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Synthesis of C_2 -Symmetric Dimeric Re(I) Peptide Complexes

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Abstract

The reactions of $[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ or $\text{Re}(\text{CO})_5\text{Cl}$ with two peptides, glycylglycine or glycylalanine, were investigated. Each reaction produced a unique, well-defined product. Structural elucidation showed the formation of chiral compounds with the formula $[\text{Re}(\text{CO})_3(\text{Gly-Xxx-O})]_2$, Xxx = Gly **1**, Ala **2**.

Each dimer displays C_2 -symmetry and a nearly rectangular shape. The ligands are bound *via* the amine and amide carbonyl at a rhenium center and *via* the pendant carboxylate to the adjacent rhenium center. Both products are fully characterized, via X-ray structure elucidation.

Keywords

Carbonyl ligands; Crystal structures; Dipeptides; Rhenium

Introduction

There is newfound interest in the organometallic chemistry of rhenium as reports of biological applications emerge.^[1–2] The first biological use for organometallic rhenium compounds was as a cold analog for $^{99\text{m}}\text{Tc}$. Technetium-99m is the most commonly used radionuclide in nuclear medicine,^[3] but technetium has no stable nuclides. Development of the Isolink® kit provides clinical access to $^{99\text{m}}\text{Tc}(\text{CO})_3\text{L}_3$ compounds,^[4] which has widened the search for radiopharmaceutical candidates and increased interest in $\text{Re}(\text{CO})_3\text{L}_3$ model compounds. More recently, as rhenium-188 (half-life of 17 hours with $\beta^- = 2.1$ MeV) becomes available carrier-free, and a clinically relevant formulation becomes available for the $^{188}\text{Re}(\text{CO})_3^+$ core,^[5–7] there is interest in theranostic treatments, where a matched pair of $^{99\text{m}}\text{Tc}$ and ^{188}Re compounds would target the same location for diagnostic and therapeutic uses, respectively.^[8] Supplementing these research ideas, d^6 rhenium compounds with fluorescent ligands tested *in vivo* provide yet another application for these compounds.^[9–11]

We have previously published studies on the possible biological relevance of the d^6 chemistry of rhenium. These include crystal structures of the triqua cation,^[12] and new compounds with monodentate,^[13] bidentate ligands^[14–16] or tridentate ligands.^[1,17–19] In addition to creating new molecules and developing aqueous methods of preparing previously reported compounds, we reported on the use of these compounds as models of metal-essential radiopharmaceuticals.^[20] We have also prepared amino acid conjugates via Schiff

base formation of diimines.^[15,21–22] Recently we have looked at reactions of the dipeptide His-His-OH to study the possibilities of using histidine peptide conjugates as the chelating portion of a target-specific radiopharmaceutical. The resulting highly stable compound had a surprising structure with two $\text{Re}(\text{CO})_3^+$ units bound very tightly to the dipeptide. The zwitterionic molecule is highlighted by a deprotonated amide nitrogen. This causes the deprotonated peptide bond unit to span the two metal centers with the carboxamido-nitrogen binding one rhenium center and the adjoining carbonyl oxygen binding the second rhenium center (Scheme 1).^[21] As proteins are biological molecules that rhenium prodrugs will encounter in plasma, it is vital to have a detailed understanding of protein and peptidoreactivity with $\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3^+$. For these reasons, we are extending our study of reactions of biological molecules with $\text{Re}(\text{CO})_3^+$.^[23–25]

Herein we report an extension of our investigations into the reactions of peptides with $\text{Re}(\text{CO})_3$ precursor molecules. In contrast to the linear complex with a 2:1 $\text{Re}(\text{CO})_3$:dipeptide stoichiometry formed by reaction with His-His-OH (Scheme 1), the reactions of the dipeptides Gly-Gly-OH and Gly-L-Ala-OH with $\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3^+$ produced a cyclic dimeric product, $[\text{Re}(\text{CO})_3(\text{Gly-Xxx-O})]_2$, Xxx = Gly **1**, Ala **2** (Scheme 2). We present the preparation, spectroscopic properties, and structural elucidation of these new compounds and discuss their striking geometries.

Results and Discussion

Scheme 2 shows the reaction for the syntheses of compounds **1** and **2**. They were prepared from $\text{Re}(\text{CO})_5\text{Cl}$ or $[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ in either mixed methanol:water or aqueous solution. Yields were modest but repeatable, and clean, white microcrystalline solids resulted for both peptides.

Crystals for structural elucidation were grown by vapor diffusion of water (**1**) or CH_2Cl_2 (**2**) into DMSO. Their structures, shown in Figures 1 and 2 respectively,^[26] reveal that each compound is a C_2 -symmetric cyclic dimer. The amine terminus and amide carbonyl oxygen of one dipeptide binds in a bidentate manner to the first rhenium center while the terminal carboxylate oxygen binds the sixth coordination site of the second rhenium center. The other dipeptide binds in an identical fashion, but in the opposite direction to connect the two metals. Each rhenium ion in the two compounds has a nearly octahedral geometry and displays facially arranged carbonyls. All bond lengths and angles are within the normal range typically observed for rhenium tricarbonyl compounds.

The structures and stoichiometries of **1** and **2** are distinctly different from the dimer resulting from reaction of $\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3^+$ with His-His-OH (Scheme 1); this difference is due to Gly-Gly-OH and Gly-Ala-OH both lacking side groups with donor atoms. Instead, the structures of **1** and **2** are reminiscent of the amino acid conjugates $[\text{Re}(\text{CO})_3(\text{pyca-Xxx-O})]_2$ (Xxx = Gly, Ala; pyca = pyridine-2-carbaldehyde imine) and share C_2 -symmetry.^[22] Like the $[\text{Re}(\text{CO})_3(\text{pyca-Xxx-O})]_2$ compounds, **1** and **2** do not form mononuclear tridentate complexes due to the restriction of motion of the α -carbon adjacent to the amide nitrogen, preventing the carboxylate oxygen from binding to the same rhenium centre as the amine and amide carbonyl oxygen. In contrast, others have shown that using $\text{L} = \text{C}_5\text{H}_4\text{N}-2\text{-CH}_2\text{NHCH}_2\text{X}$ ($\text{X} = \text{CO}_2^-$, CH_2S^- or 2-pyridyl), with an sp^3 -amine nitrogen instead of an sp^2 -amide nitrogen, produces the corresponding tridentate $\text{Re}(\text{CO})_3\text{L}$ complex with two five-member rings that show no ring strain.^[27–29] Despite the presence of halide ions in the reaction solution, the carboxylate ion forms a bridge to the second rhenium center, providing charge balance for the $\text{Re}(\text{I})$ ion. The observed modest yields in forming **1** and **2** are likely due to other reaction pathways available to the distal carboxylate, leading to byproducts that were not isolable.

Each compound forms a nearly rectangular shape as traced by the two rhenium centers and two α -carbons on the amino acids (see Figures 3 and 4). Compound **1** in particular comes close to a true rectangular shape. The Re(1)-C(6) separation is ~ 4.91 Å, while Re(1)-C(6A) is ~ 4.45 Å. The C(6)-Re(1)-C(6A) angle is $\sim 88^\circ$, while Re(1)-C(6)-Re(1A) is $\sim 92^\circ$. C(6A) lies only $\sim 2^\circ$ off the plane created by Re(1), C(6) and Re(1A). Compound **2** adopts a butterfly shape. The Re(1)-C(6) separation is ~ 4.90 Å, while Re(1)-C(6A) is ~ 4.44 Å. The C(6)-Re(1)-C(6A) angle is $\sim 89^\circ$, while Re(1)-C(6)-Re(1A) is $\sim 88^\circ$. C(6A) lies $\sim 28^\circ$ off the plane created by Re(1), C(6) and Re(1A).

The steric interaction in **2** of the methyl groups with contiguous atoms likely prevents formation of a more ideal rectangular shape. More importantly, it also prevents formation of the second diastereomer because of the steric interaction that would result between O(4) and C(7), the amide carbonyl oxygen and side-chain methyl group. Both available stereoisomers and a more symmetric shape are observed for **1** because this steric interaction is absent. The steric constraints that limit dimer formation are likely the reason that other dipeptides (e.g. Ala-Gly-OH, Ala-Ala-OH, His-Gly-OH and Gly-His-OH) did not form isolable products.

Compound **1** crystallizes in the $C2/c$ space group with a DMSO solvent molecule; each enantiomer appears in the unit cell. As Ala-Gly-OH is chiral, **2** is also chiral and crystallizes in the chiral space group $C222/1$. While C_2 symmetry is a common feature of multinuclear $\text{Re}(\text{CO})_3$ complexes with amino acid derivatized ligands, it is worth noting that trimeric structures with proline or dimethylglycine have also been reported. The former compound has a three-fold axis while the latter lacks a symmetry element.^[30]

The simple infrared metal carbonyl stretching pattern observed for **1** and **2** is consistent with each compound having identical pseudo- C_{3v} metal centers. The NMR spectra of these compounds confirm their structural features. The ^1H NMR spectrum of each compound is more complicated than the spectrum of the parent ligand due to diastereotopic methylene hydrogen atoms formed with the creation of the ring structure. The ^{13}C NMR spectrum of each compound corroborates their C_2 symmetry: one signal is reported for each pair of symmetry-related carbons. The ^1H and ^{13}C NMR spectra of **2** each verify that this compound consists of a single diastereomer.

Conclusions

Compounds **1** and **2** are rare examples of organometallic dipeptide compounds, and each shows a C_2 -symmetric dimer structure. Compound **1** has chirality enforced on it due to the chiral metal center; both enantiomers were observed. Compound **2** was prepared as a single diastereomer as steric interactions control the geometry observed in the product. While there are numerous examples of coordination compounds with peptide ligands, the His-His-OH compound in Scheme 1^[21] and the compounds reported here are the only examples of structurally elucidated metal carbonyl complexes with unmodified peptide ligands. Given the variety of chemistry already observed and the potential of $^{188}\text{Re}(\text{CO})_3$ bioconjugates in medicinal applications, we are pursuing further studies in this area.

Experimental Section

X-ray intensity data were measured at 100 K (Bruker KYRO-FLEX) on a Bruker SMART APEX CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube ($\lambda = 0.71073$ Å) operated at 2000 W power. The crystals were mounted on a cryoloop using Paratone N-Exxon oil and placed under a stream of nitrogen at 100 K. The detector was placed at a distance of 5.009 cm from the crystals. The data were corrected for absorption with the SADABS program. The structures were refined using the Bruker SHELXTL

Software Package (Version 6.1), and were solved using direct methods until the final anisotropic full-matrix, least squares refinement of F^2 converged.

Two methods were effective in preparing these compounds. Method A: $\text{Re}(\text{CO})_5\text{Cl}$ (0.150 g, 4.15×10^{-4} mol) and one equivalent of the appropriate dipeptide were added to a round-bottom flask containing 9 mL of methanol and 1 mL of deionized water. The mixture was refluxed for 4 hours, producing a clear solution. Solvent was removed yielding a light-yellow oily liquid. 2 mL of cold water was added and stirred. The water was removed by filtration and the off-white solid was dried. Method B: $[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ (0.150 g, 3.71×10^{-4} mol) and one equivalent of the appropriate dipeptide were added to a round-bottom flask containing 10 mL of deionized water. The mixture was refluxed for one hour and the compound was isolated as described above.

$[\text{Re}(\text{CO})_3(\text{Gly-Gly-O}^-)]_2$ **1**: 14% yield. IR: 3340 (w), 3252, (w), 2017 (s), 1853 (vs), 1627 (m), 1592 (m), 1567 (m) cm^{-1} . Anal. Calc. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_{12}\text{Re}_2 \cdot (\text{CH}_3\text{OH})$: C, 21.58; H, 2.17; N, 6.71. Found: C, 21.67; H, 2.09; N, 6.71. ^1H NMR (d_6 -DMSO): δ 9.39 (dd, $J = 9.6$, 2.8 Hz, 1H, CONH), 5.31 (dt, $J = 10.8$, 6.4 Hz, 1H, NH_2), 4.41 (dt, $J = 10.8$, 6.4 Hz, 1H, NH_2), 4.00 (dd, $J = 16.8$, 9.6 Hz, 1H, CH_2), 3.66 (t, $J = 6.4$, 6.4 Hz, 2H, CH_2), 3.39 (dd, $J = 16.8$, 3.2 Hz, 1H, CH_2). ^{13}C NMR (d_6 -DMSO): δ 198.2, 197.5, 197.3, 180.9, 169.6, 43.9, 42.8.

$[\text{Re}(\text{CO})_3(\text{Gly-Ala-O}^-)]_2$ **2**: 20% yield. IR: 3336 (w), 3252, (w), 2022 (s), 1908 (s), 1856 (s), 1577 (s) cm^{-1} . Anal. Calc. for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_{12}\text{Re}_2 \cdot 6\text{H}_2\text{O}$: C, 20.46; H, 3.22; N, 5.96. Found: C, 20.41; H, 2.94; N, 5.99. ^1H NMR (d_6 -DMSO): δ 9.33 (d, $J = 8.8$ Hz, 1H, CONH), 5.34 (m, 1H, NH_2), 4.39 (m, 1H, NH_2), 4.18 (m, 1H, CHCH_3), 3.64–3.25 (br m, 2H, NH_2CH_2), 1.24 (d, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (d_6 -DMSO): δ 198.2, 197.6, 197.4, 179.9, 172.5, 49.5, 43.9, 18.5.

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26. All crystallographic data was collected at 100 K (Bruker KRYOFLEX) with a Bruker SMART APEX CCD-based X-ray diffractometer (Mo-K α radiation, $\lambda = 0.71073$ Å). The structures were refined by using the Bruker SHELXTL Software Package (Version 6.10) and were solved until the final anisotropic full-matrix, least-squares refinement of R^2 converged. Crystallographic summary for **1**: C₁₈H₂₆N₄O₁₄Re₂S₂; $M_r = 958.95$; colorless block; $0.34 \times 0.29 \times 0.18$ mm; monoclinic, $C2/c$, $Z = 8$; $a = 13.596(3)$ Å, $b = 9.696(2)$ Å, $c = 25.262(8)$ Å, $\beta = 101.952(5)^\circ$; $V = 3258.0(18)$ Å³, $\rho = 1.955$ Mg m⁻³. A total of 11300 reflections were collected (3347 independent reflections). $R(000) = 1824$, $R1 = 0.0734$, $wR2 = 0.1732$ [for 3158 I_o , $I_o > 2\sigma(I_o)$]. Crystallographic summary for **2**: C₁₆H₁₈N₄O₁₂Re₂; $M_r = 830.74$; colorless block; $0.36 \times 0.32 \times 0.30$ mm; orthorhombic, $C222(1)$, $Z = 4$; $a = 9.9665(11)$ Å, $b = 15.1909(17)$ Å, $c = 19.094(16)$ Å; $V = 2890.8(6)$ Å³, $\rho = 1.904$ Mg m⁻³. A total of 11277 reflections were collected (2959 independent reflections). $R(000) = 1552$, $R1 = 0.0208$, $wR2 = 0.0519$ [for 2933 I_o , $I_o > 2\sigma(I_o)$]. CCDC 910881–910882 contain the supplementary crystallographic data for **1** and **2**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Figure 1.
Structure of **1** with 35% thermal ellipsoids. Solvent DMSO and hydrogen atoms have been omitted for clarity.

Figure 2.
Structure of **2** with 35% thermal ellipsoids. Hydrogen atoms have been omitted for clarity.

Figure 3.
Compound **1** viewed from above to highlight its rectangular shape.

Figure 4.
Compound **2** viewed from above to highlight its rectangular shape.

Scheme 1.

Preparation and connectivity of the compound formed by reaction of $\text{Re}(\text{CO})_3^+$ and His-His-OH.

Scheme 2.

General reaction scheme for preparation of **1** and **2**.