



Trimethylamine N-oxide Promoted Decarbonylation Reactions of Molybdenum and Tungsten Hexacarbonyls with Dimethylglyoxime

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ABSTRACT

Decarbonylation of Mo and W hexacarbonyls in the presence of dimethylglyoxime was carried out under the control of trimethylamine N-oxide (TMNO). The two DMG substituted carbonyl complexes were prepared in a one pot synthesis using manipulated Schlenk techniques under dinitrogen in tetrahydrofuran. The Mo complex system was successfully carried out by stirring the mixture of the molybdenum hexacarbonyl and DMG in tetrahydrofuran at room temperature for 18hrs. A similar procedure afforded the starting ligand material for the W complex analogue. However, further refluxing for 6 h gave the desired W complex. The complexes were characterized using ¹H NMR, IR, and CHN analyses. Results showed that the reactions produced analytically pure, mono-product dicarbonyl species; Mo(CO)₂(DMG)₂ **I** and W(CO)₂(DMG)₂ **II** where two DMG moieties were coordinated to the central metal atom through one N and O atoms respectively of each of the oxime groups.

Keywords: Bioorganometallic, Metal carbonyl, CO-RMs, Decarbonylation, Trimethylamine N-oxide

INTRODUCTION

Metal ions and metal containing compounds are believed to be toxic *in vivo* because of their perceived interaction with biological substances, hence organometallic compounds are rarely considered as pharmaceutical agents (Gasser and Metzler-Nolte, 2012). Generally, the development of metallodrugs have for a long time been hampered by their perceived undesired interactions with DNA and other biomolecules (Gasser and Metzler-Nolte, 2012). However, the discovery of the cancer drug, Cisplatin changed the fate of classical coordination compounds but bioorganometallic molecules continue to suffer more due to the paradigm that ‘organometallics are unstable in air and water’ (Hartinger & Dyson, 2009).

Recent research findings, in several reviews; have dealt comprehensively with founding principles and exciting medicinal applications (Jaouen, 2006, Jaouen and Salmain, 2015, Jaouen and Metzler-Nolte, 2010), challenges and prospects in exploring organometallics as drug candidate (Jaouen and Dyson, 2007, Metzler-Nolte, 2007) as well as their roles in several novel pharmaceutical screenings (Simonneaux, 2006, Fish and Jaouen, 2003). All of which have shown that certain bioorganometallic compounds are stable in air and water and in some cases metals as well as their particular complexes have a diversity of chemical properties and hence ‘the notion that they should

all come down to one and the same cellular target; DNA seems most unlikely and organometallic compounds do play vital roles in drug design and discovery (Gasser and Metzler-Nolte, 2012).

Preceding the period of the teaching paradigms that organometallics are unstable in air and water, they have played vital roles in biology. Some organometallic compounds existed naturally as biomolecules, these include the cobalamines; vitamin B₁₂ and its derivatives (Gibaud and Jaouen, 2010), the hydrogenase family (McGlynn, *et al.*, 2009) which catalyzes the useful process of the reversible conversion of dihydrogen into protons and electrons in biological system.

Despite the issue of toxicity some organometallics were used as drugs, the most popular being Paul Ehrlich’s Salversan and its analogue, Neo-Salversan. They were the only remedy for syphilis at a time when syphilis ravaged like AIDS did at the present time (Gibaud and Jaouen, 2010). For a very long time melasoprol, another organometallic drug remained the first-line treatment for patients with *Trypanosoma brucei gambiense* trypanosomiasis and is still used in African countries even though it is toxic and treatment result in the development of an extremely severe reactive arsenic encephalopathy (RAE). The reality is; in the face of this unacceptable toxicity melasoprol will be in use as it is unlikely that any new drug will replace it anytime soon (Gasser and Metzler-Nolte, 2012, Gibaud and Jaouen, 2010)

One particular class of organometallics that have caught the fancy of the Bioorganometallic Chemist is transition metal carbonyls. Appropriately substituted metal carbonyls have been recognized as a potential drug candidate due to its ability to slowly and systematically release carbon monoxide (CO) molecule in biological system, making it arguably the best class of the so called CO-releasing molecules (CO-RMs) (Romao, *et al.*, 2012)

There is Preclinical evidence that CO administration in animals have beneficial effects in cardiovascular diseases, sepsis, shock, cancer, acute lung, liver and kidney injury and etcetera (Nakatsu, *et al.*, 2002, Abraham, *et al.*, 2002, Wang, 2004). The technology for production and delivery (for inhalation) of pharmaceutical grade CO is quite limited at the moment and only available in highly specialized hospitals. CO ingestion is obviously challenging and can be carried out as pro drug and as CO-releasing molecules (CO-RMs), with CO-RMs being the most effective. Five classes of CO-RMs have been identified and of these, appropriately substituted transition metal carbonyls stand out as the most effective means of safe CO delivery to specific sites in biological systems (Romao, *et al.*, 2012).

For a full medicinal exploitation of this class of compounds a detailed understanding of their structural chemistry is required. Here we set out to synthesize and characterise two DMG substituted Mo and W carbonyl complexes.

MATERIALS AND METHOD

Materials

Molybdenum and tungsten hexacarbonyls, trimethylamine N-oxide dehydrate (TMNO), dimethylglyoxime (DMG) and tetrahydrofuran (THF) were purchased from Sigma Aldrich.

Tetrahydrofuran (THF) was purified prior to use according to the method described in literature (Armarego and Chai, 2003). All other solvents were AR grade from Sigma Aldrich and were used without further purification.

METHODS

All reactions involving metal carbonyls were performed under pure dry nitrogen gas using manipulated Schlenk techniques. Solvents were of reagent grade and purified according to standard methods. Infrared spectra were obtained using SHIMADZU Fourier transform infrared spectrometer using KBr disc pellets technique. ¹H NMR and Microanalysis were performed by Medac analytical and chemical consultancy services, UK, using Bruker Avance III HD 500 spectrometer and Thermo Flash 1112 elemental analyser respectively.

Purification of Tetrahydrofuran

The tetrahydrofuran (THF) tested negative for peroxide when tested with cobalt chloride paper. The solvent was however passed through a column of activated silica gel. The silica gel was predried in an oven at 100° C for 24 hours and thereafter allowed to cool to room temperature in a desiccator before use. The solvent was then dried by passing it over a column of the desiccant inside the glove box (Armarego and Chai, 2003).

PREPARATION OF SUBSTITUTED COMPLEXES

Preparation of [Mo(CO)₂(DMG)₂] (I)

The preparation of the complexes by decarbonylation of metal hexacarbonyls using TMNO as decarbonylating agent follow the method described in literature (Hor and Siti, 1988) with minor modifications

In a one pot synthesis, TMNO.2H₂O (0.339 g, 3.06 mmol), Mo(CO)₆ (0.792 g, 3.0 mmol), and DMG (0.348 g, 3.0 mmol) were weighed and dissolved in 20 mL THF in a flask equipped with a magnetic stirrer. The mixture was vigorously stirred under N₂. An initial light yellow solution changed to a red suspension after a few minutes. The stirring was continued for 24 hours at room temperature. The mixture was then reduced to very low volume immediately with rotary evaporator, washed with minimal quantity of CH₂Cl₂/n-hexane (1:1) and left to crystallize. The brown crystals were washed with CH₂Cl₂/n-hexane under suction (Hor and Siti, 1988). (Yield 56%)

Preparation of [W(CO)₂(DMG)₂] (II)

TMNO.2H₂O (0.339 g, 3.06 mmol), W(CO)₆ (1.056 g, 3.0 mmol), and DMG (0.348 g, 3.0 mmol) were weighed and dissolved in 20 mL THF in a flask equipped with a magnetic stirrer. The mixture was vigorously stirred under N₂. An initial light yellow solution changed to a red suspension after a few minutes. The stirring was continued for 24 hours at room temperature and further refluxed for six hours. The mixture was then reduced to low volume immediately with rotary evaporator, washed with minimal quantity of CH₂Cl₂/n-hexane (1:1) the mixture which turned yellow was left to crystallize. The yellow crystals (Yield 63%) were washed with CH₂Cl₂/n-hexane under suction (Hor and Siti, 1988).

RESULTS AND DISCUSSION

The DMG Substituted Carbonyl Complexes

The reactions of molybdenum and tungsten hexacarbonyl with dimethylglyoxime under nitrogen atmosphere in the presence of trimethylamine N-oxide yielded the dicarbonyl complexes as illustrated in scheme 1.

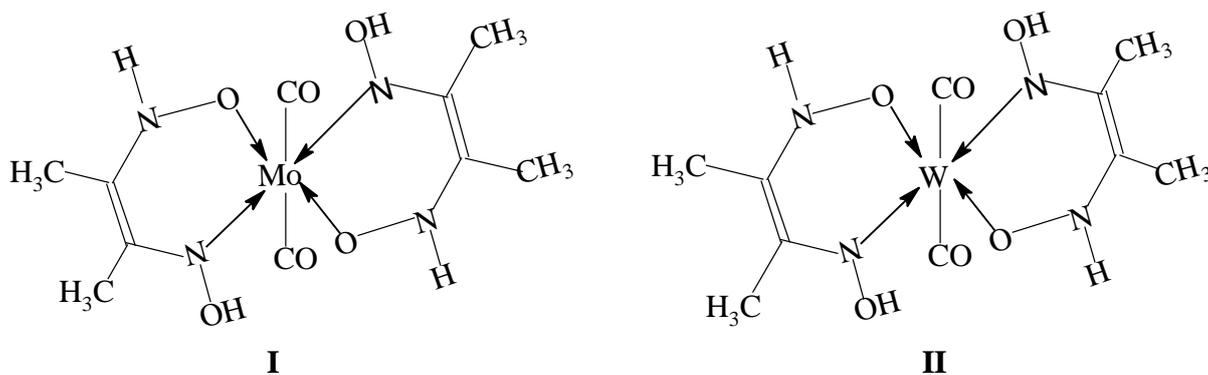


Fig 1: the proposed structure of the substituted complexes, $\text{Mo}(\text{CO})_2(\text{DMG})_2$ I and $\text{W}(\text{CO})_2(\text{DMG})_2$ II

In the ^1H NMR spectra, the resonance around 2.6 in the two complexes are assigned to the 6 H of the two equivalent allylic CH_3 groups on the dimethylglyoxime ligand, the singlets at 3.4 and 11.3 are assigned to the proton of NH and OH respectively which are consistent with NH of aryl amines and OH of oxime.

CONCLUSION

The successful decarbonylation of molybdenum and tungsten hexacarbonyls in the presence of DMG promoted by trimethylamine N-oxide is novel. Previous attempts via thermal and photolytic pathways (Ramadan, *et al.*, 1997, Ramadan, 1998) in addition to the desired product gave some undesired products and hence the cumbersome process of product separation and purification. In this method the products were definite and analytically pure not requiring rigorous separation and purification processes.

The resulting complexes with two CO ligands of decreased bond strength promises to be good candidates for CO release studies in biological system with the use of appropriate CO release activating agent, thus offering some hope for their use as CO-releasing molecules. The possible generation of a small CO molecule and other biocompatible substrates by these compounds serves as encouragement for future studies using fragment based drug approach in screening these molecules as Pharmaceutical agents.

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