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A dithiolate-bridged diiron hexacarbonyl complex $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ as a water-soluble photoCORM

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TOC Graphic

Facile release of CO from water-soluble $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ upon visible light irradiation.

ABSTRACT

A water-soluble dimercaptopropionate-bridged diiron hexacarbonyl complex $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ is prepared and the X-ray crystal structure, infrared, uv-visible and ESI spectra of the complex are obtained. The complex is shown to behave as a photoCORM whereby all six CO ligands are released within 30 minutes of visible-light irradiation. Gas-phase FTIR spectroscopy is used to quantify the release of CO into the headspace above the aqueous solution. The resulting product tentatively assigned to an iron thiolate salt is also water-soluble. Cell viability studies show that $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ complex is not cytotoxic towards normal epithelial cells.

Introduction

Carbon monoxide, CO has been shown to play a vital role as a low concentration cell-signalling molecule in living organisms¹⁻³. The physiological properties of CO have been well-studied and in the last decade, carbon monoxide-releasing molecules known as CORMs have been used to release CO. Here we restrict the discussion to only transition metal carbonyls as CORMs. The first metal carbonyls used were $\text{Mn}_2(\text{CO})_{10}$, $[\text{Ru}(\text{CO})_3\text{Cl}_2]_2$ and $\text{Ru}(\text{CO})_3\text{Cl}(\text{glycinate})^{4-6}$. The CO release can be activated or triggered photochemically or thermally. In the case of $\text{Ru}(\text{CO})_3\text{Cl}(\text{glycinate})$, the complex readily loses CO at room temperature. Molybdenum carbonyl complexes are currently being explored for biomedical applications⁷. Rhenium carbonyls are also emerging as viable CORMs⁸ while an iron dienylphosphate tricarbonyl complex is known to release CO upon interaction with an enzyme⁹.

If light has been used to trigger CO release from a molecule, the molecule is known as a photoCORM^{10,11}. PhotoCORMs can be applied in the field of laparoscopic surgery in which light pulses are delivered to a targeted area of the body via an optical fibre¹². While many metal carbonyl complexes which release CO upon uv irradiation are known, it is only recently that efficient visible light-initiated photoCORMs are described, such as manganese carbonyl scorpionates¹³ and iron carbonyls containing cysteamine ligands¹⁴.

A suitable photoCORM used in laparoscopic surgery has to satisfy many criteria such as water solubility, facile synthesis, ability to release CO quickly upon mild visible-light irradiation and able to form water-soluble final products to prevent clogging the arteries. In this work, we have synthesized a water-soluble dithiolate-bridged diiron complex using mercaptopropionate as the bridging thiolate, $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$. Analogous diiron complexes have already been extensively studied as [Fe-Fe] hydrogenase model compounds in reducing protons to dihydrogen¹⁵. In fact the photochemistry of such complexes has also been studied and even suggested as suitable therapeutic CO release agents¹⁶. We will show that our complex can indeed act as an efficient photoCORM by releasing CO within 30 minutes of broadband visible light irradiation. Instead of using myoglobin for CO quantification, we will also show that the concentration of CO released into the headspace of the photolytic mixture can be determined directly using gas-phase FTIR spectroscopy.

Results and Discussion

The orange diiron carbonyl complex containing mercaptopropionic acid (MPA) as the bridging thiolate ligand, $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$ was prepared by heating $\text{Fe}_3(\text{CO})_{12}$ and three equivalents of MPA in toluene¹⁷. The IR bands obtained for $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$ in toluene

as shown in Figure 1 are in excellent agreement with reported values for similar diiron dithiolato complexes¹⁵. ESI mass spectrometry carried out on the complex in ethanol shows an intense signal at $m/z = 488.40$ corresponding to its molecular ion peak. The uv-visible spectrum recorded for the complex in toluene shows an intense band at $\lambda_{\max} = 330$ nm and a weaker band at $\lambda_{\max} \approx 460$ nm. The absorption of the complex tails off at about 600 nm in the visible region.

Figure 1: IR and uv-visible absorption spectra of $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$ recorded in toluene.

Single crystals of $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$ obtained by slow vaporisation of toluene were subjected to X-ray diffraction studies for structural determination (Figure 2). The complex crystallizes in the monoclinic space group $P2(1)/n$, with unit cell dimensions $a = 7.794(11) \text{ \AA}$, $b = 25.126(3) \text{ \AA}$, $c = 9.179(12) \text{ \AA}$, $\beta = 97.415(4)^\circ$. The overall structure resembles other previously-characterized thiolate-bridged diiron complexes¹⁵. The Fe(I) centre is coordinated to the sulfur end of MPA, thus freeing the carboxylic acid for further functionalization. In our case, a simple deprotonation of the acid groups is sufficient to render the complex water-soluble. The Fe–Fe distance is $2.5119(11) \text{ \AA}$, indicating the formation of a single Fe – Fe bond. The Fe–CO bonds almost parallel to the Fe–Fe bond are of a similar length ($1.805(6) \text{ \AA}$) compare to the other four Fe–CO bonds ($1.794(6) \text{ \AA}$).

Figure 2: Single X-ray crystal analysis of $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$. Selected bond lengths : Fe(1)-Fe(2) $2.5119(11) \text{ \AA}$; Fe(1)-C(8) $1.805(6) \text{ \AA}$; Fe(1)-C(9) $1.794(6) \text{ \AA}$; Fe(1)-S(1) $2.2515(16) \text{ \AA}$. Selected bond angles : Fe(1)-S(1)-Fe(2) $67.75(5)^\circ$; C(10)-Fe(2)-C(11) $100.0(3)^\circ$; C(11)-Fe(2)-C(12) $101.1(3)^\circ$; Fe(1)-Fe(2)-C(12) $102.91(19)^\circ$.

By monitoring the IR bands, we have tested that the diiron complex is air-stable in the dark both as a solid and in solution (dichloromethane, toluene, hexane) over a wide temperature range from 298K to 370K. The solid can be stored for many weeks before use while a toluene solution of the diiron complex only showed signs of decomposition after a week. The solid is readily dissolved in water upon deprotonation by sodium carbonate. The complex remains intact in water as a carboxylate salt $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ since the uv-visible spectrum of the complex recorded in water has the same appearance as the parent molecule in toluene over 1 day. NMR data obtained for the complex are also consistent with a carboxylate structure. Solubilities of up to 0.02 g/ml for the sodium complex have been estimated by observing the complete dissolution of a known mass of the complex by eye. In an attempt to simulate physiological conditions, an equivalent mole quantity of cysteine, glycine and glucose were added into the aqueous solution containing the complex at 35°C to 45°C and around pH 7 (controlled by a phosphate buffer) but no reaction or decomposition of the complex was observed in the dark over 24 hours.

Although diiron complexes with bridging thiolate ligands have been known to release CO upon nucleophilic substitution, the reaction is slow at room temperature unless strong donors such as PMe_3 are used¹⁸. Hence $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ has been subjected to broadband visible light irradiation in order to release the CO ligand. In previous studies, the quantification of CO was mostly carried out by measuring the conversion of deoxymyoglobin to CO-bound myoglobin via their uv-visible absorbances. This presents some problems during UV-vis measurements. One, the presence of coloured complexes can cause a background that hinders uv-vis detection. Two, in the myoglobin assay, a strong reducing agent such as dithionite is required and in some cases, the dithionite interferes with the CO release from metal carbonyls¹⁹. Finally, the binding constant of CO to myoglobin needs to be larger than that to the CORM. Therefore another method of measuring the CO

concentration in the absence of myoglobin would be useful since any CO release can easily be traced to the photodissociation of the complex and thus confirms its role as a photoCORM.

We have used FTIR spectroscopy to quantify CO by monitoring its gas-phase rovibrational spectrum in the headspace above the aqueous solution^{10,20}. The headspace was directly connected to a 15cm-long gas cell equipped with CaF₂ windows for IR transmission. Since the solubility of CO in water is very low, most of the CO would be released into the headspace and gas cell hence minimising the error in determining its concentration. An added advantage is the CO quantification can be carried out *insitu*, without removing aliquots of the solution for sampling. Furthermore as the CO pressures are in the range of tens of Torr, pressure broadening effects are small and hence do not affect the peak absorbances significantly. Figure 3 shows a typical spectrum of the CO fundamental band centered at $\nu_0 = 2143\text{cm}^{-1}$. As the line strength of each rovibrational line has been determined accurately, the concentration of CO can be calculated directly using the following equation²⁰:

$$A = \sum_i S_i \frac{1}{\Delta\nu_i} \quad (1)$$

where A is the experimental absorbance, S_i is the line strength ($\text{cm}^{-2}\text{atm}^{-1}$), c is the concentration (atm), L is the path length (cm) and $\Delta\nu_i$ is half width of the line (cm^{-1}). In this work, $L = 15$ cm and a few P ($m = -J''$) and R-branch ($m = J''+1$) lines have been used to determine the average concentration of CO. For example, the S values for the intense P(7) and P(8) rovibrational lines are $11.367 \text{ cm}^{-2}\text{atm}^{-1}$ and $11.241 \text{ cm}^{-2}\text{atm}^{-1}$ respectively.

In our experiments, we have irradiated an aqueous solution containing $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ at room temperature and monitored the appearance of gas-phase CO in the gas cell. By applying the equation, we found that each $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ releases all six CO ligands within 30 to 40 minutes of broadband irradiation (Figure 3). In fact, CO signals can already be observed within a few minutes of

irradiation. The uv-visible absorbance of the complex at $\lambda_{\text{max}} = 330$ nm was also monitored and found to decrease rapidly also within the same period. The period of irradiation for which all CO are released depends on the easily-adjusted distance of the lamp from the reaction mixture. For accuracy of CO quantification, the irradiation was fixed at a distance such that sufficient datapoints can be collected and repeated. The same results were obtained in both aerated and deaerated aqueous solutions, indicating that air or oxygen does not affect the CO release.

Figure 3. Change in the gas-phase CO quantity expressed as mole equivalent of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ with respect to the period of irradiation detected using FTIR spectroscopy (full line). The change in the uv-visible absorbance of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ against the irradiation period is also shown (dashed line). Inset : typical FTIR spectrum recorded for the fundamental band of gas-phase CO.

The quantum yield of the initial photodissociation of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ at 390nm was estimated to be 0.4 ± 0.1 by comparison to $\text{CpMn}(\text{CO})_3$ photodissociation which has a known quantum yield of near-unity²¹. The wavelength of 390nm was chosen as both complexes have moderate absorbances in this region. While the quantum yield may not be very high, the photodissociation of the diiron thiolate can still proceed equally efficiently in air or in vacuum.

We are unable to detect any intermediates during irradiation although stepwise release of CO from the complex is expected. Thiolate-bridge diiron complex is known to lose two CO molecules upon nucleophilic substitution and becomes a diiron tetracarbonyl species¹⁸. However in the absence of strong donors or nucleophiles, the intermediate complex or complexes most likely decompose quickly to release the remaining CO molecules. At the end of photolysis, the aqueous solution turns red without any observable deposits. The uv-visible spectrum of the red solution shows a small absorption band at $\lambda_{\text{max}} = 475 \text{ nm}$ while the ESI spectrum taken of the solution in methanol shows a signal at $m/e = 407$ (negative mode) tentatively assigned to a $\text{Na}_3[\text{Fe}^{\text{III}}(\text{SCH}_2\text{CH}_2\text{COO})_3]\text{-methanol}$ adduct. The actual structure of this water-soluble product is currently being investigated.

Figure 4: Viability of mammary epithelial cells after 24 hours incubation with diiron dithiolate, as determined by the MTS assay. Cell viabilities have been normalized to DMSO control.

We have also carried out preliminary cell viability studies of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ towards mammary epithelial cells MCF-10A. These cells were used as a representative of normal cells in the human body. As shown in Figure 4, treatment of the cells using a range of diiron complex concentration from 1 to 40 $\mu\text{mol/L}$ did not lead to any observable cytotoxicity within 24 hours, as determined via the MTS assay²². In fact we are unable to determine an IC_{50} value since hardly any cell deaths occur over this range of concentration and time. Hence even if the CO photorelease period takes place in an hour, the diiron complex is expected to have minimal undesirable effect on the cells.

In summary, we have prepared and characterized a diiron dithiolate complex which functions as a photoCORM although such complexes are usually used as [Fe-Fe] hydrogenase models. Our iron complex is stable, water-soluble, does not exhibit cytotoxicity and can release CO via mild visible light irradiation in minutes. These are some of the more important criteria expected of a suitable photoCORM. We have used a very simple method to quantify CO release in the gas phase, hence circumventing problems associated with the normal myoglobin/dithionite method.

Experimental Materials and Methods

Materials. Iron dodecarbonyl (95%) was purchased from Strem Chemicals. Chloroform – d (99.8%), stabilised with 0.5 wt% Ag, 0.03% TMS was purchased from Cambridge Isotope

Laboratories. 3-mercaptopropionic acid (99%), sodium carbonate, ethanol and toluene (AR grade) were purchased from Sigma Aldrich. All solvents and reagents were used without further purification.

Instrumentation. Photochemical experiments were conducted with a Legrand broadband lamp (350 – 800nm, 11W). All IR spectra were obtained with Shimadzu IR Prestige-21 Fourier – transformed infrared spectrometer (1000 – 4000 cm^{-1} , 1 cm^{-1} resolution, 16 scans co-added for spectra averaging) using a 0.05mm path – length CaF_2 cell for liquid samples, and a 15 cm path – length CaF_2 gas cell for gas samples. The IR instrument was calibrated using standard CO gas from a CO cylinder prior to photoCORMs measurement. Quantum yield measurements were made using a Lumencor SPECTRA X light engine with 25mW output at 390nm. ^1H NMR spectra were recorded in CDCl_3 , unless otherwise stated, on Bruker AC300 Fourier-transformed spectrometers operating at ca. 300MHz at room temperature. All uv-visible absorption spectra were obtained with a Shimadzu UV-2550 spectrophotometer. Electrospray ionisation (ESI) was conducted using a Finnigan MAT LCQ spectrometer. Single crystal X-ray structural studies were performed on Bruker-AXS Smart Apex CCD Single-Crystal Diffractometers. Data were collected at 100(2)K using graphite-monochromated Mo K_α radiation ($\lambda=0.71073\text{\AA}$). Data collection was evaluated using SMART CCD system.

Preparation of $[(\mu\text{-MPA})\text{Fe}(\text{CO})_3]_2$ and $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$

$\text{Fe}_3(\text{CO})_{12}$ (20.3mg, 40 μmol) and 3-mercaptopropionic acid (10.5 μL , 120 μmol) were dissolved in toluene and refluxed under N_2 atmosphere until a colour change from green to orange was observed. The excess MPA (bp = 110°C/15 mmHg) and toluene were removed by distillation leaving behind an orange solid. The solid was purified by recrystallization in toluene. Single crystals of $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$ suitable for X-ray crystallography were

obtained by slow vaporisation of toluene. Yield: 13.7 mg (47%, 27.9 μ mol). Expt IR (toluene): 2073, 2037, 1997 cm^{-1} . ESI mass spec (ethanol): 488.4 (M+) and 460 (M+-CO). ^1H NMR (300 MHz, C_6D_6): 2.04-2.08, (t, J = 6.2 Hz, 2H, CH_2S), 2.15-2.20 (t, J = 7.3 Hz 2H, CH_2COOH). Analysis % found (calc.) : Fe 22.0 (22.8), C 30.4 (29.4), H 1.7 (2.0), S 10.3 (13.1)

An aqueous solution containing Na_2CO_3 was added to a toluene solution containing $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$. The toluene layer became light yellow. The aqueous layer turned orange, indicating the formation of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$. ^1H NMR (300 MHz, D_2O): 2.57-2.62, (t, J = 7.0 Hz, 2H, CH_2S), 2.89-2.94 (t, J = 7.0 Hz 2H, CH_2COO^-). Analysis found (calc.) : Fe 21.2 (20.9), C 28.2 (27.0), H 2.0 (1.5), S 11.0 (12.0)

CO quantification

The quantification of CO present can be determined from its CO rovibrational line strength. As tabulated by Medvecz²⁰. The equation used is $S(m) = \frac{A(v_0)L}{\gamma(m)C}$, where S(m) refers to the line strength, A(v_0) refers to the absorbance intensity, $\gamma(m)$ refers to the width at half length, L refers to the path length and C refers to the amount of CO present in atm.

A sample of 2.0 mg of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ in 0.5mL deaerated water was subjected to visible light irradiation (Legrand broadband Lamp, 300-800nm) at room temperature for one hour at a fixed distance (10 cm). The reaction flask was equipped with a 15 cm long gas cell connected to the headspace above the aqueous solution. The FTIR spectrum of the fundamental band of CO was scanned over 60 minutes. The absorbance values of a few rovibrational P and R-branch lines were recorded and an average value obtained and converted into CO pressure using the equation. The ideal gas equation

($PV=nRT$ where V =volume of the gas cell and headspace) then converts the pressure to the number of moles of CO. The experiment was repeated using the same compound dissolved in aerated water. Identical data was obtained, indicating that oxygen does not interfere with the photochemistry to a significant extent.

Quantum yield measurement

The quantum yield of the photodissociation of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ was measured by comparison to $\text{CpMn}(\text{CO})_3$ photodissociation which has a known quantum yield of near-unity. 10mg of $\text{CpMn}(\text{CO})_3$ (5.0 mmol) was dissolved in 10 ml of toluene and an initial IR spectrum was taken. The intensities of both ν_{CO} bands (with initial absorbances < 1.0) were used to monitor the decomposition of the metal carbonyl. The flask was then evacuated and subject to 390nm irradiation for 30 minutes. A second IR spectrum was taken after irradiation and the intensity of the same peaks were recorded. The measurements were repeated for the diiron dithiolate (6.2 mmol) under the same conditions. The quantum yield was then determined by ;

$$\text{QY} = [(\text{Abs}_{\text{Fe, initial}} - \text{Abs}_{\text{Fe, 30 mins}}) \times \text{Abs}_{\text{Mn, initial}}] / [(\text{Abs}_{\text{Mn, initial}} - \text{Abs}_{\text{Mn, 30 mins}}) \times \text{Abs}_{\text{Fe, initial}}]$$

Cell Viability studies

Experimental culture of the mammary epithelial cells MCF-10A were obtained from the American Type Culture Collection (ATCC) and cultured in tissue culture dishes (Nunc Inc., Naperville, IL, USA). The cells were maintained in Dulbecco's modified Eagle's medium (DMEM, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS), 1% l-glutamate (GIBCO Laboratories), and 1% penicillin/streptomycin (GIBCO Laboratories) at 37°C in 5% CO_2 atmosphere. Cell cultures were maintained in an antibiotic-free condition during cell growth and experiments. Phosphate buffered saline (PBS) was obtained from 1st

Base. A range of concentrations of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ was used (1 to 40 $\mu\text{mol/L}$) for incubation with the cells for 24 hours.

For the proliferation assay, approximately 10,000 cells per well were placed in a 96-well plate and allowed to adhere for approximately 24 hours. To each well, 20% of Cell Titer 96 Aqueous One Cell Proliferation Assay (Promega) was added and then left to incubate in a 37°C incubator with 5% CO_2 over 2 hours. Each sample was done in triplicates. The absorbance intensities at 490nm were then measured and cell viabilities relative to the control (DMSO) were calculated. The IC_{50} values may be established by plotting the cell viabilities data against the dosage administered.

The Supporting Information contains the mass spectrum and table of crystallographic data for $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Figures

Figure 1: IR and uv-visible absorption spectra of $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$ recorded in toluene.

Figure 2: Single X-ray crystal analysis of $(\mu\text{-MPA})_2[\text{Fe}(\text{CO})_3]_2$. Selected bond lengths : Fe(1)-Fe(2) 2.5119(11) Å; Fe(1)-C(8) 1.805(6) Å; Fe(1)-C(9) 1.794(6) Å; Fe(1)-S(1) 2.2515(16) Å. Selected bond angles : Fe(1)-S(1)-Fe(2) 67.75(5)°; C(10)-Fe(2)-C(11) 100.0(3)°; C(11)-Fe(2)-C(12) 101.1(3)°; Fe(1)-Fe(2)-C(12) 102.91(19)°.

Figure 3. Change in the gas-phase CO quantity expressed as mole equivalent of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ with respect to the period of irradiation detected using FTIR spectroscopy (full line). The change in the uv-visible absorbance of $\text{Na}_2[(\mu\text{-SCH}_2\text{CH}_2\text{COO})\text{Fe}(\text{CO})_3]_2$ against the irradiation period is also shown (dashed line). Inset : typical FTIR spectrum recorded for the fundamental band of gas-phase CO.

Figure 4: Viability of mammary epithelial cells after 24 hours incubation with diiron dithiolate, as determined by the MTS assay. Cell viabilities have been normalized to DMSO control.