



Complexes formed from reactions of $\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3^+$ with amines used for biological buffering

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ABSTRACT

Aqueous reactions of $[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ with tris, tricine and 1,3-diamino-2-propanol, three polyfunctional amine ligands commonly used to buffer protein solutions, led to three new metal complexes. $\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{OH}, \text{O}^- \text{-tris}) \cdot 3\text{H}_2\text{O}$ (**1** · 3H₂O), $[\text{HNET}_3][\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{O}^-, \text{CO}_2^- \text{-tricine})] \cdot [\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{OH}, \text{CO}_2^- \text{-tricine})] \cdot 2\text{H}_2\text{O}$ (**2** · 2H₂O), and $[\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{O}^-, \text{NH}_2 \text{-diaminopropanol})] \cdot [\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{OH}, \text{NH}_2 \text{-diaminopropanol})][\text{Br}]$ (**3**) were isolated and characterized spectroscopically and by X-ray crystallography. Each of the three compounds displays intermolecular alcohol-alkoxide OH...O bonding. Ramifications of this reactivity as it relates to buffering agents competing as chelating agents when proteins bind $\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3^+$ is discussed.

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1. Introduction

For several years, $M(\text{CO})_3^+$ ($M = {}^{99m}\text{Tc}$, Re) has been studied as a potential core for radiopharmaceuticals [1–3]. Many small molecule complexes have been prepared and closely studied to explore that possibility [4]. Among the new compounds reported are many with amine, alcohol and carboxylic acid donor groups [5–9]. However, information about reactivity toward proteins is also important as reactions between rhenium prodrugs or drug model complexes and proteins can be crucial to the biological processing of Tc/Re based imaging agents, since proteins, rather than nucleotides or single amino acids, would be encountered in plasma. As a first attempt to understand these interactions, we recently reported the X-ray crystal structure of the lysozyme– $\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3^+$ adduct [10,11]. Protein solutions are typically prepared containing stabilizing agents such as various small molecules or salts that frequently contain amine, alcohol and carboxylic acid functional groups known to bind to $\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3^+$. As a result, it is important to know if the rhenium cation forms unwanted bonding interactions with these small compounds. To investigate these interactions, we have explored reactions of $[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ with tris, tricine and 1,3-diamino-2-

propanol, three polyfunctional compounds commonly used for controlling protein solution pH.

Exposure of the $\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3^+$ cation to each of these three buffers results in the formation of new $\text{Re}^I(\text{CO})_3$ coordination complexes. Each compound binds as a tridentate ligand; three carbonyl ligands bound in a facial geometry complete the coordination sphere. The product formed with tris (tris(hydroxymethyl)aminomethane) is the simple complex, $\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{OH}, \text{O}^- \text{-tris}) \cdot 3\text{H}_2\text{O}$ (**1** · 3H₂O). Reaction with tricine or 1,3-diamino-2-propanol each yields more complex salts which can be formally represented as $[\text{HNET}_3][\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{O}^-, \text{CO}_2^- \text{-tricine})] \cdot [\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{OH}, \text{CO}_2^- \text{-tricine})] \cdot 2\text{H}_2\text{O}$ (**2** · 2H₂O), and $[\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{O}^-, \text{NH}_2 \text{-diaminopropanol})] \cdot [\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2, \text{OH}, \text{NH}_2 \text{-diaminopropanol})][\text{Br}]$ (**3**) (Scheme 1). Herein, we report the synthesis, characterization and structural elucidation of compounds **1–3**. In all cases, these common buffer reagents form tripodal complexes with $\text{Re}^I(\text{CO})_3$, and may interfere in investigations into the biological chemistry of labile $\text{Re}^I(\text{CO})_3$ compounds.

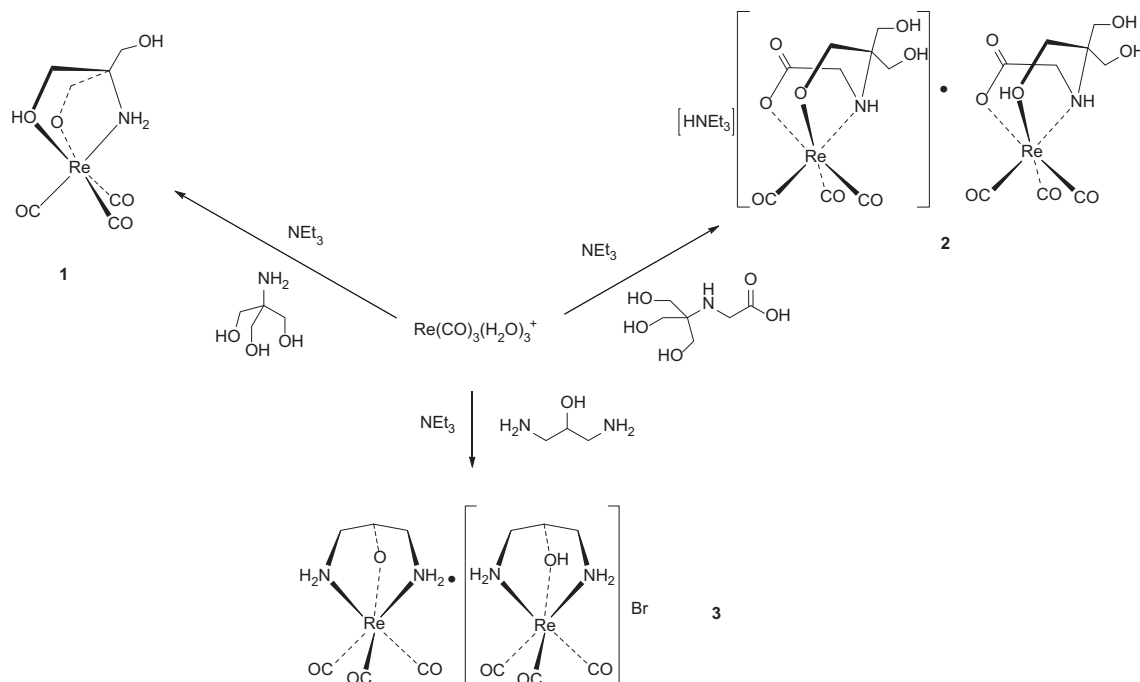
2. Experimental

2.1. Materials and methods

All reagents were purchased from commercial sources and used as received. Solution NMR spectroscopy was performed on a Varian

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Scheme 1. General reaction scheme for synthesis of compounds **1–3**.

400 MHz NMR spectrometer. IR spectra were recorded on a Nicolet Series II Magna-IR 750 spectrometer. Elemental analyses were carried out at the School of Chemical Sciences Microanalytical Laboratory at the University of Illinois at Urbana-Champaign or Atlantic Microlab of Norcross, GA 30091. The synthesis of $[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ was carried out as previously described [12].

2.2. $[\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2,\text{OH},\text{O}^-)\text{-tris}(\text{hydroxymethyl})\text{aminomethane}]\text{Br}$ (**1**)

$[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ (0.150 g, 0.371 mmol), tris(hydroxymethyl)aminomethane (0.0539 g, 0.0445 mmol), and 3 equivalents of triethylamine (0.113 g, 1.12 mmol) were heated at reflux in 10 mL of deionized water for 0.5 h. The solvent was removed, and after washing with ether, the product was isolated in 90% yield as a white solid. Crystals suitable for X-ray diffraction were grown by slow evaporation of a deionized water solution of **1**. IR (cm^{-1}): 3613 (m) (ν_{OH}); 3322 (m) (ν_{NH}); 2021 (s), 1848 (vs, b) ($\nu_{\text{C}=\text{O}}$) cm^{-1} . Anal. Calc. for $\text{C}_7\text{H}_{16}\text{NO}_9\text{Re}$; C, 18.92; H 3.63; N 3.15%. Found: C, 19.06; H, 3.17; N, 3.63%.

2.3. $[\text{HNEt}_3][\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2,\text{O}^-, \text{CO}_2^-)\text{-tricine}]\cdot[\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2,\text{OH}, \text{CO}_2^-)\text{-tricine}]\cdot 2\text{H}_2\text{O}$ (**2**)

$[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ (0.150 g, 0.371 mmol), tricine (0.0798 g, 0.0445 mmol), and 3 equivalents of triethylamine (0.113 g, 1.12 mmol) were heated at reflux in 10 mL of deionized water for 0.5 h. The solvent was removed, yielding a clear gel. After washing with acetone, the product was isolated as a white solid in 88% yield. Crystals suitable for X-ray diffraction were grown by vapor diffusion of chloroform into a DMSO solution of **2**. IR (cm^{-1}): 3374 (m) (ν_{NH}); 2021 (s), 1883 (s, sh), 1851 (vs) ($\nu_{\text{C}=\text{O}}$); 1627 (s) ($\nu_{\text{C}=\text{O}}$) cm^{-1} . Anal. Calc. for $\text{C}_{24}\text{H}_{43}\text{N}_3\text{O}_{19}\text{Re}_2$; C, 27.88; H 4.19; N 4.06%. Found: C, 28.52; H, 4.29; N, 4.33%. ^1H NMR (d_6 -DMSO): δ 6.04 (br, 1H, NH), 4.98 (br, 1H, OH), 3.70 (m, 2H, CH_2), 3.55 (m, 2H, CH_2), 3.43 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 3.03 (q, 3H, NCH_2), 1.12 (t, 4.5H, CH_3) ppm. ^{13}C NMR (d_6 -DMSO): δ 198.9, 198.7, 197.7, 179.8, 66.0, 63.4, 60.2, 57.0, 49.2, 45.2, 8.9 ppm.

2.4. $[\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2,\text{O}^-, \text{NH}_2)\text{-diaminopropanol}]\cdot[\text{Re}(\text{CO})_3(\kappa^3\text{-NH}_2,\text{OH}, \text{NH}_2)\text{-diaminopropanol}]\text{Br}$ (**3**)

$[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ (0.200 g, 0.495 mmol), 1,3-diamino-2-propanol (0.0535 g, 0.594 mmol), and 3 equivalents of triethylamine (0.149 g, 1.48 mmol) were heated at reflux in 10 mL of deionized water for 0.5 h. The solvent was removed to yield a slightly pink solid. After washing with water, the product was isolated in 85% yield. Crystals suitable for X-ray diffraction were grown by slow evaporation from a distilled water solution of **3**. Anal. Calc. for $\text{C}_{12}\text{H}_{19}\text{BrN}_4\text{O}_8\text{Re}_2$; C, 18.02; H 2.39; N 7.01%. Found: C, 18.12; H, 2.33; N, 7.01%. IR (cm^{-1}): 3357 (m), 3315 (m) (ν_{NH}); 2011 (s), 1843 (vs, b) ($\nu_{\text{C}=\text{O}}$). ^1H NMR (d_6 -DMSO): δ 8.14 (br s, 4H, NH_2), 6.03 (br s, 0.5 H, OH), 3.99 (m, 1H, CH), 2.97 (dd, 13 Hz, 4 Hz, 2 H CH_2), 2.95 (dd, 13 Hz, 8 Hz, 2H, CH_2) ppm. ^{13}C NMR (d_6 -DMSO): δ 197.7, 75.5, 43.6 ppm.

2.5. X-ray crystallography

Data was collected at 100 K (Bruker KRYOFLEX) on a Bruker SMART APEX CCD-based X-ray diffractometer equipped with a Mo-target X-ray tube ($\lambda = 0.71073 \text{ \AA}$) operated at 2000 W power. 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 [13]. Crystal data and structure refinement parameters are shown in Table 1. Key distances and angles for compounds **1–3** are listed in Table 2.

3. Results and discussion

3.1. Syntheses

Complexes **1–3** were prepared by reflux of an aqueous solution of $[\text{Re}(\text{CO})_3(\text{H}_2\text{O})_3]\text{Br}$ with a stoichiometric amount of the appropriate ligand and a slight excess of NEt_3 . NEt_3 was used to assist with proton removal and to supply an appropriate counterion if needed. The products were retrieved as solids in good yield following washing to remove excess amine and ammonium ions.

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