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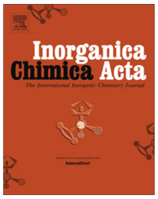

New photo-CORMs: Deeply-coloured biocompatible rhenium complexes for the controlled release of carbon monoxide

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ABSTRACT

Air- and water-stable rhenium carbonyl complexes are investigated as CO-carriers for studying the light-dependent release of small amounts of carbon monoxide under physiological conditions. The reported very low quantum yields are in a suitable range for studying potential applications as photochemical CO-releasing molecules (Photo-CORMs) without rapidly reaching cytotoxic levels of carbon monoxide. Preliminary results on bio-compatibility and selective uptake of the compounds into human colon carcinoma cells (Caco-2 cell line) are described.

1. Introduction

Carbon monoxide usually is considered to be highly toxic to humans, due to its fatal function as a respiratory inhibitor. Nevertheless, small quantities of this gaseous molecule are essential for a healthy life. As a result of enzymatic heme oxidation, a significant amount of gaseous CO is generated naturally in the human body where it acts as a small molecular messenger and plays an important role in regulating different cell functions. CO gas is known to dilate blood vessels and to induce beneficial anti-inflammatory, neuroprotective and anti-apoptotic effects [1]. Synthetic CO-releasing molecules (CORMs) are therefore widely used to explore the therapeutic potential of future carbon monoxide based drugs including applications in wound healing, organ transplantation and cardiovascular protection.

An interesting approach to control the release of small amounts of carbon monoxide under physiological conditions is to develop biocompatible precursor compounds that can be photochemically activated with visible light as an external signal (Photo-CORMs) [2,3]. Here we describe the investigation of air- and water-stable rhenium carbonyl complexes that can be applied as non-cytotoxic CO-carriers for triggering the release of carbon monoxide under physiological conditions. Quantum yields for photochemical CO-release and preliminary studies on the incorporation of the metal complexes into cells of the human colon adeno-carcinoma cell line Caco-2 are reported.

2. Results and discussion

The intensely red-brown coloured organometallic compounds **1**–**3** (Fig. 1) of the type *fac*-Re(1,2-diimine)$(CO)_3X$ with $X = Cl$ selected for the present study have recently been synthesized and structurally characterized in our group [4]. In the solid state and in solution under ambient conditions, these chloro-tricarbonyl rhenium complexes display an excellent stability with no indication of decomposition or loss of CO. When exposed to light, however, the compounds are gradually transformed in a photochemical reaction sequence leading to permanent spectral changes shown here for the neutral complex **2** (Fig. 2). Irradiated solutions of **1** and **3** display a very similar behaviour (ESI[†]). Closer analysis of the light-induced spectral variations indicates a loss of the isosbestic

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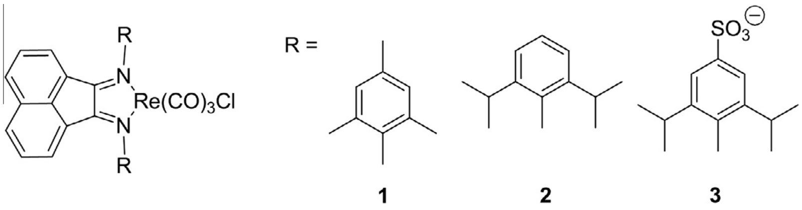

Fig. 1. Structures of the investigated rhenium(I)-complexes.

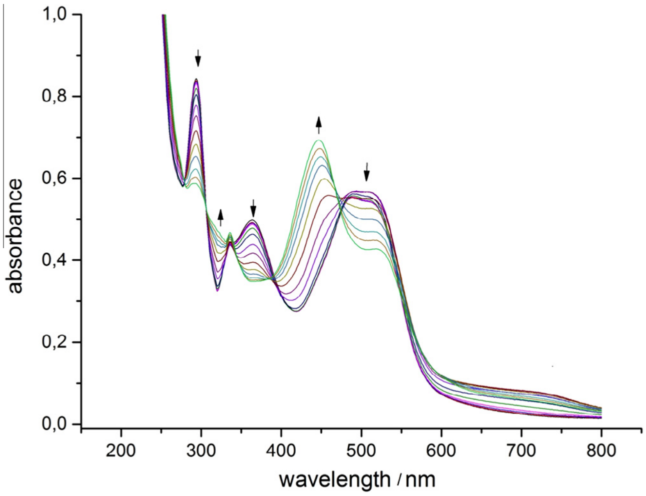

Fig. 2. Absorption spectral changes during irradiation of the rhenium carbonyl complex **2** in acetonitrile solution (298 K, 1 cm cell, $c = 8.7 \times 10^{-5}$ M, $t = 0$–2 h exposure to a 150 W Xe-lamp equipped with a water filter).

points in the visible spectral region, which is consistent with the occurrence of a stepwise conversion.

The quantum yields for this UV-light dependent photolysis of the rhenium complexes are rather low (<1%). Values of $\varphi(280\,\text{nm}) = 2.9 \times 10^{-3}$, 4.8×10^{-3} and 3.8×10^{-3} were measured for compounds **1** and **2** in CH_3CN solution and for the water-soluble derivative **3** in aqueous solution, respectively. A quite similar reactivity with an irreversible wavelength-dependent photolysis in CH_3CN and a quantum yield maximum of $\varphi = 3 \times 10^{-3}$ in the UV-spectral region has been reported before for the corresponding rhenium complex with R = phenyl (Fig. 1).[5] The quantum yield for this decomposition reaction rapidly drops to zero with monochromatic light in the visible spectral range. In agreement with our earlier study and also considering the UV-photoreactivity reported for the closely related family of *fac*-Mn(1,2-diimine)$(CO)_3$X systems [3,6], the spectral changes observed here (Fig. 2) are tentatively interpreted as a UV-light induced *fac* → *mer* isomerization of the complexes **1**–**3** and a photosubstitution of the coordinated chloro ligand against a solvent molecule. Such a reactivity pattern was also supported by positive ESI-mass spectrometry of the photolyzed samples. Comparing the trend of the quantum yield data confirms our assumption that the presence of more bulky aryl substituents on the nitrogen atoms of the 1,2-diimine ligand can favour the release of the rhenium bound chloride ligand, which is also of considerable interest for catalytic applications of these compounds [7]. Note that the UV-light induced reactivity described above, which is most probably involving the direct population of a high-lying repulsive metal-centered excited state of ligand field (^{1}MC) origin, does not lead to a permanent loss of CO. This is also consistent with the IR-spectroscopic data obtained after photolysis [5].

Upon polychromatic irradiation in solution, however, the completely dark-stable complexes **1**–**3** were found to release free carbon monoxide in significant amounts. This is indicating a branching of the excited state deactivation pathways at lower energies, which can open additional photoreactivity patterns involving the chromophoric charge transfer (CT) excited state manifold [5,6] which is dominating the absorption properties of the compounds in the visible spectral region. It is interesting to note, that such a an additional photochemical reactivity arising from lower-lying charge transfer excited states of otherwise emissive metal-to-ligand (MLCT) or ligand-to-ligand (LLCT) origin could also explain the unusual non-luminescent behaviour reported earlier for this kind of rhenium complexes [5].

Quantitative detection of photoinduced CO-loss by the complexes **1**–**3** was carried out with a direct FTIR-spectroscopic method described elsewhere in detail [7] (Fig. 3).

In a typical experiment, 2 mg (2.5 μmol) of **2** were dissolved in 6 ml of dry CH_3CN and the sample vial was sealed with a gas-tight septum inside a glove box. From dark control and irradiated samples, headspace gas was drawn with a syringe and injected into the FTIR measurement cell to detect the amount of free carbon monoxide. While no CO was lost in the dark, a quantum yield of $\varphi(CO) = 0.04$ was determined for CO-photorelease of the rhenium complex **2**. Comparable values of $\varphi(CO) = 0.03$ and $\varphi(CO) = 0.01$ were obtained with this method for complex **1** in CH_3CN and complex **3** in aqueous solution, respectively (ESI[†]).

Light-induced formation of free carbon monoxide with Photo-CORMs such as **2** is therefore in the activity range of 160 nmol CO/h/mg under the conditions reported here. It can be estimated that in 4 h of photolysis about 50% conversion of the Photo-CORM takes place, assuming that only one carbon monoxide molecule per rhenium center can be ejected. Such a slow process may be partially due to a competing back-reaction of the photolyzed complex in the presence of dissolved CO. In aqueous solution the water soluble complex **3** is permanently releasing carbon monoxide with a rate of 40–50 nmol CO/h/mg when activated by light under the conditions reported here. Compared to many other compounds suggested as CORMs for potential biomedical applications, these low values at the first glance seem to be not very promising. It should be kept in mind, however, that the balance between any beneficial therapeutic action of carbon monoxide and negative effects of CO on oxygen transport and cellular respiration has to be very carefully controlled [1a]. In fact, the activity of natural heme oxygenase (HO) enzymes responsible for the controlled release of carbon monoxide in cells and tissues is typically in the range of around 1 nmol CO/h/mg [8,9], which is still 50 times lower than the value of Photo-CORM **3** reported here. It should also be mentioned in this context that a convenient up- or down-regulation of this inducible heme oxygenase-like activity can be achieved at a given intrinsic quantum yield by controlling the applied light-intensity, which is a well-known general advantage of photochemical enzyme model systems [10].