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Controlled CO release using photochemical, thermal and electrochemical approaches from the amino carbene complex $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]^\ddagger$

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Multimodal photo, thermal and electrochemical approaches toward CO release from the amino carbene complex $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ is reported. Picosecond time resolved infrared spectroscopy was used to probe the photo-induced early state dynamics leading to CO release, and DFT calculations confirmed that CO release occurs from a singlet excited state.

CO releasing molecules (CORMs) are an area of current interest due to the physiological role of CO in the body.^{1,2} CO is endogenously generated during oxidative heme degradation by the heme oxygenase (HO) enzymes.³ The potential therapeutic applications of CO include vasodilation, anti-inflammatory and anti-proliferative effects. CORMs have been developed to deliver CO in a controlled manner. However, there is a major challenge in controlled CO release, be it photochemically, thermally or enzymatically induced. It is well known that chromium carbene complexes can release CO both thermally and photochemically, as the resulting tetracarbonyl reactive intermediates have been used as synthons in organic chemistry.⁴ Recently, Lynam *et al.* reported the suitability of heteroatom (amino, methoxy and thio) stabilised chromium carbenes as thermal CORMs.⁵ Rapid CO release was observed for the thio- and methoxy carbenes ($t_{1/2} = 313$ s and 306 s, respectively, for a 60 μM solution of the complex to achieve an Mb-CO concentration of 30 μM), compared to slow release in the case of the amino analogue which required more than 2 h for a 60 μM solution of the complex to form 10 μM of carboxy-myoglobin (Mb-CO). In addition the chromium carbonyls investigated, demonstrated the fastest and most regulated CO

release characteristics compared to the molybdenum or tungsten complexes studied.⁵

In this communication we set out to compare the rate of CO release from $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ using photochemical, thermal and electrochemical stimulation. To the best of our knowledge this is first example of a CORM involving electrochemical stimulation. In the present study we report our findings on a ps-time resolved infrared (ps-TRIR) study on $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ in conjunction with DFT calculations to investigate the excited state responsible for the CO release. Chromium Fischer carbenes have received significant attention as photochemical synthons for a range of organic compounds. Photolysis of $[(\text{CO})_5\text{CrC}(\text{XR})\text{R}']$ in the presence of imines, olefins, aldehydes, or alcohols are known to yield β -lactams, cyclobutanones, β -lactones or amino esters respectively.⁶ The proposed mechanism for these reactions involves a metal-to-ligand charge transfer photoexcitation resulting in the formation of a ketene intermediate which is formed by the insertion of a *cis*-CO ligand into the adjacent Cr–carbene bond (Fig. 1). Experimental and theoretical calculations reported by Sierra *et al.* support the proposal that this occurs through a MLCT triplet excited state.⁷

Although a number of low temperature and time-resolved studies have investigated photo-induced CO release from chromium carbenes,^{8–10} no previous data have been reported on the picosecond time scale or on using modern theoretical calculations to identify the nature of the excited state involved in CO release.

The CO-releasing ability of $[(\text{CO})_5\text{CrC}(\text{C}_4\text{H}_8\text{N})\text{CH}_3]$ was determined both photochemically using 355 nm (LED) excitation and thermally (at 37 °C) using a myoglobin (Mb) assay.^{2,11} Fig. 2 illustrates the CO release profile for the photo activated CORM.

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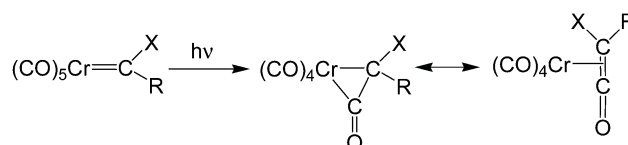


Fig. 1 Chromium–ketene intermediate proposed following photolysis of $[(\text{CO})_5\text{CrC}(\text{XR})\text{R}']$. X = amino, alkoxy, and R = alkyl, aryl, H.

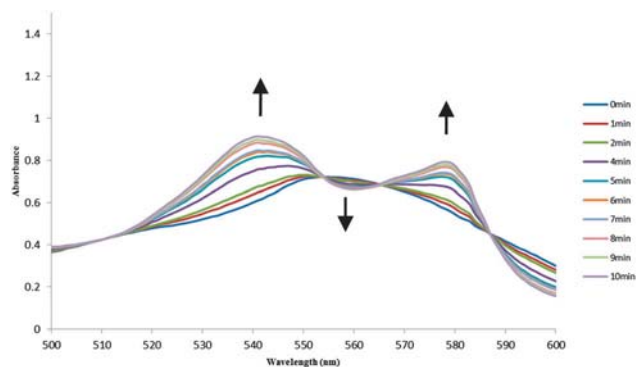


Fig. 2 CO release profile for $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ ($60 \mu\text{M}$) measuring the conversion of deoxy-Mb to Mb-CO against time, photochemically at 355 nm, see ESI[†] for experimental conditions.

During the experiments the intensity of the Mb Q-band at $\sim 554 \text{ nm}$ decreases while the characteristic peaks of Mb-CO appears at 540 nm and 578 nm (indicated by the arrows in Fig. 2). The major notable difference between the two methods employed for CO release is the difference in $t_{1/2}$ values. Complete saturation of deoxy-Mb by $[(\text{CO})_5\text{CrC}(\text{C}_4\text{H}_8\text{N})\text{CH}_3]$ was observed, but required $\sim 3 \text{ h}$ at 37°C ($60 \mu\text{M}$), ($t_{1/2} = 4544 \text{ s}$). This is significantly slower than that observed photochemically where $t_{1/2} = 266 \text{ s}$.

Electrochemical analysis of $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ in 0.1 M TBAPF₆ in acetonitrile using cyclic voltammetry reveals three redox processes within the potential window investigated (Fig. 3). These include two oxidative processes and one reductive process ($+0.34 \text{ V}$, $+1.03 \text{ V}$ and -2.80 V vs. Fc/Fc^+). The first oxidation is assigned to the $\text{Cr}^{0/1}$ redox couple as previously reported.^{12,13} Oxidation of these types of metal carbene complexes is reported as being predominantly metal based¹² with reduction centred on the metal-carbene double bond, consistent with the HOMO and LUMO images illustrated in ESI[†] Fig. S7.¹³ Varying scan rates did not promote reversibility for the redox processes observed. *In vivo* studies using electrochemical methods as potential therapeutics for diseases such as cancer have been reported in the literature.^{14–16} In the present study, electrochemical initiation of CO-release from the complex was confirmed and quantified *via* headspace analysis using gas chromatography

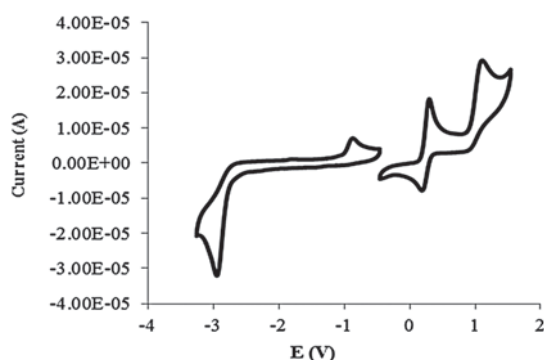


Fig. 3 Cyclic voltammogram of oxidation and reduction of $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ in 0.1 M TBAPF₆ in CH_3CN , vs. Fc/Fc^+ . Scan rate = 0.1 V s^{-1} .

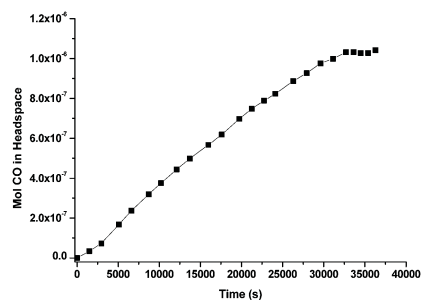


Fig. 4 Profile for the electrochemically induced CO release over time from $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ in acetonitrile under potentiostatic conditions ($E = +0.36 \text{ V}$ vs. Fc/Fc^+). Concentration of $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ was 0.1 mM and the solution was stirred continuously.

(ESI[†] Fig. S6). Displayed in Fig. 4 is the electrochemical CO-release profile over 10 hours of controlled potential electrolysis ($E = +0.36 \text{ V}$). The concentration of CO in the headspace suggests loss of one CO molecule per Fischer carbene centre. As one-electron oxidation of $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ is primarily characterised by the $\text{Cr}(I/0)$ couple, it is likely that the reduced capacity of $\text{Cr}(I)$ for π back-donation likely results in a more labile $\text{Cr}-\text{CO}$ bond. To the best of our knowledge this is the first report where electrochemically initiated CO loss from a CO-RM has been quantified.

Since photochemically CO release is significantly faster than the thermal approach, the early state dynamics leading to CO loss following excitation of $[(\text{CO})_5\text{CrC}(\text{C}_4\text{H}_8\text{N})\text{CH}_3]$ at 400 nm was probed using pico-second TRIR (see ESI for experimental conditions). The IR spectrum of the parent $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ complex in *n*-heptane exhibits metal carbonyl stretching bands at 2055, 1967, and 1928 cm^{-1} . The spectral changes observed following pulsed (50 fs) excitation of $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ at 400 nm are presented in Fig. 5.¹⁷ The spectrum obtained 3 ps after excitation shows depletion of the parent bands as the negative features in the difference spectrum. New bands at 2016, 1913 and 1897 cm^{-1} are formed within this timescale and these are assigned to an excited state species. Over the subsequent 50 ps these bands decay with concomitant formation

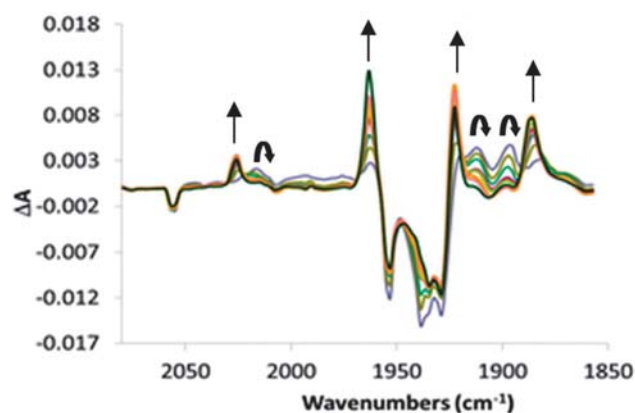


Fig. 5 Picosecond TRIR difference spectra following 400 nm photolysis of $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ in *n*-heptane solution at selected time intervals; 4, 12, 21, 37, 44, 68, 90, 1000 ps.

of bands at 2025, 1963, 1923 and 1886 cm^{-1} . These bands are assigned to the solvated species, $[(\text{heptane})(\text{CO})_4\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ and are consistent with the bands previously reported for the CO loss species in low temperature matrices at 20 K.⁹ The extent of parent band recovery provides an estimate of the overall quantum yield for the CO-loss process of 0.65. No evidence for the ketene intermediate proposed in Fig. 1 was found in this study.

$[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$ was modelled using a hybrid Density Functional Theory (B3LYP)^{18,19} using a triple zeta quality basis set (Tzvp)²⁰ as implemented in Gaussian 09 (Revision D.01).²¹ Full details are provided in the ESI.† The Cr–*cis*CO distance was chosen as a suitable reaction coordinate to model the CO loss reaction. A relaxed potential energy scan was performed along this reaction coordinate and at each point time-dependent DFT calculations provided the vertical excitation energies to the five lowest energy singlet excited states (TDDFT/B3LYP/Tzvp). These data were then used to construct an energy profile along this reaction coordinate for these excited states (Fig. 6). The plots confirm that CO can be liberated from the lowest energy singlet excited state (metal-to-carbene charge-transfer in character) by surmounting a small thermal barrier (5.6×10^{-4} kJ mol^{-1}), the latter formed by crossing with the 2nd singlet excited state which is metal centred in character. Thus CO-loss from this system will be arrested compared to CO-loss from $\text{Cr}(\text{CO})_6$. In the case of $\text{Cr}(\text{CO})_6$ ($\Phi_{\text{CO}} = 0.72$), CO loss occurs on the ultrafast time scale (< 100 fs).²¹ Along this reaction coordinate the Cr–CO distance on only one *cis* CO is increased and consequently the symmetry and therefore the IR spectrum of the excited state will resemble that of the CO-loss product. The lowest energy singlet excited state has substantial metal-to-carbene charge-transfer character (ESI,† Fig. S9) while the second singlet excited state is mainly a metal-centred state (ESI,† Fig. S10). The DFT calculations reported here do not indicate the population of a triplet excited state.

In conclusion, we have identified three stimuli to induce CO-release from $[(\text{CO})_5\text{CrC}(\text{NC}_4\text{H}_8)\text{CH}_3]$. Thus proving that, a single type of CORM can be used for either fast or slow CO release simply by altering the means of excitation. The ps-TRIR highlight that a singlet excited state yields CO loss within 50 ps

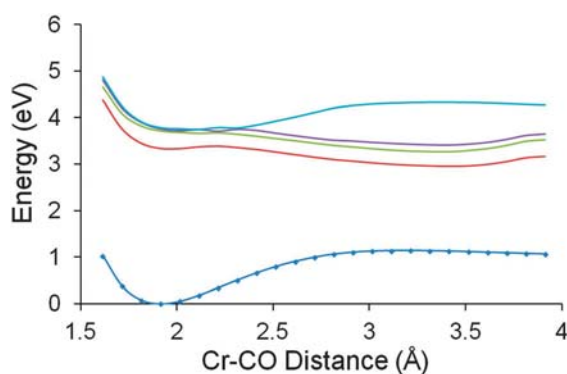


Fig. 6 The energy of the ground state (blue) and the four lowest energy singlet excited states as the Cr–*cis*CO distance is varied, (the data interval is indicated by data point markers on the ground state curve but omitted from the excited state curves for clarity).

which translates to a 17-fold increase in the rate of CO-uptake by deoxy-Mb at 37 °C in phosphate buffered saline buffer when $t_{1/2}$ for both thermal and photochemical are compared. DFT calculations confirm a *cis*-CO ligand is expelled from the lowest energy excited state which has substantial metal-to-carbene charge-transfer character. Electrochemically, CO loss was detected and quantified at a low potential which is important for physiological applications.^{22,23} Current studies are in progress on water soluble analogues of Fischer carbene complexes.

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