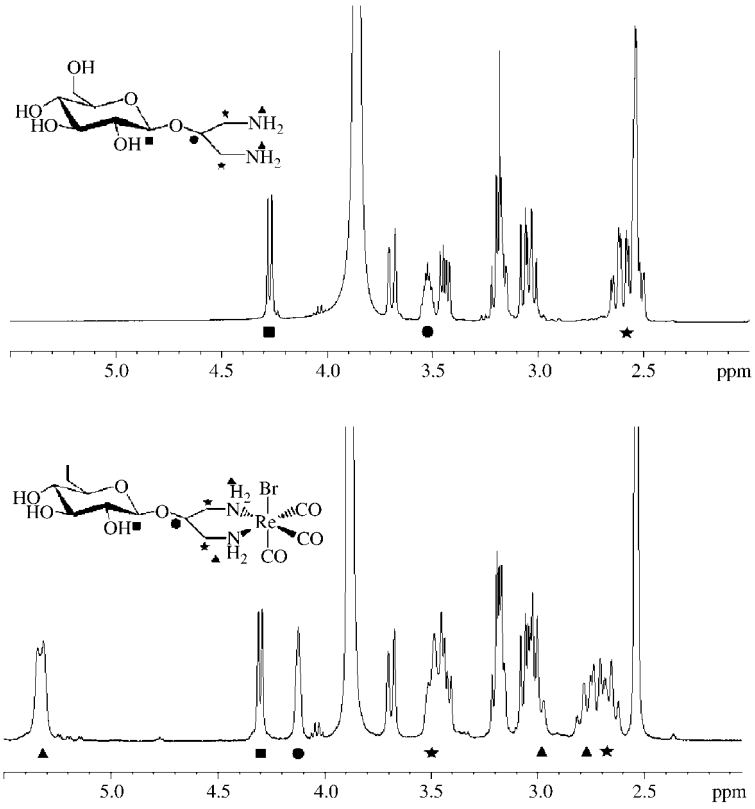


Figure 3. ^{1}H NMR spectra of $\mathbf{L^1}$ (upper) and [Re($\mathbf{L^1}$)Br(CO)$_3$] (lower) in [D$_6$]DMSO/D$_2$O; signals were assigned with the aid of ^{1}H,^{1}H COSY and ^{1}H,^{15}N HSQC experiments.

functions in solution. Interestingly, binding of $\mathbf{L^7}$, the bis-glucose derivative, to the $\{Re(CO)_3\}^+$ core resulted in two sets of similar yet distinct ^{1}H and ^{13}C NMR resonances for the carbohydrate moieties. This is in contrast to the free ligand $\mathbf{L^7}$ which displays only one set of resonances for the carbohydrate groups.[12] Evidently metal coordination exerts a far-reaching (yet minor) effect with this derivative.

Conductivity, IR spectroscopy, and mass spectrometry investigations: The identity of the Re complexes in solution was probed by a number of methods. Based on previous work,[30,31] it has been concluded that the weakly coordinated Br$^-$ ligands of $[ReBr_3(CO)_3]^{2-}$ (destabilized by the strong *trans* influence of the carbonyl ligand) undergo facile exchange in aqueous conditions. The extent of this exchange for [Re($\mathbf{L^1}$–$\mathbf{L^7}$)(CO)$_3$Br] was probed directly by conductivity measurements. The Re compounds (10^{-3} M) were dissolved in deionised water and the conductivity was measured and compared to a number of 1:1 electrolyte solutions (NaCl = 125 Ω^{-1} cm^2 mol^{-1}, [NBu$_4$]Br = 113 Ω^{-1} cm^2 mol^{-1}, [MePPh$_3$]Br = 108 Ω^{-1} cm^2 mol^{-1}). The conductivity values for Re compounds correspond to 1:1 electrolytes[32] at the concentrations measured (Table 1). The values offer clear evidence that facile H$_2$O for Br$^-$ exchange is occurring in solution with the complexes exclusively existing therein in the form [Re($\mathbf{L^1}$–$\mathbf{L^7}$)(H$_2$O)(CO)$_3$]Br.

Table 1. HPLC retention times (t_R), labelling yields (%), and conductivity measurements for the [M($\mathbf{L^1}$–$\mathbf{L^7}$)(H$_2$O)(CO)$_3$]$^+$ (M = ^{99m}Tc, Re) complexes.

Complex [M(L)(H$_2$O)(CO)$_3$]$^+$	t_R [min] M = Re (254 nm)	t_R [min] M = ^{99m}Tc (radiometric)	Labelling Yield [%] ± SD (n = 3)	Conductivity (M = Re) (H$_2$O) Λ_m (Ω^{-1} cm^2 mol^{-1})
$\mathbf{L^1}$	10.7	10.6	99 ± 1	98
$\mathbf{L^2}$	11.2	11.3	99 ± 1	108
$\mathbf{L^3}$	10.4	10.5	97 ± 1	93
$\mathbf{L^4}$	10.7	10.8	99 ± 1	100
$\mathbf{L^5}$	10.9	11.2	99 ± 1	110
$\mathbf{L^6}$	9.7	9.7	97 ± 1	150
$\mathbf{L^7}$	9.1	9.1	99 ± 1	140
[M(**His**)(H$_2$O)(CO)$_3$]	–	13.2	99 ± 1	–
[M(H$_2$O)$_3$(CO)$_3$]$^+$	–	13.9	–	–

The IR spectra of the Re compounds were consistent with the proposed structures as bands attributable to the $\{Re(CO)_3\}^+$ core were present between 2100 and 1800 cm^{-1}.[29,30] In most cases, three bands were present (indicative of a low symmetry environment) however overlap of the two lower energy bands occurred with the Re complexes of $\mathbf{L^1}$, $\mathbf{L^4}$, and $\mathbf{L^5}$. Bands attributable to the NH_2 group were also present ~3300, and 1580 cm^{-1}.[33]

The Re compounds were further examined by mass spectrometry. Re exists as a mixture of ^{185}Re/^{187}Re isotopes (37.4 and 62.6% abundance, respectively) affording diagnostic peak isotope patterns. The compounds were run as dilute solutions in MeOH and in all cases displayed molecular ion plus sodium peaks $[M+Na]^+$. This shows indirectly that the Re compounds exist (at least partially) in the neutral form in this solvent. The addition of NaBr further increased the intensity of the $[M+Na]^+$ ion peaks. Peaks due to the loss of weakly coordinated Br$^-$ ligand $[M-Br]^+$ were always present and of a greater intensity compared with that of the molecular ion. Further fragmentation patterns were also consistent with the proposed structures. Peaks due to the loss of a sugar moiety (fragmentation at C-1) for Re compounds of $\mathbf{L^1}$–$\mathbf{L^6}$ were present in

each spectrum. These high intensity peaks further corroborate the proposed structures and also indicate the tight binding of the 1,3-propanediamine to the metal center. Fragments corresponding to the successive loss of two glucose moieties were present for the bis-glucose derivative [Re(-$\mathbf{L}^7$)(Br)(CO)$_3$].

X-ray crystallography: Two of the Re compounds, [Re-($\mathbf{L}^2$)(CO)$_3$Br], and [Re($\mathbf{L}^3$)(CO)$_3$Br], were crystallized from methanol solutions and analyzed by X-ray crystallography. The data represent the first reported structures of Re organometallic carbohydrate compounds. A manganese dicarbonyl(carbohydratocarbene) complex[34] is the only other Group 7 organometallic carbohydrate X-ray structure that has been described. Structures of oxorhenium(v) complexes with carbohydrate moieties directly bound to the metal center have also been reported,[35] by using hydridotris(pyrazolyl)borato as the ancillary tridentate ligand.

The molecular structure of [Re($\mathbf{L}^2$)(CO)$_3$Br], the atomic labelling scheme, and selected bond lengths and angles are presented in Figure 4. A salient feature of this structure is the pendant carbohydrate (xylose) group in accordance with the solution characterization data. The Re coordination sphere is approximately octahedral occupied by three facially arranged carbonyls, two amino groups from the 1,3-diamino-2-propyl linker group, with the bromine occupying the remaining position. All bond lengths and angles involving Re and its ligating donor atoms are within typical values.[25,29] The amine functions form a six-membered chelate ring with the Re center in a chair conformation. Interestingly, the bulky xylose moiety is present in an axial position which is generally a higher energy conformation. This geometry is evidently stabilized by the presence of hydrogen bonding interactions between the N1-H1b···O2, N2-H2a···O1, and N2-H2a···O2 atoms. Crystal structures of Pd[36] and Pt[13] with 1,3-diaminocarbohydrate ligands also exhibit the carbohydrate moiety in the same axial orientation. Hydrogen bonding between the bromine ligand and hydrogen atoms attached to the chelating amines may account for the orientation of the six-membered ring. The interatomic separation of H1b and Br1 (2.90 Å) and H2a and Br1 (2.84 Å) are less than 2.97 Å, the sum of their van der Waals radii.[37] Finally, the xylose moiety exists exclusively as the β-anomer in the solid-state structure, correlating with solution NMR data.

The molecular structure of [Re($\mathbf{L}^3$)(CO)$_3$Br], the atomic labelling scheme, and selected bond lengths and angles are presented in Figure 5. The crystal structure of [Re($\mathbf{L}^3$)-(CO)$_3$Br], while similar to the xylose derivative, exhibited notable differences. The asymmetric unit was determined to contain one water molecule and two symmetry-independent [Re($\mathbf{L}^3$)(CO)$_3$Br] molecules where the metal ions exhibit similar coordination environments (see Supporting Information). The difference between the two molecules of the asymmetric unit lies in the orientation of the sugar moiety with respect to the Re center. While the sugar moiety occupies an axial position of the six-membered chelate ring in

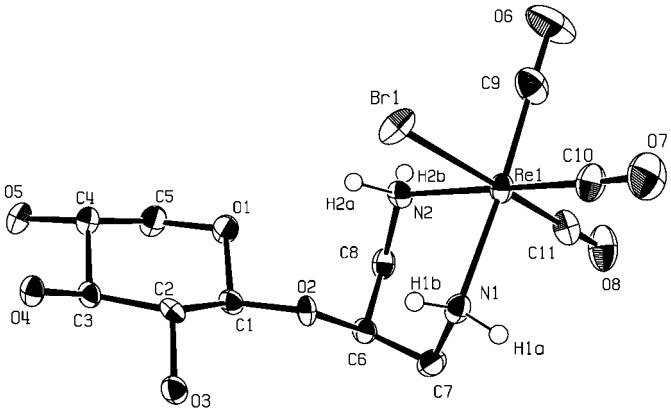


Figure 4. View of the complex molecule in the structure of [Re($\mathbf{L}^2$)-Br(CO)$_3$] (50% probability ellipsoids). Distances [Å] and angles [°] (standard deviations in parentheses): Re1–Br1 2.6382(6), Re1–N1 2.236(4), Re1–N2 2.230(4), Re1–C9 1.902(6), Re1–C10 1.917(5), Re1–C11 1.890(6), N1–C7 1.489(7), N2–C8 1.482(7), C6–C8 1.536(7), C6–C7 1.499(7), C6–O2 1.433(5), C1–O2 1.397(6); N1-Re1-N2 83.00(16), N1-Re1-Br1 85.54(11), N2-Re1-Br1 84.38(11), C11-Re1-N1 95.2(2), C10-Re1-Br1 91.23(17), C9-Re1-C10 86.5(2), C9-Re1-C11 88.5(3), C10-Re1-C11 91.9(2); intramolecular hydrogen bonds: N1(H1b)···Br(1) 2.90, N2(H2a)···Br(1) 2.84, N(1)-H(1b) ···O(2) 2.32, N(2)-H(2a)···O(1) 2.44, N(2)-H(2a)···O(2) 2.44.

each molecule, rotation around the C1–O2/C13–O11 bond, attaching the sugar ring to the propane moiety, results in the two symmetry independent molecules. The mannose moiety exists exclusively as the α-anomer in the solid state structure, correlating nicely with the solution NMR data.

In vitro characterization and stability of the ^{99m}Tc-labelled carbohydrates: The ^{99m}Tc-labelled carbohydrate compounds were synthesized utilizing a previously established

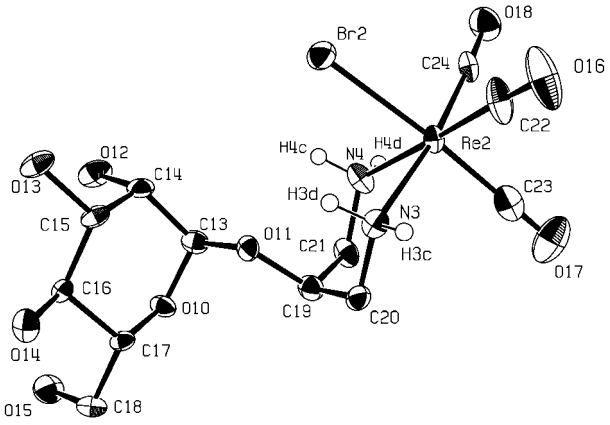


Figure 5. View of one of the complex molecules in the asymmetric unit of [Re($\mathbf{L}^3$)Br(CO)$_3$] (50% probability ellipsoids). Distances [Å] and angles [°] (standard deviations in parentheses): Re2–Br2 2.6249(10), Re2–N3 2.247(7), Re2–N4 2.230(7), Re2–C22 1.931(9), Re2–C23 1.924(11), Re2–C24 1.911(9), N3–C20 1.497(9), N4–C21 1.486(10), C19–C20 1.534(10), C19–C21 1.518(10), C19–O11 1.444(8), C13–O11 1.408(8); N3-Re2-N4 83.9(3), N3-Re2-Br2 82.73(19), N4-Re2-Br2 84.1(2), C22-Re2-Br2 93.5(3), C24-Re2-Br2 90.6(3), C23-Re2-N3 95.1(7), C22-Re2-C23 89.8(4), C22-Re2-C24 89.3(4), C23-Re2-C24 91.3(4); intramolecular hydrogen bonds: N3(H3d)···Br(2) 2.79, N4(H4c)···Br(2) 2.83, N3(H3d)···O(11) 2.41, N4(H4c)···O(11) 2.55.

method.[27,38] The formation of the $[^{99m}Tc(H_2O)_3(CO)_3]^+$ precursor was verified by HPLC ($t_R = 13.9$ min, Table 1) before labelling with the carbohydrate ligands $\mathbf{L^1}$–$\mathbf{L^7}$. The labelled derivatives were then characterized by their associated radioactive HPLC traces and compared, by co-injection, with the corresponding Re complexes (monitored at 254 nm). In all cases the retention times of the Re and ^{99m}Tc complexes were identical within experimental error (Table 1). This result confirms that the complexes produced on the tracer level are identical to Re complexes produced and characterized (see above) on the macroscopic scale. The labelling yields for the seven compounds were essentially quantitative under the conditions studied and the yields shown in Table 1 are the average of at least three separate experiments.

The in vitro stability of the ^{99m}Tc complexes was assessed by incubation with solutions of either cysteine or histidine.[27] The susceptibility of the complexes to ligand exchange by these amino acids was assessed over a 24 h period. While both cysteine and histidine are potentially tridentate mono-anionic ligands, it has been previously determined that histidine displays a much higher affinity[39] for the $\{M(CO)_3\}^+$ core. On the basis of the work with the Re complexes of $\mathbf{L^1}$–$\mathbf{L^7}$ it is clear that these ligands chelate in a bidentate fashion to the $\{M(CO)_3\}^+$ core via the primary amine functions. While it has been previously shown that primary amines are a good match for the $\{M(CO)_3\}^+$ core, the ligands studied herein leave a coordination site open for potential attack by adventitious ligands. However, incubation with solutions of either cysteine or histidine showed that the complexes were quite stable over the test period.

Cysteine was found to have a very minor effect on complex stability over the 24 h period as the complexes were $\geq 90\,\%$ intact at 24 h. Histidine only exhibited a measurable effect at the 24 h time point as the appearance of a second peak in the HPLC trace ($[^{99m}Tc(His)(CO)_3]$, confirmed by the preparation of an authentic sample) established that ligand exchange was occurring (Figure 6). The ^{99m}Tc complexes of $\mathbf{L^1}$–$\mathbf{L^7}$ were determined to be from 61 to 86 % intact at 24 h which is well within the window required for medical imaging. The stability of the complexes roughly parallels the steric size of the carbohydrate ligands as the disaccharide $\mathbf{L^6}$ and the bis-glucose analogue $\mathbf{L^7}$ were the most stable towards ligand substitution. The increased steric bulk of these ligands likely reduces the exchange of the coordinated water molecule for cysteine or histidine, thus inhibiting the ligand exchange process.

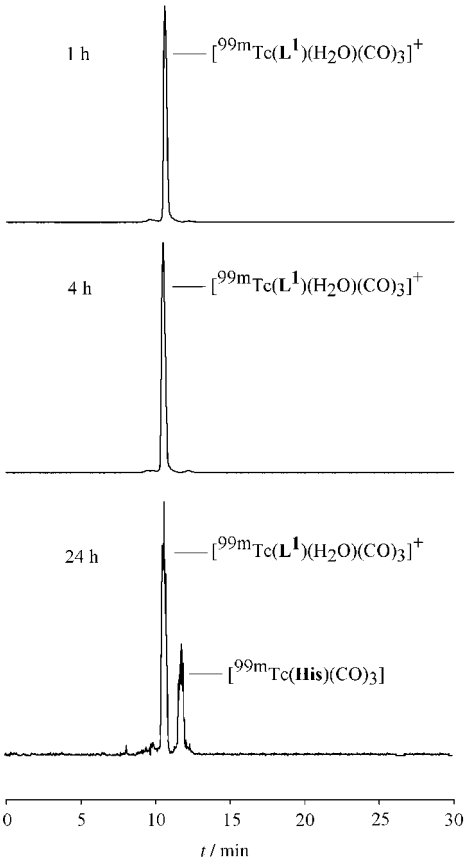


Figure 6. HPLC radiation traces for the histidine challenge experiment with $[^{99m}Tc(\mathbf{L^1})(H_2O)(CO)_3]^+$.

Concluding Remarks

In this work we have described the synthesis, and resultant solution and solid-state properties of a series of novel carbohydrate-appended metal complexes utilizing the $\{M(CO)_3\}^+$ ($M = {}^{99m}$Tc/Re) core. The pendant nature of the carbohydrate groups was confirmed for the Re compounds in solution by NMR as well as in the solid state by X-ray crystallography. Two analogues $[Re(\mathbf{L^2})Br(CO)_3]$ and $[Re(\mathbf{L^3})Br(CO)_3]$ were analyzed by X-ray crystallography and represent the first reported structures of Re organometallic carbohydrate compounds. Conductivity measurements showed that ligand exchange of the weakly coordinated Br^- ligand for H_2O in aqueous media was a facile process to afford complexes of the general formula $[Re(\mathbf{L^{1-7}})(H_2O)(CO)_3]Br$. Radiolabelling of the 1,3-diaminocarbohydrates by using the labelling precursor $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was essentially quantitative and afforded compounds identical to the Re analogues on the basis of HPLC comparison. The radiolabelled compounds were determined to be quite stable to ligand exchange in the presence of an excess of either cysteine or histidine over a 24 h period. On the basis of these promising results we are planning to evaluate the biodistribution of the ^{99m}Tc complexes in suitable model systems. In addition, labelling studies of the carbohydrate ligands with the therapeutic isotope ^{186}Re are underway.

Experimental Section

General methods: All solvents and chemicals (Fisher, Aldrich) were reagent grade and used without further purification unless otherwise specified. The 1,3-diaminocarbohydrates $\mathbf{L^1}$–$\mathbf{L^7}$[12] and $[NEt_4]_2[Re(CO)_3Br_3]$[30] were synthesized according to previously published procedures. ^{1}H and

^{13}C NMR spectra were recorded on either a Bruker AV-300 or an AV-400 instrument at 300.13 (75.48 for ^{13}C NMR) or 400.13 (100.62 for ^{13}C NMR) MHz, respectively. Infrared spectra were recorded as KBr disks in the range 4000–400 cm^{-1} on a Galaxy Series FTIR spectrometer. Mass spectra (positive ion) were obtained on dilute MeOH solutions using a Macromass LCT (electrospray ionization) instrument. C, H, N analyses were performed either at U.B.C. by Mr. M. Lakha (Carlo Erba analytical instrumentation) or by Prof. C. Ohtsuki (Perkin Elmer PE2400 Series II CHNS/O Analyzer) at the Nara Institute of Science and Technology, Nara, Japan. Conductivity measurements were performed by using a Serfass conductance bridge model RCM151B (Arthur Thomas Co. Ltd.) connected to a 3403 cell (Yellow Springs Instrument Co.) The cell was calibrated using a 0.01000 M KCl solution with a molar conductance (Λ_m) of 141.3 $\Omega^{-1}cm^2mol^{-1}$ at 25 °C to determine the cell constant to be 1.016 cm^{-1}.[32] Solutions were prepared at 10^{-3} M.

X-ray crystallography: Colourless crystals of both [Re(**L^2**)(CO)$_3$Br] and [Re(**L^3**)(CO)$_3$Br] were obtained from slow evaporation of methanol solutions. The crystals were mounted on a glass fibre, cooled to −100.0 ± 0.1 °C, and the data collected on a Bruker X8 APEX diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation to a maximum 2θ value of 55.6° for [Re(**L^2**)(CO)$_3$Br] and 55.8° for [Re(**L^3**)(CO)$_3$Br]. Data were collected and integrated using the Bruker SAINT[40] software package and corrected for Lorentz and polarization effects, as well as absorption (SADABS[41]). The structures were solved by direct methods (SIR92[42]) with all non-hydrogen atoms refined anisotropically. Hydrogen atoms were added but not refined. The final refinement (SHELXL-97[43]) with anisotropic thermal parameters for all non-hydrogen atoms converged with $R=0.025$ and $Rw=0.062$. The maximum and minimum peaks in the final differential Fourier map were 1.20 and −0.85 $e^-Å^{-3}$, respectively, for [Re(**L^2**)(CO)$_3$Br].

[Re(**L^3**)(CO)$_3$Br] crystallized with two Re complexes and one water molecule in the asymmetric unit. One mannose moiety was disordered and was refined in two orientations. The major disordered fragment was refined anisotropically, while the minor fragment was refined isotropically. All other non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions but not refined. The final refinement (SHELXL-97[43]) converged with $R=0.026$ and $Rw=0.062$. The maximum and minimum peaks in the final differential Fourier map were 1.27 and −0.76 $e^-Å^{-3}$, respectively for [Re(**L^3**)(CO)$_3$Br].

CCDC-244538 [Re(**L^2**)Br(CO)$_3$], and -244539 [Re(**L^3**)Br(CO)$_3$] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.can.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44)1223-336033; or deposit@ccdc.cam.ac.uk).

[^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ Labelling studies: The organometallic precursor [^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ was prepared from a saline solution of Na[^{99m}TcO$_4$] (1 mL, 200 MBq) using an Isolink kit provided by Mallinckrodt. Briefly, a 1 mL solution of Na[^{99m}TcO$_4$] was added to an IsoLink kit and the vial was heated to reflux for 20 min. Upon cooling, a 0.1 M HCl solution (1 mL) was added to adjust the pH to 9–10. Labelling was achieved by mixing an aliquot (200 μL) of the [^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ precursor with a 1 mM solution of **L^1**–**L^7** or histidine in PBS (pH 7.4, 1 mL) and incubating at 75 °C for 30 min. HPLC analyses were performed on a Knauer Wellchrom K-1001 HPLC equipped with a K-2501 absorption detector and a Capintek radiometric well counter. A Synergi 4 μm C-18 Max-RP analytical column with dimensions of 250×4.6 mm was used. HPLC solvents consisted of 0.1% trifluoroacetic acid in water (solvent A) and acetonitrile (solvent B). Samples were analyzed with a linear gradient method (100% solvent A to 100% solvent B over 30 min).

Cysteine and histidine challenge experiments: A solution of the ^{99m}Tc complex (final ligand concentration 10^{-4} M) was added to a 900 μL solution of either cysteine or histidine in PBS (10^{-3} M, pH 7.4). The samples were incubated at 37 °C and aliquots were removed at 1, 4, and 24 h for analysis by HPLC.

(1,3-Diamino-κ*N*,κ*N*′-2-propyl β-D-glucopyranosyl)tricarbonylrheniumbromide [Re(L^1)Br(CO)$_3$]: A solution of [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (0.076 g, 0.099 mmol) and **L^1** (0.025 g, 0.099 mmol) in MeOH (10 mL) was heated to reflux for 6 h. The solvent was then removed in vacuo and the residue purified by silica gel chromatography (EtOAc/MeOH 9:1) to afford the product as a white solid (0.033 g, 55%). ^{1}H NMR ([D$_6$]DMSO/D$_2$O, 400.13 MHz): δ = 5.38 (s, 1H; NH), 5.37 (s, 1H; NH), 4.28 (d, $^3J_{1,2}$ = 7.6 Hz, 1H; H-1), 4.07 (m, 1H; CH-propyl), 3.66 (dd, $^3J_{5,6a}$ = 6.0, $^2J_{6a,6b}$ = 11.6 Hz, 1H; H-6a), 3.44 (m, 2H; CH$_2$-propyl (Ha, Ha′)), 3.40 (dd, $^3J_{5,6b}$ = 2.5 Hz, $^2J_{6a,6b}$ = 11.6 Hz, 1H; H-6b), 3.13 (m, 2H; H-3, H-5), 2.98 (m, 3H; H-2, H-4, NH), 2.70 (m, 3H; NH, CH$_2$-propyl (Hb, Hb′)); ^{13}C{^{1}H} NMR ([D$_6$]DMSO/D$_2$O, 100.62 MHz): δ = 195.55, 195.45, 192.99 (*fac*-Re(*C*O)$_3$), 102.69 (*C*1), 77.06, 76.39 (*C*3/*C*5), 73.96 (*C*H-propyl), 73.44 (*C*2), 69.98 (*C*4), 61.07 (*C*6), 48.07, 47.17 (*C*H$_2$-propyl); IR (KBr disk): $\tilde{\nu}$ = 3335 (br) (ν(NH$_2$), ν(OH)), 2023 (vs), 1881 (vs, br) (ν(*fac*-Re(CO)$_3$)), 1581 cm^{-1} (δ(NH$_2$)); ES-MS: *m*/*z* (%): 625 (40) [*M*+Na]$^+$, 523 (95) [*M*−Br]$^+$, 361 (100) [*M*−Br−C$_6$H$_{10}$O$_5$]$^+$; Λ_M = 98 $\Omega^{-1}cm^2mol^{-1}$ (1:1 electrolyte); elemental analysis calcd (%) for C$_{12}$H$_{20}$BrN$_2$O$_9$Re: C 23.93, H 3.35,N 4.65; found: C 23.53, H 3.40, N 4.57.

(1,3-Diamino-κ*N*,κ*N*′-2-propyl β-D-xylopyranosyl)tricarbonylrheniumbromide [Re(L^2)Br(CO)$_3$]: The title compound [Re(**L^2**)Br(CO)$_3$] (0.075 g, 44%) was prepared from [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (0.226 g, 0.293 mmol) and **L^2** (0.065 g, 0.293 mmol) by a procedure analogous to that described for [Re(**L^1**)Br(CO)$_3$]. ^{1}H NMR ([D$_6$]DMSO/D$_2$O, 400.13 MHz): δ = 5.49 (d, $^2J_{NH,NH}$ = 9.6 Hz, 1H; NH), 5.41 (d, $^2J_{NH,NH}$ = 11.2 Hz, 1H; NH), 4.28 (d, $^3J_{1,2}$ = 7.5 Hz, 1H; H-1), 4.09 (m, 1H; CH-propyl), 3.70 (dd, $^3J_{4,5a}$ = 5.2 Hz, $^2J_{5a,5b}$ = 11.2 Hz, 1H; H-5a), 3.33 (m, 2H; CH$_2$-propyl (Ha, Ha′)), 3.24 (ddd, $^3J_{3,4}$ = 9.7 Hz, $^3J_{4,5a}$ = 5.2 Hz, $^3J_{4,5b}$ = 8.8 Hz, 1H; H-4), 3.03 (m, 4H; H-2, H-3, H-5b, NH), 2.67 (m, 3H; NH, CH$_2$-propyl (Hb, Hb′)); ^{13}C{^{1}H} NMR ([D$_6$]DMSO/D$_2$O, 100.62 MHz): δ = 195.50, 195.35, 192.95 (*fac*-Re(*C*O)$_3$), 103.50 (*C*1), 76.30 (*C*3), 73.98 (*C*H-propyl), 73.31 (*C*2), 69.38 (*C*4), 65.83 (*C*5), 47.99, 47.10 (*C*H$_2$-propyl); IR (KBr disk): $\tilde{\nu}$ = 3300 (br) (ν(NH$_2$), ν(OH)), 2033 (vs), 1902 (vs), 1871 (vs) (ν(*fac*-Re(CO)$_3$)), 1585 cm^{-1} (δ(NH$_2$)); ES-MS: *m*/*z* (%): 595 (20) [*M*+Na]$^+$, 492 (50) [*M*−Br]$^+$, 361 (100) [*M*−Br−C$_5$H$_8$O$_4$]$^+$; Λ_M = 108 $\Omega^{-1}cm^2mol^{-1}$ (1:1 electrolyte); elemental analysis calcd (%) for C$_{11}$H$_{18}$BrN$_2$O$_8$Re·H$_2$O: C 22.38, H 3.41, N 4.74; found: C 22.19, H 3.74, 4.76; crystal data: C$_{11}$H$_{18}$BrN$_2$O$_8$Re·CH$_3$OH, M_r = 604.43 g mol^{-1}, monoclinic (0.25×0.15×0.03 mm), *C*2 (no. 5), a = 15.142(1), b = 6.4896(5), c = 20.026(2) Å, α = 90.0, β = 104.814(4), γ = 90.0°, V = 1902.5(3) Å^3, Z = 4, ρ = 2.110 g cm^{-3}, T = 173.0 K, μ(Mo$_{K\alpha}$) = 85.33 cm^{-1}, absorption correction via multi-scan technique, $2\theta_{max}$ = 55.6°, 28862 reflections, 4313 unique, 4147 with I = 2σ(I), R_{int} = 0.034, mean σ(I)/I = 0.0227, R1(all data) = 0.026, $wR2$ = 0.062, S = 1.06, max/min residual electron density: 1.20/−0.85 $e^-Å^{-3}$, shift/error$_{max}$ = 0.00.

(1,3-Diamino-κ*N*,κ*N*′-2-propyl α-D-mannopyranosyl)tricarbonylrheniumbromide [Re(L^3)Br(CO)$_3$]: The title compound [Re(**L^3**)Br(CO)$_3$] (0.054 g, 50%) was prepared from [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (0.144 g, 0.187 mmol) and **L^3** (0.047 g, 0.187 mmol) by a procedure analogous to that described for [Re(**L^1**)Br(CO)$_3$]. ^{1}H NMR ([D$_6$]DMSO/D$_2$O, 400.13 MHz): δ = 5.23 (m, 2H; 2×NH), 4.77 (d, $^3J_{1,2}$ = 1.5 Hz, 1H; H-1), 4.08 (m, 1H; CH-propyl), 3.69 (dd, $^3J_{1,2}$ = 1.5, $^3J_{2,3}$ = 3.9 Hz, 1H; H-2), 3.60 (m, 2H; H-3, H-6a), 3.40 (m, 2H; CH$_2$-propyl (Ha, Ha′)), 3.35 (m, 4H; H-4, H-5, H-6b, NH), 2.63 (m, 3H; NH, CH$_2$-propyl (Hb, Hb′)); ^{13}C{^{1}H} NMR ([D$_6$]DMSO, 100.62 MHz): δ = 195.50, 195.39, 192.91 (*fac*-Re(*C*O)$_3$), 98.63 (*C*1), 74.84 (*C*4/*C*5), 70.73 (*C*H-propyl), 70.29 (*C*3), 70.25 (*C*2), 67.00 (*C*4/*C*5), 61.21 (*C*6), 47.74, 45.40 (*C*H$_2$-propyl); IR (KBr disk): $\tilde{\nu}$ = 3300 (br) (ν(NH$_2$), ν(OH)), 2029 (vs), 1924 (vs), 1863 (vs) (ν(*fac*-Re(CO)$_3$)), 1582 cm^{-1} (δ(NH$_2$)); ES-MS: *m*/*z* (%): 625 (20) [*M*+Na]$^+$, 523 (40) [*M*−Br]$^+$, 361 (100) [*M*−Br−C$_6$H$_{10}$O$_5$]$^+$; Λ_M = 94 $\Omega^{-1}cm^2mol^{-1}$ (1:1 electrolyte); elemental analysis calcd (%) for C$_{12}$H$_{20}$BrN$_2$O$_9$Re: C 23.93 H 3.35, N 4.65; found: C 23.95, H 3.59, N 4.57; crystal data: C$_{12}$H$_{21}$BrN$_2$O$_{9.5}$Re, M_r = 611.41 g mol^{-1}, triclinic (0.25×0.07×0.03 mm), *P*1 (no. 1), a = 6.6037(7), b = 7.8941(9), c = 18.899(2) Å, α = 93.946(5), β = 95.075(5), γ = 111.779(5)°, V = 905.8(2) Å^3, Z = 2, ρ = 2.242 g cm^{-3}, T = 173.0 K, μ(Mo$_{K\alpha}$) = 89.64 cm^{-1}, absorption correction via multi-scan technique, $2\theta_{max}$ = 55.8°, 22644 reflections, 7894 unique, 7438 with I = 2σ(I), R_{int} = 0.028, mean σ(I)/I = 0.0319, C- and N-bonded H-atoms fixed at idealized positions (0.92 Å bond length), R1(all data) = 0.024, $wR2$ = 0.062, S = 1.10, max/min^{-1} residual electron density: 1.27/−0.76 $e^-Å^{-3}$, shift/error$_{max}$ = 0.00.

(1,3-Diamino-$\kappa N,\kappa N'$-2-propyl α-D-galactopyranosyl)tricarbonylrheniumbromide [Re($\mathbf{L^4}$)Br(CO)$_3$]: The title compound [Re($\mathbf{L^4}$)Br(CO)$_3$] (0.037 g, 51%) was prepared from [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (0.093 g, 0.121 mmol) and $\mathbf{L^4}$ (0.030 g, 0.121 mmol) by a procedure analogous to that described for [Re($\mathbf{L^1}$)Br(CO)$_3$]. ^{1}H NMR ([D$_6$]DMSO/D$_2$O, 400.13 MHz): δ = 5.53 (d, $^2J_{NH,NH}$ = 11.2, 1H; NH), 5.35 (d, $^2J_{NH,NH}$ = 11.4 Hz, 1H; NH), 4.81 (d, $^3J_{1,2}$ = 3.9 Hz, 1H; H-1), 4.00 (m, 1H; CH-propyl), 3.78 (dd, $^3J_{5,6a}$ = 6.0 Hz, $^3J_{5,6b}$ = 6.0 Hz, 1H; H-5), 3.68 (m, 1H; H-4), 3.64 (dd, $^3J_{3,4}$ = 3.2 Hz, $^3J_{2,3}$ = 11.2 Hz, 1H; H-3), 3.51 (dd, $^3J_{1,2}$ = 3.9 Hz, $^3J_{2,3}$ = 11.2 Hz. 1H; H-2), 3.54 (dd, $^3J_{5,6a}$ = 6.0 Hz, $^2J_{6a,6b}$ = 12.4 Hz, 1H; H-6a), 3.49 (dd, $^3J_{5,6b}$ = 6.0 Hz, $^2J_{6a,6b}$ = 12.4 Hz, 1H; H-6b), 3.40 (m, 2H; CH$_2$-propyl (Ha, Ha′)), 3.16 (m, 1H; NH), 2.70 (m, 2H; CH$_2$-propyl (Hb, Hb′)), 2.59 (m, 1H; NH); ^{13}C{^{1}H} NMR ([D$_6$]DMSO/D$_2$O, 100.62 MHz): δ = 195.50, 195.36, 193.03 (*fac*-Re(*C*O)$_3$), 99.69 (*C*1), 73.24 (*C*H-propyl), 72.27 (*C*5), 69.49, 68.93 (*C*3/*C*4), 68.27 (*C*2), 60.80 (*C*6), 47.88, 46.43 (*C*H$_2$-propyl); IR (KBr disk): $\tilde{\nu}$ = 3350 (br) (ν(NH$_2$), ν(OH)), 2023 (vs), 1879 (vs, br) (ν(*fac*-Re(CO)$_3$)), 1581 cm^{-1} (δ(NH$_2$)); ES-MS: *m*/*z* (%): 625 (50) [*M*+Na]$^+$, 523 (60) [*M*−Br]$^+$, 361 (100) [*M*−Br−C$_6$H$_{10}$O$_5$]$^+$; Λ_M = 100 Ω^{-1}cm^{2}mol^{-1} (1:1 electrolyte); elemental analysis calcd (%) for C$_{12}$H$_{20}$BrN$_2$O$_9$Re: C 23.93, H 3.35, N 4.65; found: C 23.99, H 3.50, N 4.71.

(1,3-Diamino-$\kappa N,\kappa N'$-2-propyl β-D-galactopyranosyl)tricarbonylrheniumbromide [Re($\mathbf{L^5}$)Br(CO)$_3$]: The title compound [Re($\mathbf{L^5}$)Br(CO)$_3$] (0.033 g, 49%) was prepared from [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (0.086 g, 0.112 mmol) and $\mathbf{L^5}$ (0.028 g, 0.112 mmol) by a procedure analogous to that described for [Re($\mathbf{L^1}$)Br(CO)$_3$]. ^{1}H NMR ([D$_6$]DMSO/D$_2$O, 300.13 MHz): δ = 5.49 (d, $^2J_{NH,NH}$ = 10.5 Hz, 1H; NH), 5.41 (d, $^2J_{NH,NH}$ = 11.1 Hz, 1H; NH), 4.24 (d, $^3J_{1,2}$ = 7.2 Hz, 1H; H-1), 4.10 (m, 1H; CH-propyl), 3.66 (d, $^3J_{3,4}$ = 3.3 Hz, 1H; H-4), 3.56 (m, 2H; H-6a, H-6b), 3.40 (m, 5H; H-2, H-3, H-5, CH$_2$-propyl (Ha, Ha′)), 3.11 (m, 1H; NH), 2.91 (m, 3H; NH, CH$_2$-propyl (Hb, Hb′)); ^{13}C{^{1}H} NMR ([D$_6$]DMSO/D$_2$O, 75.48 MHz): δ = 195.51, 195.39, 192.95 (*fac*-Re(*C*O)$_3$), 103.11 (*C*1), 75.40 (*C*5), 73.61 (*C*3), 73.19 (*C*H-propyl), 70.53 (*C*2), 67.89 (*C*4), 60.35 (*C*6), 48.19, 46.97 (*C*H$_2$-propyl); IR (KBr disk): $\tilde{\nu}$ = 3350 (br) (ν(NH$_2$), ν(OH)), 2023 (vs), 1908 (vs), 1877 (sh) (ν(*fac*-Re(CO)$_3$)), 1582 cm^{-1} (δ(NH$_2$)); ES-MS: *m*/*z* (%): 625 (10) [*M*+Na]$^+$, 523 (20) [*M*−Br]$^+$, 361 (100) [*M*−Br−C$_6$H$_{10}$O$_5$]$^+$; Λ_M = 110 Ω^{-1}cm^{2}mol^{-1} (1:1 electrolyte); elemental analysis calcd (%) for C$_{12}$H$_{20}$BrN$_2$O$_9$Re: C 23.93, H 3.35, N 4.65; found: C 24.39, H 3.59, N 4.39.

(1,3-Diamino-$\kappa N,\kappa N'$-2-propyl β-(α-D-glucopyranosyl-(1,4)-D-glucopyranosyl)tricarbonylrheniumbromide [Re($\mathbf{L^6}$)Br(CO)$_3$]: A solution of [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (0.060 g, 0.078 mmol) and $\mathbf{L^6}$ (0.032 g, 0.078 mmol) in MeOH (10 mL) was heated to reflux for 6 h. The solvent was then removed in vacuo and the residue purified by silica gel chromatography (EtOAc/MeOH 4:1) to afford the product as a white solid (0.040 g, 68%). ^{1}H NMR ([D$_6$]DMSO/D$_2$O, 400.13 MHz): δ = 5.27 (s, 1H; NH), 5.25 (s, 1H; NH), 5.02 (d, $^3J_{1',2'}$ = 3.5 Hz, 1H; H-1′), 4.31 (d, $^3J_{1,2}$ = 7.7 Hz, 1H; H-1), 4.12 (s, 1H; CH-propyl), 3.68 (d, $^2J_{6a,6b}$ = 11.6 Hz, 1H; H-6a), 3.59 (d, $^2J_{6a',6b'}$ = 9.6 Hz 1H; H-6a′), 3.41 (m, 6H; H-3, H-4, H-6b, H-6b′, CH$_2$-propyl (Ha, Ha′)), 3.33 (m, 1H; H-3′), 3.25 (m, 2H; H-4, H-5), 3.22 (dd, $^3J_{1',2'}$ = 3.5 Hz, $^3J_{2',3'}$ = 9.7 Hz, 1H; H-2′), 3.07 (m, 2H; H-2, H-5′), 2.94 (m, 1H; NH), 2.65 (m, 3H; NH, CH$_2$-propyl (Hb, Hb′)); ^{13}C{^{1}H} NMR ([D$_6$]DMSO/D$_2$O, 100.62 MHz): δ = 195.96, 193.41 (*fac*-Re(*C*O)$_3$), 102.71 (*C*1), 101.09 (*C*1′), 79.59 (*C*4), 76.51 (*C*3), 75.66 (*C*5), 74.60 (*C*H-propyl), 73.80 (*C*4′), 73.55 (*C*3′), 73.40 (*C*2), 72.65 (*C*2′), 70.22 (*C*5′), 61.26, 61.08 (*C*6/*C*6′) 48.61, 47.70 (*C*H$_2$-propyl); IR (KBr disk): $\tilde{\nu}$ = 3350 (br) (ν(NH$_2$), ν(OH)), 2021 (vs), 1903 (vs), 1881 (vs) (ν(*fac*-Re(CO)$_3$)), 1582 cm^{-1} (δ(NH$_2$)); ES-MS: *m*/*z* (%): 787 (70) [*M*+Na]$^+$, 685 (70) [*M*−Br]$^+$, 361 (100) [*M*−Br−C$_{12}$H$_{20}$O$_{10}$]$^+$; Λ_M = 150 Ω^{-1}cm^{2}mol^{-1} (1:1 electrolyte); elemental analysis calcd (%) for C$_{18}$H$_{30}$BrN$_2$O$_{14}$Re: C 28.28, H 3.95, N 3.66; found: C 28.38, H 4.17, N 3.26.

(Bis(aminomethyl-$\kappa N,\kappa N'$)bis[(β-D-glucopyranosyloxy)methyl]methane) tricarbonylrheniumbromide [Re($\mathbf{L^7}$)Br(CO)$_3$]: The title compound [Re($\mathbf{L^7}$)Br(CO)$_3$] (0.030 g, 45%) was prepared from [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (0.064 g, 0.083 mmol) and $\mathbf{L^7}$ (0.038 g, 0.083 mmol) by a procedure analogous to that described for [Re($\mathbf{L^6}$)Br(CO)$_3$]. ^{1}H NMR ([D$_6$]DMSO/D$_2$O, 400.13 MHz): δ = 5.24 (m, 2H; NH), 4.14 (d, $^3J_{1,2}$ = 7.6 Hz; H-1), 4.11 (d, $^3J_{1',2'}$ = 7.6 Hz; H-1′), 3.77 (d, $^2J_{link}$ = 10.0 Hz, 1H; CH$_2$-link), 3.67 (m, 2H; H-6a, H-6a′), 3.58 (d, $^2J_{link'}$ = 9.8 Hz, 1H; CH$_2$-link′), 3.53 (d, $^2J_{link}$ = 10.0 Hz, 1H; CH$_2$-link), 3.45 (m, 2H; H-6b, H-6b′), 3.31 (d, $^2J_{link'}$ = 9.8 Hz, 1H; CH$_2$-link′), 3.13 (m, 11H; C-2, C-2′, C-3, C-3′, C-4, C-4′, C-5, C-5′, NH, CH$_2$-propyl (Ha, Ha′)), 3.02 (m, 1H; NH), 2.66 (m, 2H; CH$_2$-propyl (Hb, Hb′)); ^{13}C{^{1}H} NMR ([D$_6$]DMSO/D$_2$O, 100.62 MHz): δ = 195.91, 192.97 (*fac*-Re(*C*O)$_3$), 103.84 (*C*1), 103.61 (*C*1′), 77.27, 77.26, 77.08, 76.94 (*C*3/*C*3′/*C*5/*C*5′), 73.69, 73.40 (*C*2/*C*2′), 72.42 (CH$_2$-link′), 71.34 (CH$_2$-link), 70.36, 70.21 (*C*4/*C*4′), 61.39, 61.27 (*C*6/*C*6′), 47.33, 47.18 (*C*H$_2$-propyl), 42.12 (*C*-quarternary); IR (KBr disk): $\tilde{\nu}$ = 3350 (br) (ν(NH$_2$), ν(OH)), 2023 (vs), 1898 (vs, br) (ν(*fac*-Re(CO)$_3$)), 1582 cm^{-1} (δ(NH$_2$)); ES-MS: *m*/*z* (%): 831 (10) [*M*+Na]$^+$, 729 (60) [*M*−Br]$^+$, 567 (50) [*M*−Br−C$_6$H$_{10}$O$_5$]$^+$, 405 (100) [*M*−BrC$_{12}$H$_{20}$O$_{10}$]$^+$; Λ_M = 140 Ω^{-1}cm^{2}mol^{-1} (1:1 electrolyte); elemental analysis calcd (%) for C$_{20}$H$_{35}$BrN$_2$O$_{15}$Re·H$_2$O: C 29.03, H 4.51, N 3.38; found: C 28.83, H 4.13, N 3.11.

Acknowledgement

The authors gratefully acknowledge the Natural Sciences and Engineering Research Council (NSERC) of Canada for Strategic funding and the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan for a Grant-in-Aid for Scientific Research. T.S. acknowledges NSERC for a postgraduate scholarship as well as the Japanese Society for the Promotion of Science (JSPS) for a travel award. Prof. C. Ohtsuki is acknowledged for analytical measurements, Mallinkrodt Inc. for the Isolink boranocarbonate kits, and the UBC Hospital Department of Nuclear Medicine for supplying [^{99m}TcO$_4$].

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Received: July 13, 2004
Published online: November 11, 2004

