Carbon Monoxide: Silent Killer or Therapeutic Ligand?

Christopher Letko Literature Seminar November 27, 2007

The leading cause of fatal poisoning in the United States can be attributed to exposure to lethal concentrations (about 1950 ppm) of carbon monoxide (CO).[1] CO has been shown to poison humans by attacking the active sites of hemoglobin, cytochrome oxidase, and myoglobin.[2] The greater affinity for CO by either of these metal hemes over O_2 (30 times greater towards myoglobin)[3] leads to formation of a strong metal-CO bond, preventing the protein from performing its regular functions. However, recent discoveries have shown that CO has biological functions in addition to its known toxicity towards humans. In fact, humans produce CO internally at a rate of 20 μmol h^{-1}.[4] Generation of CO in the human body through heme degradation to biliverdin catalyzed by heme oxygenase was discovered previously.[5] CO has recently been found to act as a signaling agent that has many beneficial effects, including vasodilation, anti-inflammation, and suppression of organ graft rejection.[6]

New therapeutic methods are being devised that take advantage of the biological functions of CO. Due to the low solubility of CO in water (0.00276 g L^{-1} at 25 °C),[7] molecules that contain CO must be designed to transport CO in physiological media. Two promising areas of therapeutic CO research are carbon monoxide releasing molecules (CO-RMs) and $[Tc(CO)_3]^+$ imaging agents. Both approaches incorporate CO as a part of a larger host molecule, but differ greatly in how the CO ligands are used. CO-RMs designed to deliver CO to a specified target are carbonyl complexes exhibiting labile carbon monoxide ligands. On the other hand, $[Tc(CO)_3]^+$ imaging agents rely on the chemical inertness of the Tc-CO bond to transport the metal to its destination for radio imaging.

Initial study of CO-RMs began with investigations of the homoleptic carbonyls iron pentacarbonyl and dimanganese decacarbonyl.[8] The binding of CO to myoglobin (Mb) was used to measure the total amount of CO liberated by the CO-RM, due to the high affinity of Mb for CO. Photodissociation of the metal-CO bond via a UV-light source liberated CO (Figure 1). This proof-of-concept experiment led to the exploration of CO-RMs that could be used *in vivo*.

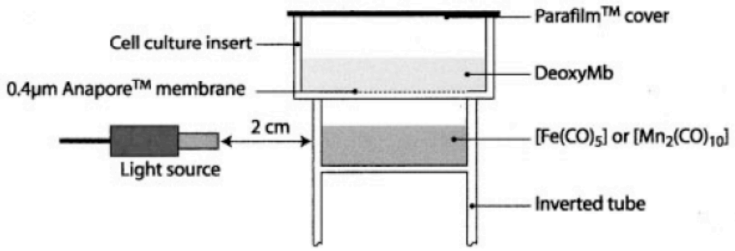

Figure 1. Experimental set-up for CO-RM photolysis.

Success with the homoleptic metal carbonyls led to the study of CO-RMs that could be used under physiological conditions. Important properties of CO-RMs include the rate of CO dissociation, the molecular structure at physiological pH, and the toxicity of the byproducts formed after liberation of CO. CO dissociation has been correlated with the electron deficiency of the metal and can be monitored by IR spectroscopy. Mann and coworkers have found that the structure of $[Ru(CO)_3Cl(glycinate)]$ varies significantly with pH, raising questions about the identity of the active species under physiological conditions (Figure 2a).[9] Structural changes made to the active species results in byproducts that are potentially harmful. Fairlamb has sought to avoid creating toxic byproducts by incorporating 2-pyrone as a ligand (Figure 2b).[10] The degradation pathway of 2-pyrone in the human body is known to form non-toxic products.[11]

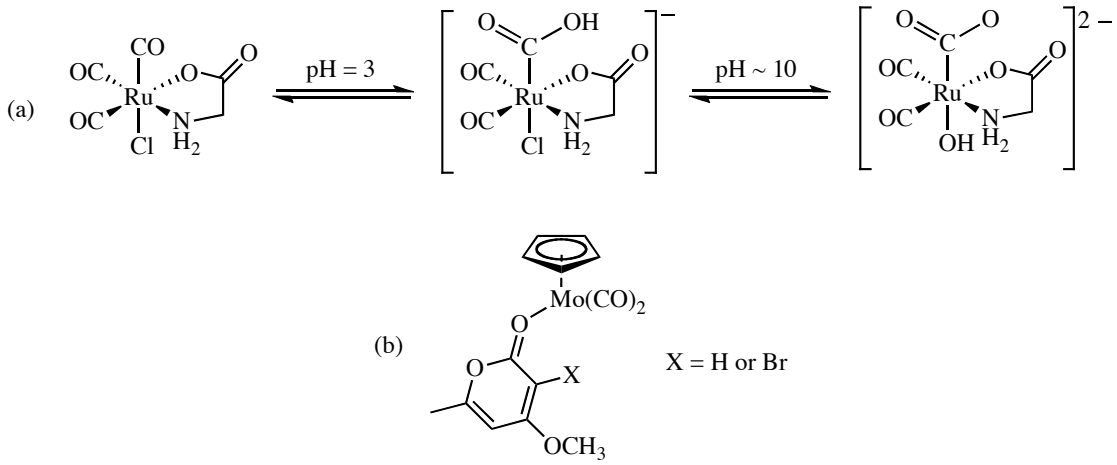

Figure 2. (a) Structural dependence of $RuCl(CO)_3$(glycinate) on pH. (b) η^1-2-Pyrone CO-RM.

A second biomodecial application of CO is its use a ligand in radio imaging agents. About 80% of radiopharmaceuticals contain ^{99m}Tc, which has a half-life of 6 h that allows medical personnel enough time to use this nuclide in a clinical setting.[12] An ideal Tc radiopharmaceutical platform incorporates an inert ligand set and enough open coordination sites to allow the binding of a biomolecule having recognition properties. The molecular weight of the inert ligands is important, because drastic changes in the diffusion kinetics of a biological signaling process could disturb bodily functions. The biomolecule can either be directly coordinated to the Tc center or can be a pendant substituent of a ligand.[13]

The $[Tc(CO)_3]^+$ fragment is shown to be a promising candidate platform for clinical use, but the use of gaseous CO to form the fragment was viewed as impractical. Alberto and coworkers have shown that addition of boranocarbonate ($K_2[H_3BCO_2]$) to pertechnitate in water affords $[Tc(OH_2)_3(CO)_3]^+$ in yields greater than 98 %.[14] The lability of the water ligands of $[Tc(OH_2)_3(CO)_3]^+$ allows for facile derivatization of the precursor. As the mechanism of signaling by CO, further advancements should lead to the design of effective carbonyl therapeutics with selective targets.

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