The Potential Use of Rhodium N-Heterocyclic Carbene Complexes as Radiopharmaceuticals: The Transfer of a Carbene from Ag(I) to $RhCl_3 \cdot 3H_2O$

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In order to use radioactive rhodium N-heterocyclic carbene (Rh NHC) complexes for possible cancer therapy, it is required to start with $RhCl_3 \cdot xH_2O$, a synthesis not previously accomplished. We have successfully synthesized and characterized two new Rh (NHC) complexes starting from $RhCl_3 \cdot xH_2O$ via a silver transfer mechanism.

Introduction

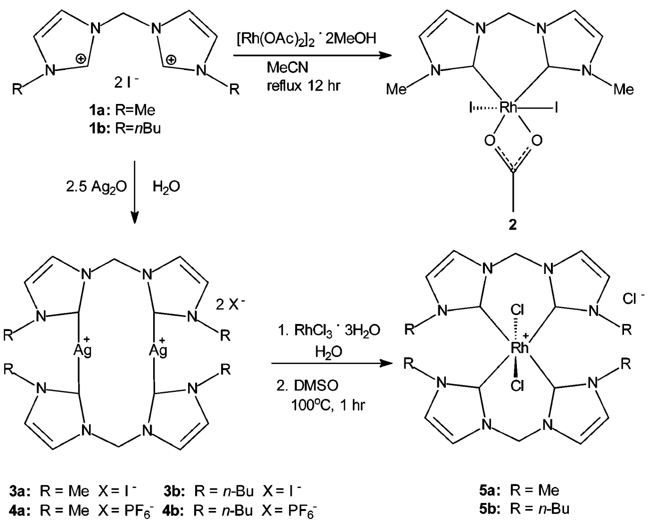
The goal of our research is to evaluate the possibility of using chelated rhodium N-heterocyclic carbene (Rh NHC) complexes as ^{105}Rh radiopharmaceuticals. ^{105}Rh is an excellent choice for tumor therapy because it emits beta particles in the ratio of 70% 0.560 MeV to 30% 0.250 MeV that are suitable for radiation therapy as well as a 319 keV gamma particle that is suitable for imaging.[1]

It has a $t_{1/2}$ of 36.4 h, which is sufficient time to kill tumor cell lines, but also short enough to avoid significant accumulation of radioactive Rh in the body. Because radioactive ^{105}Rh is available only as $RhCl_3 \cdot xH_2O$, the challenge exists of making a robust Rh NHC complex starting from this reagent well within the 36.4 h half-life with relatively simple chemistry. This could be done in two ways: (a) by rapidly transforming the $RhCl_3 \cdot xH_2O$ into a form that had been previously used to form rhodium carbene complexes[2] or (b) by the direct synthesis of Rh NHC complexes from $RhCl_3 \cdot xH_2O$. Both approaches are reported here.

Herein, we report the syntheses of the Rh NHC complex **2**, the first reported Ag complexes of bisimidazole derivatives (**3a**, **3b**, **4a**, and **4b**), and the first reported carbene transfer from silver to $RhCl_3 \cdot 3H_2O$ to form the Rh NHC complexes **5a** and **5b**.

Results and Discussion

Scheme 1



The synthesis of the Rh complex **2** is illustrated in Scheme 1. $(Rh(OAc)_2)_2 \cdot 2MeOH$ was obtained from refluxing $RhCl_3 \cdot 3H_2O$ with 4 equiv of sodium acetate in 50/50 ethanol/acetic acid.[3] The $(Rh(OAc)_2)_2 \cdot 2MeOH$ was combined with **1a**,[4] sodium acetate, and KI in acetonitrile at reflux for 12 h to give **2** after workup. The major problems with this approach are (a) the synthesis is performed in acetonitrile, a toxic solvent that is not suitable for medicinal use, and (b) if applied to ^{105}Rh, it would require several synthetic steps with radioactive materials, making this approach impractical.

Notable features in the ^{1}H NMR spectrum for **2** include the absence of a resonance at ca. 9 ppm, which is diagnostic for the loss of the carbonium proton, as well as the appearance of a resonance at 1.82 ppm for the acetate ligand. In the ^{13}C NMR spectrum, the resonance for the carbonium carbon at ca. 136 ppm is replaced with a doublet at 151.34 ppm, which is diagnostic for a Rh−C bond ($J_{Rh-C} = 42.4$ Hz). Complex **2** has been crystallographically characterized and is similar to the butyl analogue previously reported.[2b]

The transfer of NHC ligands from Ag to Rh(I) using $[Rh(COD)Cl]_2$ has been reported.[5] It is the goal of our research to find conditions that would allow the transfer

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of a carbene from silver to $RhCl_3 \cdot xH_2O$ directly. The syntheses of the Ag complexes **3a**,**b** are shown in Scheme 1. The addition of Ag_2O to an aqueous solution of **1a** or **1b**[6] in air gives the quantitative formation of silver complexes **3a** and **3b** in 12 min and 2 h, respectively. Decomposition of **3a** begins to occur within 15 min, as shown at first by the formation of a brown solution and later by the deposition of a silver mirror. Decomposition of **3b** begins to occur in 2.5 h. Decomposition of **3a** and **3b** occurs rapidly when attempting to remove the solvent by evaporation, and thereby, no crystals could be obtained. Addition of NH_4PF_6 to aqueous solutions of **3a** and **3b** yields **4a** and **4b**, respectively. The thermal stability of these complexes seems to be anion dependent, with the hexafluorophosphate salts, **4a** and **4b**, being much more stable than the iodide salts, **3a** and **3b**.

Notable features in the ^1H NMR spectrum for **3a** and **3b** include the absence of a resonance at ca. 9 ppm, which is diagnostic for the loss of the carbonium proton, and the occurrence of only one resonance for the two protons in the backbone of the imidazolium ring at 7.77 ppm for **3a** and 7.56 ppm for **3b**. In the ^{13}C NMR spectrum, the resonance for the carbonium carbon at ca. 136 ppm is absent. However, the peak for the Ag-carbene carbon resonance for **3a** and **3b** could not be detected. The ^1H NMR spectra of the hexafluorophosphate salts show distinct resonances for the two C−H bonds in the backbone of the imidazolium ring at 7.24 and 7.48 ppm for **4a** and 7.24 and 7.52 ppm for **4b**. The ^{13}C NMR spectra show the Ag-C peak at 196.01 ppm for **4a** and at 196.27 ppm for **4b**. No coupling of the silver to the carbene carbon is observed.

Single crystals suitable for X-ray diffraction studies of **4b** were grown from a concentrated solution of acetonitrile. The asymmetric unit consists of two dicationic dimers with four hexafluorophosphate anions. Compound **4b**, depicted in Figure 1, forms a “shell-like” structure with the alkyl chains having the same directionality. The asymmetric unit has eight silver−carbene bonds ranging from 2.083(5) to 2.091(5) Å with an average 2.087(5) Å. The C−Ag−C bond angles deviate significantly from linearity with angles ranging from 166.7(2)° to 173.4(2)°, with an average of 170.3(2)°. The reason for this deviation is likely due to the restriction imposed by the linking methylene group on the N-heterocyclic carbene rings. Structural analysis of the methyl analogue **4a** was also completed. Structurally the N-heterocyclic carbene rings of both **4a** and **4b** bind to the silver cations in a similar manner.

The syntheses of the Rh complexes **5a** and **5b** are outlined in Scheme 1. After filtering off any unreacted Ag_2O and any formed AgI, 0.5 molar equiv of $RhCl_3 \cdot 3H_2O$ was added to the aqueous filtrate containing the solvated Ag NHC complex **3a** or **3b** in air, causing the immediate precipitation of a red powder. Heating this red powder in DMSO at 100 °C for 1 h in air, followed by the removal of the solvent in vacuo, gave **5a** (62%) and **5b** (56%) as fine orange powders.

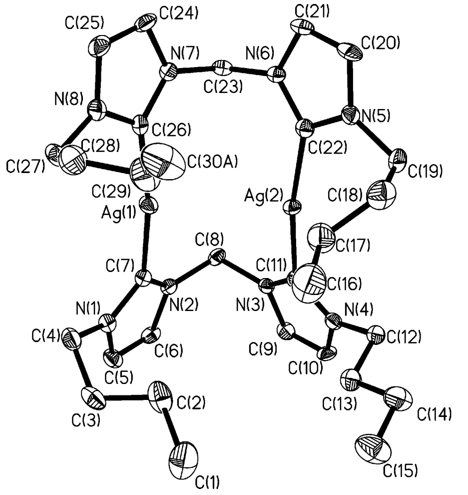

Figure 1. TEP of the cationic portion of **4b** depicted at 50% probability. The anisotropic parameters of the alkyl chains were artificially fixed, and the hydrogen atoms are omitted for clarity. Pertinent bond lengths (Å) and bond angles (deg) are as follows: Ag(1)−C(7) = 2.088(5), Ag(1)−C(26) = 2.083(5), Ag(2)−C(11) = 2.085(5), Ag(2)−C(22) = 2.083(5), C(7)−Ag(1)−C(26) = 171.2(2), C(11)−Ag(2)−C(22) = 169.7(2).

Notable features in the ^1H NMR spectrum for **5a** and **5b** include the absence of a resonance at ca. 9 ppm. Due to the conformational rigidity of the ligand, rotation about the methylene linker is hindered, producing two doublets at 6.39 ppm ($J_{H-H} = 12.5$ Hz) and 7.02 ppm ($J_{H-H} = 12.5$ Hz) for **5a** and at 6.44 ppm ($J_{H-H} = 12.4$ Hz) and 7.08 ppm ($J_{H-H} = 12.4$ Hz) for **5b** for the two inequivalent protons. In addition, for **5b**, due to the rigidity imposed on the ligand by the metal, the protons on each of the three inner carbon atoms of the butyl chains are diastereotopic, thus producing a relatively complex spectrum. In the ^{13}C NMR, the Rh-carbene resonance occurs as a doublet at 169.82 ppm for **5a** ($J_{Rh-C} = 32.1$ Hz) and at 168.05 ppm for **5b** ($J_{Rh-C} = 32.1$ Hz). Both complexes **5a** and **5b** are extremely stable, with decomposition points of 208−210 and 237−238 °C, respectively, in air. They are stable in sodium chloride solution for months.

Crystals of **5b** suitable for single-crystal X-ray diffraction studies were grown from a concentrated acetonitrile solution. The crystal structure of **5b** is shown in Figure 2. Each Rh(III) center is bound to two bidentate carbene ligands and two coordinating chlorides, forming a distorted octahedron. The remaining chloride is noncoordinating. Bond angles about the Rh centers deviate significantly from 90°, with C−Rh−C angles to each chelating NHC being acute for C5−Rh−C13A (83.7(2)°) and C20−Rh−C29A (84.1(2)°) and C−Rh−C angles between two NHC ligands being obtuse for C5−Rh−C13 (96.3(2)°) and C20−Rh−C29 (95.9(2)°). The C−Rh−Cl bonds range from 86.6(1)° to 93.4(1)° with an average of 90.0°. The asymmetric unit contains four rhodium NHC bonds ranging from 2.050(5) to 2.067(5) Å with an average of 2.058(5) Å. Crystals of **5a** have not yet been obtained due to its very limited solubility.

In conclusion, we have demonstrated the first N-heterocyclic carbene transfer from Ag to $RhCl_3 \cdot 3H_2O$. The very high stability of the rhodium complexes **5a** and

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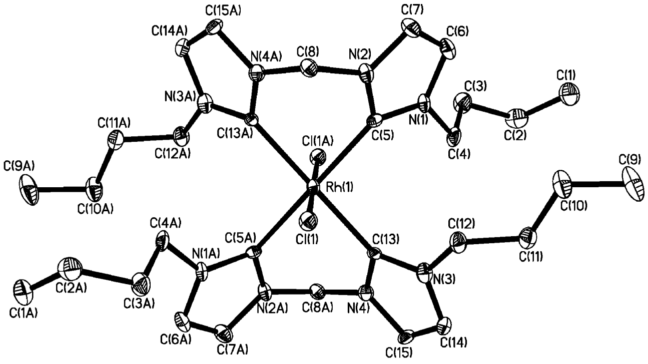

Figure 2. TEP of the cationic portion of **5b** depicted at 50% probability. Hydrogen atoms are omitted for clarity. Pertinent bond lengths (Å) and bond angles (deg) are as follows: Rh(1)−C(5) = 2.053(5), Rh(1)−C(13) = 2.062(5), C(5)−Rh(1)−C(13A) = 83.7(2), C(5)−Rh(1)−C(13) = 96.3(12).

5b indicates that ^{105}Rh complexes of bisimdazole ligands with targeting substituents such as peptides may be appropriate complexes for radiation therapy. The conditions for the synthesis are suitable for working with a radioactive material with a relatively short half-life in biologically benign solvents. DMSO is a medicinally benign solvent and has been approved for use in humans since 1971.[7] Work continues in order to improve the synthesis, ideally completing it solely in water.

Experimental Section

General Procedures. Bis(1,1′-methylimidazolium)-3,3′-methylenediiodide and bis(1,1′-*n*-butylimidazolium)-3,3′-methylenediiodide were prepared according to literature procedures.[4,6] All other chemicals were obtained commercially and used without further purification.

Elemental analyses were performed by Complete Analysis Laboratories, Inc. ^{1}H and ^{13}C NMR spectra were obtained on a Varian 300 MHz instrument.

Rh Complex 2. To a stirring solution of 0.056 g (0.121 mmol) of **1a** in 30 mL of acetonitrile was added 0.030 g (0.068 mmol) of $(Rh(OAc)_2)_2 \cdot 2MeOH$, 0.003 g (0.243 mmol) of sodium acetate, and 0.081 g (0.487 mmol) of KI. The initially purple solution became red after refluxing for 10 min and orange after a further 1.5 h. The solution was allowed to reflux for 10 h more before it was cooled and filtered. The solvent was removed by rotary evaporation, leaving an orange residue. The residue was taken up in $CHCl_3$, washed with 3 × 25 mL of H_2O, and dried over Na_2SO_4. Removal of the solvent in vacuo afforded 0.025 g (68.1%) of a fine orange powder. Single crystals suitable for X-ray analysis were grown by slow evaporation from a concentrated acetonitrile solution.

$C_{11}H_{15}N_4O_2I_2Rh$ (2). ^{1}H NMR (DMSO-d_6): δ 1.82 (s, 3H, CH_3), 3.94 (s, 6H, CH_3), 6.08 (s, 2H, CH_2), 7.57 (d, 2H, CH), 7.59 (d, 2H, CH). ^{13}C NMR (DMSO-d_6): δ 24.17 (CH_3), 37.50 (CH_3), 62.04 (CH_2), 121.47 (CH), 125.01 (CH), 151.34 (d, Rh-C, $J_{Rh-C} = 42.39$ Hz), 186.52 (O-C-O). Mz^+ ESI (M − $C_2H_3O_2$): calcd 332.9, found 532.8.

Ag Complexes 3a,b and 4a,b. To a 100 mL round-bottomed flask was added 1.00 g of either **1a** or **1b** and 50 mL of deionized H_2O. An excess, 2.5 molar equiv, of Ag_2O was added to the solution. This suspension was stirred at RT for 15 min for **3a** or for 2 h for **3b**. The solution was filtered over Celite. Monitoring the solution by ^{1}H NMR showed complete conversion to the Ag complexes. Removal of the volatile components under vacuum caused the decomposition of **3a** and **3b**. Alternatively, the addition of 2 molar equiv of NH_4PF_6 to each solution resulted in precipitation of **4a** (1.77 g, 89.3%) and **4b** (1.84 g, 92.7%) as white powders. Slow evaporation of concentrated acetonitrile solutions gave colorless crystals of **4a** and **4b** suitable for X-ray analysis.

$C_{18}H_{24}N_8Ag_2I_2$ (3a). ^{1}H NMR (D_2O): δ 3.96 (s, 3H, CH_3), 6.70 (s, 2H, N-CH_2-N), 7.77 (s, 2H, CH). ^{13}C NMR (D_2O): δ 38.63 (CH_3), 64.32 (N-CH_2-N), 123.84 (2 CH), Ag-C not observed. Mz^+ ESI: calcd 692.9, found 693.9.

$C_{18}H_{24}N_8Ag_2P_2F_{12}$ (4a). ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H, CH_3), 6.39 (br s, 2H, N-CH_2-N), 7.24 (d, 1H, CH), 7.48 (d, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 39.68 (CH_3), 65.11 (N-CH_2-N), 122.44 (CH), 125.19 (CH), 196.01 (Ag-C). Mz^+ ESI (M − PF_6^-): calcd 710.97, found 712.5. Anal. Calcd for $C_{18}H_{24}N_8Ag_2P_2F_{12}$: C 25.14, H 3.05, N 13.03. Found: C 24.93, H 2.67, N 12.85.

$C_{30}H_{48}N_8Ag_2I_2$ (3b). ^{1}H NMR (D_2O): δ 0.81 (t, 3H, CH_3), 1.24 (sextet, 2H CH_2), 1.79 (q, 2H, CH_2), 4.17 (t, 2H, CH_2), 6.61 (s, 1H, N-CH_2-N), 7.56 (br s, 2H, 2 CH). ^{13}C NMR (D_2O): δ 12.89 (CH_3), 19.06 (CH_2), 31.17 (CH_2), 50.40 (CH_2), 59.11 (N-CH_2-N), 123.96 (2 CH), Ag-C not observed.

$C_{30}H_{48}N_8Ag_2P_2F_{12}$ (4b). ^{1}H NMR (DMSO-d_6): δ 0.78 (t, 3H, CH_3), 0.98 (sextet, 2H CH_2), 1.67 (q, 2H, CH_2), 4.01 (t, 2H, CH_2), 6.41 (br s, 1H, N-CH_2-N), 7.24 (d, 1H, CH), 7.52 (d, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 13.97 (CH_3), 20.44 (CH_2), 34.33 (CH_2), 52.99 (CH_2), 65.33 (N-CH_2-N), 122.56 (CH), 123.89 (CH), 196.27 (Ag-C). Mz^+ ESI: calcd 883.17, found 880.8. Anal. Calcd for $C_{30}H_{48}N_8Ag_2P_2F_{12}$: C 35.11, H 4.71, N 10.92. Found: C 34.25, H 4.25, N 10.63.

Rh Complexes 5a,b. To the aqueous filtrate containing the appropriate Ag salt (**3a** or **3b**) was added 0.5 molar equiv of $RhCl_3 \cdot 3H_2O$, resulting in the immediate precipitation of brick red powders. The mixtures were stirred at RT for a further 20 min and filtered through a medium frit. The red powders were dried with an aspirator and heated in DMSO at 100 °C for 1 h as the DMSO solution turned a bright orange. Removal of the solvent in vacuo afforded 0.663 g (62.1%) of **5a** and 0.796 g (56.3%) of **5b**. Crystals of **5b** suitable for X-ray analysis were grown by slow evaporation of a concentrated acetonitrile solution.

($C_{16}H_{24}N_8Cl_2Rh$)Cl (5a). ^{1}H NMR (DMSO-d_6): δ 3.39 (s, 3H, CH_3), 6.39 (d, 1H, N-CH_2-N ($J_{H-H} = 12.5$ Hz)), 7.02 (d, 1H, N-CH_2-N ($J_{H-H} = 12.5$ Hz)), 7.44 (d, 1H, CH), 7.70 (d, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 36.50 (CH_3), 61.86 (N-CH_2-N), 122.32 (CH), 123.25 (CH), 169.82 (d, Rh-C, $J_{Rh-C} = 32.1$ Hz). Mz^+ ESI (M − Cl): calcd 526.3, found 525.1.

($C_{30}H_{48}N_8Cl_2Rh$)Cl (5b). ^{1}H NMR (DMSO-d_6): δ 0.72 (t, 3H, CH_3), 1.10 (m, 2H CH_2), 1.51 (m, 1H, CH_2), 1.70 (m, 1H, CH_2) 3.64 (m, 1H, CH_2), 3.88 (m, 1H, CH_2), 6.44 (d, 1H, N-CH_2-N ($J_{H-H} = 12.4$ Hz)), 7.08 (d, 1H, N-CH_2-N($J_{H-H} = 12.4$ Hz)), 7.58 (br s, 1H, CH), 7.75 (br s, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 11.15 (CH_3), 17.45 (CH_2), 28.68 (CH_2), 46.55 (CH_2), 59.77 (N-CH_2-N), 119.03 (CH), 120.56 (CH), 168.05 (d, Rh-C, $J_{Rh-C} = 32.1$ Hz). Mz^+ ESI (M − Cl): calcd 694.5, found 693.4.

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Supporting Information Available: X-ray crystallographic files for **2**, **4a**, **4b**, and **5b** and NMR spectra for **2**, **5a**, and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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