

Design, synthesis, characterization and releasing properties of carbon monoxide releasing molecules

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Carbon monoxide (CO) is known as fundamental gaseous neurotransmitter in humans and there is a growing interest in its pharmacological or medical applications. CO is acknowledged to be involved in several cellular, physiological and pathological pathways, such as endothelial injuries, vasodilatation, inflammation. Organometallic carbonyl complexes are best suited to play the role of CO carriers. Targeting of the molecules to local injuries can thus be achieved by modifying the coordination sphere of the metal ion via a proper selection of ligands or by appending CO releasing molecules (CORMs) to biomolecules. Manganese-based CORMs, for example, are activated by exposure to UV-light and are known as photoCORMs, whereas rhenium-based CORMs are known to deliver the gas moiety spontaneously in physiological media.

This thesis pivots around 4 projects directed towards the characterization, the development, as well as investigations on CO delivery properties, stability and cytotoxicity of novel potential CO releasing molecules.

First project was meant as a screening of potential ancillary ligands envisaged in substitution reactions with the starting cis -[Re^{III}(CO)₂Br₄]⁻ and cis -[Re^{II}(CO)₂Br₄]²⁻ complexes. The fundamental aim was the synthesis of novel CORMs complexes bearing ligands as a basis for the attachment of specific biomolecules in order to target specific diseased tissues. Rapidly, we found that isocyanides ligands presented convenient and straightforward synthesis with interesting properties. Based on those considerations, the same ligands were used in reaction with cis -[Re^{III}(CO)₂Br₄]⁻, cis -[Re^{II}(CO)₂Br₄]²⁻ and Mn(CO)₅Br. Hence, all the resulting compounds were fully characterized and the stability in organic solvent as well as the CO release properties were investigated.

Then, we showed that, in order to reduce the energy required for the photoactivation, the systematic substitution of the 2,2'-azopyridine ligand with weak donating to strong deactivating substituents lead to the progressive bathochromic shift of the MLCT absorption band maximum from 625 nm to 693 nm in a series carbonyl Mn(I) complexes. Exposure of solutions of these 5 complexes to low-power visible light (≥ 625 nm, red light) resulted in CO photorelease. Furthermore, the MLCT band of complexes with strong EWG tails beyond the visible region of the spectrum in the near infrared and in one case photodecomposition could also be promoted at 810 nm.

In the next chapter, in order to attempt a predictive correlation between the cytotoxicity and the structure of CORMs, we report the effects on mouse cancer cells of 18 different complexes. Three metallic carbonyl cores, Mn(I), Re(I) *bis*-CO, Re(I) *tris*-CO, with two series of three similar ligands (isocyanide and bipyrimidine-type) were tested. Seven crystal structures were determined by X-ray diffraction. The kinetics of the degradation of Mn(I) and Re(I) *bis*-CO complexes as their CO delivery capabilities were also investigated.

The last of the four projects raised when we noticed that the MLCT transition absorption band exhibited a linear red-shift from the tris-carbonyl Re(I) compounds to the Mn(I) analogs. Starting with this consideration, we screened the corresponding literature in order to find other *fac*-[M(CO)₃BrL], with M = Mn or Re, and with L as bidentate pyridine and/or imine derivatives. Thus, 7 Re(I) based complexes were synthesized for comparison with the existing Mn(I) analogs and finally a series of 24 pairs was employed to tentatively draw a first trend to predict the MLCT position of specific *fac*-[M(CO)₃BrL] species with Mn or Re as metallic center.

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