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Group 6 Carbon Monoxide-Releasing Metal Complexes with Biologically-Compatible Leaving Groups

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A series of carbon monoxide-releasing molecules (CO-RMs) based on the $M(CO)_5$ framework (M = Cr, Mo, W) is reported. The metal carbonyl anions $[MCl(CO)_5]^-$ are shown to be highly versatile precursors to Group 6 pentacarbonyl complexes containing amino-ester groups, namely, $[M(CO)_5(NH_2CH\{R\}CO_2R')]$. The structures of five of the complexes, including an enantiomeric pair based on (*R*) and (*S*)-alanine, were determined by single crystal X-ray diffraction. These species exhibit rapid CO-release, as shown by a myoglobin-based assay. The rate of release is affected by the nature of both the metal and the amino-ester employed. A mechanistic study shows that a common intermediate is formed corresponding to loss of the amino-ester from the metal. In addition, a further series of potential CO-RMs have been prepared based on Fischer-type carbenes complexes, which contain either amino esters or amino acids. The amino esters and amino acids are introduced into the coordination sphere of the metal by a nucleophilic substitution reaction at the carbene carbon atom. The Michael addition of $NH_2CH_2CO_2Et$ across the triple bond in $[Cr(CO)_5(=C\{OMe\}—C\equiv CPh)]$ affords crystallographically characterized $[Cr(CO)_5(=C\{OMe\}\text{-}(Z)—CH=C\text{-}\{Ph\}NHCH_2CO_2Et)]$. The rate of CO-release from the carbene complexes depends primarily on the specific heteroatom connected to the carbene center. Rapid CO-release is observed in the case of sulfur- and methoxy-stabilized carbenes whereas in the case of amino-substituted carbenes, release is far more sluggish. This may be correlated with the electrophilic character at the carbene carbon atom.

Introduction

The role of the small molecules NO and CO as fundamental signaling molecules in biological systems is now well-established.[1−5] In the case of CO this is somewhat paradoxical, given its well-established toxicity; however, the human body generates approximately 3−6 cm^3 of CO on a daily basis. The vast majority of this CO arises from the oxidation of heme, a process catalyzed by the heme oxygenase series of enzymes.[6] In addition, it has been established that CO may elicit a range of beneficial effects. For example, it is anti-inflammatory;[7] protects against ischemic damage and reperfusion injury,[8] regulates blood pressure under stress conditions;[9,10] and is an antibacterial agent.[11,12] CO also suppresses organ graft rejection,[13] and assists with the treatment of cerebral malaria.[14]

Because of its inherent toxicity, gaseous CO does not represent a long-term solution for the exploitation of these effects; in addition, the precise dosing of the gas is problematic. To develop an efficient form of CO-therapy, in which issues such as dosage and delivery may be carefully controlled, a range of CO-releasing molecules (CO-RMs) have been developed. Conceptually, CO-RMs are designed to act as benign reservoirs, which may be tuned to liberate their CO under certain conditions and at a predefined rate.

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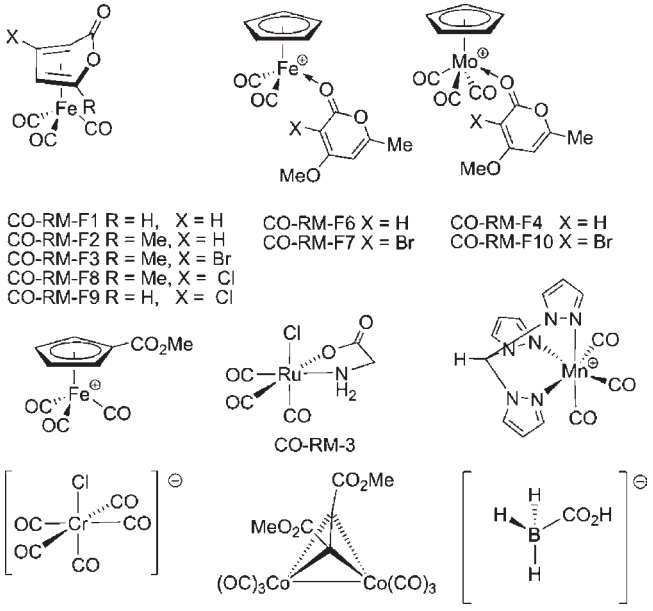

Figure 1. Structures of previously reported CO-RMs.

Transition metal−carbonyl complexes are attractive CO-RMs and several classes have been investigated (Figure 1). For example, the water-soluble ruthenium glycinate complex, CO-RM-3, has been shown to elicit the same biological effects as gaseous CO in a number of applications.[15−23] Water-soluble complexes based on half sandwich iron(II) complexes have also been reported.[24]

We have developed a series of CO-RMs which possess the biologically compatible 2-pyrone motif bound to metals in both η^4- and η^1-(O)-binding modes.[25−27] This series of compounds generally exhibits low toxicity, and the rate and extent of the CO-release may be controlled by the choice of both metal and substituents on the 2-pyrone group. In addition, we have investigated the mechanism of CO-release for a range of dimers based on the $[Co_2(CO)_6(\mu\text{-}C_2R_2)]$ framework.[28]

The photochemical activation of CO-RMs has also been investigated.[29] For example $Mn_2(CO)_{10}$ and $Fe(CO)_5$ only release CO after photolysis.[17] In a similar vein $[Mn(CO)_3$-(tpm)] [tpm = *tris*(pyrazolylmethane)] has been shown to be cytotoxic to human colon cancer cells only when irradiated.[30] Complexes containing tpm groups modified with peptides have also been reported,[31] as has the CO-releasing behavior and cytoprotective effects of open shell Re(II) complexes.[32]

Although the majority of CO-RMs reported to date have focused on the use of transition metal complexes, it is important to note that the water-soluble borate $Na_2[H_3BCO_2]$ has been shown to effectively release CO.[33,34]

CO-releasing molecules based on the $M(CO)_5$ unit are attractive targets as they may potentially release up to five molecules of CO per metal. This has the advantage that lower overall quantities of CO-RM may be required for a given dose of CO to be generated. An additional advantage of this system is that, in addition to CO, only one further ligand is required to complete the coordination sphere of the metal. This minimizes the potential side effects from other supporting groups. In a previous study, designed to probe the factors which control the rate and extent of CO-release from a diverse library of metal carbonyl complexes, we established that CO-release from the metal carbonyl anions $[MX(CO)_5]^-$ (M = Cr, Mo, W; X = Cl, Br, I) could be modulated by the metal and halide substituents.[35] The rate of CO-release varied over two orders of magnitude increasing in the order Cr > Mo > W and Cl > Br > I. A mechanistic study demonstrated that the CO-release process was initiated by water addition, resulting in the hydrolysis of the M−X bond. An intermediate from the CO-release process $[NEt_4][\{Cr(CO)_5\}_2$-$(\mu\text{-Cl})]$ was isolated and crystallographically characterized. It appears that a further reaction of the bridging halide species with water resulted in the in situ generation of species "$Cr(CO)_5$" which were the "active" CO-releasing molecules.

The next step in this program was to investigate the potential for the incorporation of biologically compatible leaving groups into the coordination sphere of these Group 6 metal complexes with a view to aiding water solubility and reducing potential toxicity. As the generation of "$M(CO)_5$" appeared to be a crucial step in the mechanism of CO-release, it was anticipated that species $[M(CO)_5L]$ (in which L is the biologically compatible leaving group) would be an attractive target. Darensbourg and co-workers have previously demonstrated that glycinate complex $[NEt_4][M(CO)_4(\kappa^2\{NO\}$-$NH_2CH_2CO_2)]$ (M = Cr, W) could be prepared and possessed labile CO ligands.[36,37] Consequently neutral complexes were targeted in which the leaving group L was an amino ester.

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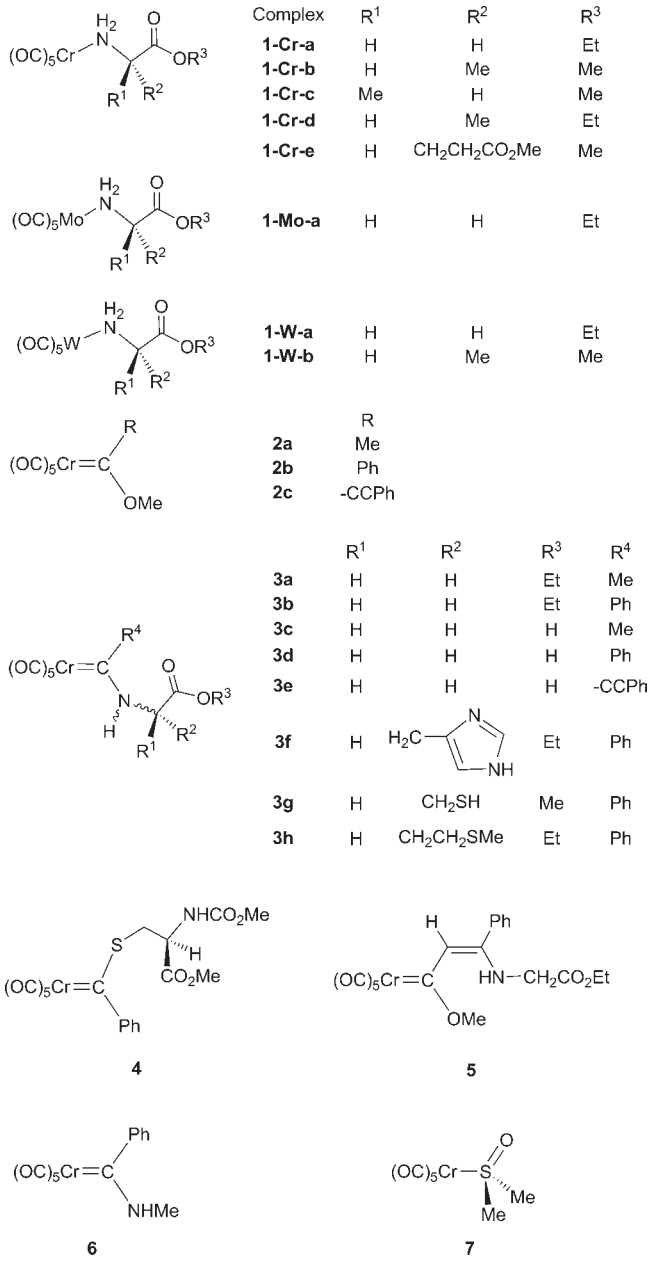

Figure 2. Structures and labeling scheme for CO-RMs in this study.

The synthesis, characterization, and CO-release behavior is now reported of a range of novel amino ester-substituted Group 6 metal carbonyls of the general form $[M(CO)_5L]$. In addition, we have exploited the synthetic chemistry of a range of Group 6 carbene complexes to incorporate amino acids into the secondary coordination sphere of the metal center.

Results and Discussion

The structure and labeling scheme for the complexes employed in this study are detailed in Figure 2. All complexes were characterized by a combination of NMR and IR spectroscopy, coupled, in certain instances, with mass spectrometry. In addition, the structures of complexes **1-Cr-a**, **1-Cr-b**, **1-Cr-c**, **1-Mo-a**, **1-W-b**, **3b**, and **5** were determined by single crystal X-ray diffraction. Selected bond lengths for these complexes are gathered in Table 1, and details of the data collection and structure refinement in Table 2.

Preparation of Compounds $M(CO)_5L$, 1. Tungsten complexes of amino esters can be prepared by irradiation of $W(CO)_6$ with the appropriate ligand.[38−40] However, we sought to develop an alternative procedure for the preparation of these species which could, in principle, be applied to large scale syntheses. As it has previously been demonstrated that hydrolysis of salts $[NEt_4][MX(CO)_5]$ provided a source of "$M(CO)_5$"[35] it was reasoned that these easily prepared materials may be versatile precursors to the required amino ester compounds. This indeed proved to be the case. For example, reaction of $[NEt_4][CrCl(CO)_5]$ with base-free $NH_2CH_2CO_2Et$ in a CH_2Cl_2/water mixture resulted in the rapid formation of the *N*-bound glycine complex **1-Cr-a**. Similar reactions with (*S*)-$NH_2CH(Me)CO_2Me$, (*R*)-$NH_2CH(Me)CO_2Me$, (*S*)-$NH_2CH(Me)CO_2Et$, and (*S*)-$NH_2CH(CH_2CH_2CO_2Me)$-CO_2Me produced complexes **1-Cr-b**, **1-Cr-c**, and **1-Cr-d**, respectively. The complexes $[Mo(CO)_5(NH_2CH_2CO_2Et)]$, **1-Mo-a**, and $[W(CO)_5(NH_2CH_2CO_2Et)]$, **1-W-a**, were prepared from the reaction of $NH_2CH_2CO_2Et$ with $[NEt_4][MoCl(CO)_5]$ and $[NEt_4][WCl(CO)_5]$, respectively, $[W(CO)_5(NH_2CH\{Me\}CO_2Et)]$, **1-W-b**, was also prepared by this method.

The single crystal X-ray diffraction studies on **1-Cr-a**, **1-Cr-b**, **1-Cr-c**, **1-Mo-a**, **1-W-b** (Figure 3) demonstrated that these complexes form an isostructural series in which the amino ester is *N*-bound to the metal. The complexes are distorted octahedra with N(1) and C(6) lying in a plane containing C(1) and two of the other carbonyl ligands. This ensures that the two amine protons and the substituents attached to C(6) sit out of the plane of the carbonyl ligands. The M−C(1) bond (which is *trans* to the amino ester ligand) is notably shorter than the remaining metal−carbon bonds.

In all cases, intermolecular H-bonding is observed between the amino group and the oxygen of the ester carbonyl group in a neighboring molecule (Figure 4). In the case of the glycine complexes **1-Cr-a** and **1-Mo-a** this hydrogen bond is noticeably shorter (N−H···O distances of 2.9089(14) Å and 2.9132(17) Å, respectively) than in the corresponding alanine-containing species (N−H···O distance of 3.1939(15) in **1-Cr-b**, 3.1930(14) in **1-Cr-c**, and 3.159(2) in **1-W-a**). This may simply reflect the different steric properties of the two amino acids with the methyl-substituent in alanine inhibiting short hydrogen bonds. Although this is a common feature to all the solid state structures in this series of compounds, the intermolecular hydrogen bonds are unlikely to persist in the aqueous medium employed for the CO-release measurements (*q.v*). Within the chromium series, it is evident that the glycine ligand is more tightly bound to the metal {Cr(1)−N(1) bond length 2.1829(11) Å} in **1-Cr-a** than in the two alanine enantiomers **1-Cr-b** and **1-Cr-c** {Cr-(1)−N(1) 2.1972(12) Å and 2.1968(11) Å, respectively} which likely reflects the differing steric demands of these ligands.

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Table 1. Selected Bond Lengths (Å) and Angles (deg) for Complexes **1-Cr-a**, **1-Cr-b**, **1-Cr-c**, **1-Mo-a**, **1-W-b**, **3b**, and **5**

metric	1-Cr-a	1-Cr-b	1-Cr-c	1-Mo-a	1-W-b	3b	5
M−C(1)	1.8531(13)	1.8379(14)	1.8379(13)	1.9786(17)	1.966(2)	1.8792(12)	1.8734(17)
M−C(2)	1.8982(14)	1.9077(14)	1.9066(13)	2.0434(17)	2.034(2)	1.8858(13)	1.8960(17)
M−C(3)	1.9147(13)	1.9144(14)	1.9147(13)	2.0568(17)	2.044(2)	1.9171(13)	1.9097(17)
M−C(4)	1.9230(13)	1.9085(14)	1.9085(13)	2.0303(16)	2.0446(19)	1.8911(13)	1.9074(17)
M−C(5)	1.8940(13)	1.9217(13)	1.9208(12)	2.0702(17)	2.059(2)	1.9111(12)	1.8900(18)
M−C(6)						2.0813(11)	2.0904(15)
M−N(1)	2.1829(11)	2.1972(12)	2.1968(11)	2.3197(13)	2.3161(17)		
N(1)−H···O(6)							2.6027(17)
C(1)−M−N(1)	178.80(5)	175.08(6)	175.15(5)	178.84(6)	174.72(8)		
C(2)−M−C(3)	174.59(6)	173.61(6)	173.59(6)	174.41(7)	173.25(8)	179.12(5)	178.50(7)
C(4)−M−C(5)	175.99(6)	177.59(5)	177.58(5)	175.42(8)	177.94(8)	176.84(5)	178.52(7)
M−N(1)−C(6)	118.34(7)	120.75(8)	120.75(8)	117.68(9)	120.33(12)		
C(1)−M−C(6)						177.73(5)	176.02(6)
M−C(6)−N(1)						114.69(10)	
M−C(6)−O(6)							109.67(13)

Table 2. Data Collection and Structural Refinements Details for Single Crystal X-ray Diffraction Studies for Complexes **1-Cr-a**, **1-Cr-b**, **1-Cr-c**, **1-Mo-a**, **1-W-b**, **3b**, and **5**

	1-Cr-a	1-Cr-b	1-Cr-c	1-Mo-a	1-W-b	3b	5
empirical formula	$C_9H_9CrNO_7$	$C_9H_9CrNO_7$	$C_9H_9CrNO_7$	$C_9H_9MoNO_7$	$C_9H_9NO_7W$	$C_{16}H_{13}CrNO_7$	$C_{19}H_{17}CrNO_8$
formula weight	295.17	295.17	295.17	339.11	427.02	383.27	439.34
temperature [K]	110(2)	110(2)	110(2)	110(2)	110(2)	110(2)	110(2)
wavelength [Å]	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
crystal system	monoclinic	orthorhombic	orthorhombic	monoclinic	orthorhombic	monoclinic	monoclinic
space group	*Cc*	*P*2(1)2(1)2(1)	*P*2(1)2(1)2(1)	*Cc*	*P*2(1)2(1)2(1)	*C*2/*c*	*P*2(1)/*c*
a [Å]	12.8978(12)	6.5836(4)	6.5865(3)	13.0857(8)	6.6638(4)	23.559(2)	12.0095(15)
b [Å]	15.4219(14)	10.1932(7)	10.1935(5)	15.5170(8)	10.1858(6)	7.6899(6)	7.7905
c [Å]	6.8108(6)	18.1889(12)	18.2009(9)	6.9481(4)	18.5634(11)	21.4427(18)	21.250(3)
α [deg]	90°	90.	90	90	90	90	90
β [deg]	115.838(2)	90	90	116.0150(10)	90	118.841(3)°.	95.114(3)
γ [deg].	90	90	90	90	90	90	90
volume [Å^3]	1219.29(19)	1220.62(14)	1222.00(10)	1267.87(12)	1260.01(13)	3402.9(5)	1980.3(4)
Z	4	4	4	4	4	8	4
density (calculated) [Mg/m^3]	1.608	1.606	1.604	1.777	2.251	1.496	1.474
absorption coefficient [mm^{-1}]	0.963	0.962	0.961	1.059	9.192	0.710	0.624
F(000)	600	600	600	672	800	1568	904
crystal size [mm]	0.40 × 0.36 × 0.31	0.22 × 0.12 × 0.09	0.29 × 0.26 × 0.26	0.41 × 0.14 × 0.13	0.47 × 0.08 × 0.06	0.30 × 0.14 × 0.07	0.16 × 0.13 × 0.04
θ range for data collection [deg]	2.20 to 30.01°.	2.24 to 29.99	2.24 to 28.33	2.17 to 30.00°.	2.19 to 30.02°.	1.97 to 30.02	1.70 to 28.31
index ranges	$-17 \le h \le 18$ $-21 \le k \le 21$ $-9 \le l \le 9$	$-9 \le h \le 9$ $-14 \le k \le 14$ $-25 \le l \le 25$	$-8 \le h \le 8$ $-13 \le k \le 13$ $-24 \le l \le 24$	$-17 \le h \le 18$ $-21 \le k \le 21$ $-9 \le l \le 9$	$-9 \le h \le 9$ $-14 \le k \le 14$ $-25 \le l \le 26$	$-32 \le h \le 32$ $-10 \le k \le 10$ $-29 \le l \le 29$	$-16 \le h \le 16$ $-10 \le k \le 10$ $-28 \le l \le 28$
reflections collected	6761	18645	12688	9425	18830	18543	19732
independent reflections	3393 [*R*(int) = 0.0145]	3544 [*R*(int) = 0.0265]	3047 [*R*(int) = 0.0166]	3633 [*R*(int) = 0.0153]	3649 [*R*(int) = 0.0204]	4889 [*R*(int) = 0.0170]	4921 [*R*(int) = 0.0297]
completeness to *θ*	99.2% (to 22.51°)	100.0% (to 29.99°)	100.0% (to 28.33°)	99.5% (to 30.00°)	99.7% (to 30.02°)	98.3% (to 30.02)	99.8% (to 28.31°)
absorption correction	semi-empirical from equivalents						
max. and min transmission	0.742, 0.643	0.917, 0.840	0.779, 0.628	0.871, 0.682	0.576, 0.321	0.952, 0.796	0.9755, 0.8093
refinement method	full-matrix least-squares on F^2						
data/restraints/parameters	3393/2/172	3544/0/173	3047/0/171	3633/2/172	3649/0/173	4889/0/239	4921/0/272
GoF on F^2	1.076	1.066	1.051	1.054	1.049	1.041	1.037
final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0193 wR2 = 0.0506	R1 = 0.0224 wR2 = 0.0571	R1 = 0.0183 wR2 = 0.0496	R1 = 0.0149 wR2 = 0.0345	R1 = 0.0113 wR2 = 0.0261	R1 = 0.0294 wR2 = 0.0784	R1 = 0.0329 wR2 = 0.0821
R indices (all data)	R1 = 0.0195 wR2 = 0.0507	R1 = 0.0239 wR2 = 0.0580	R1 = 0.0190 wR2 = 0.0499	R1 = 0.0153 wR2 = 0.0346	R1 = 0.0114 wR2 = 0.0262	R1 = 0.0336 wR2 = 0.0815	R1 = 0.0448 wR2 = 0.0876
absolute structure parameter	0.023(9)	−0.001(12)	0.002(11)	0.006(17)	−0.008(5)		
largest diff. peak and hole [e Å^{-3}]	0.294, −0.159	0.362, −0.169	0.239, −0.151	0.624, −0.282	1.091, −0.417	0.492, −0.299	0.367, −0.265

Preparation of Chromium Carbene Compounds. In previous investigation into the general CO-release properties of a range of metal carbonyl complexes, the carbene complexes $[M(CO)_5(=C\{OMe\}Me)]$ were evaluated as potential CO-RMs (M = Cr, Mo, W).[35] As was the case of the metal carbonyl anions $[MX(CO)_5]^-$, the rate of CO-release decreased in the order Cr > Mo > W. Given the versatile reactivity of these carbene complexes it was anticipated that it would also be possible to introduce the amino acid substituent into the carbene ligand. Jaouen and co-workers have previously demonstrated that amino acids may be introduced into the tungsten carbene complex $[W(CO)_5(=C\{OMe\}Me)]$ with a view to developing these species as novel protein-labeling

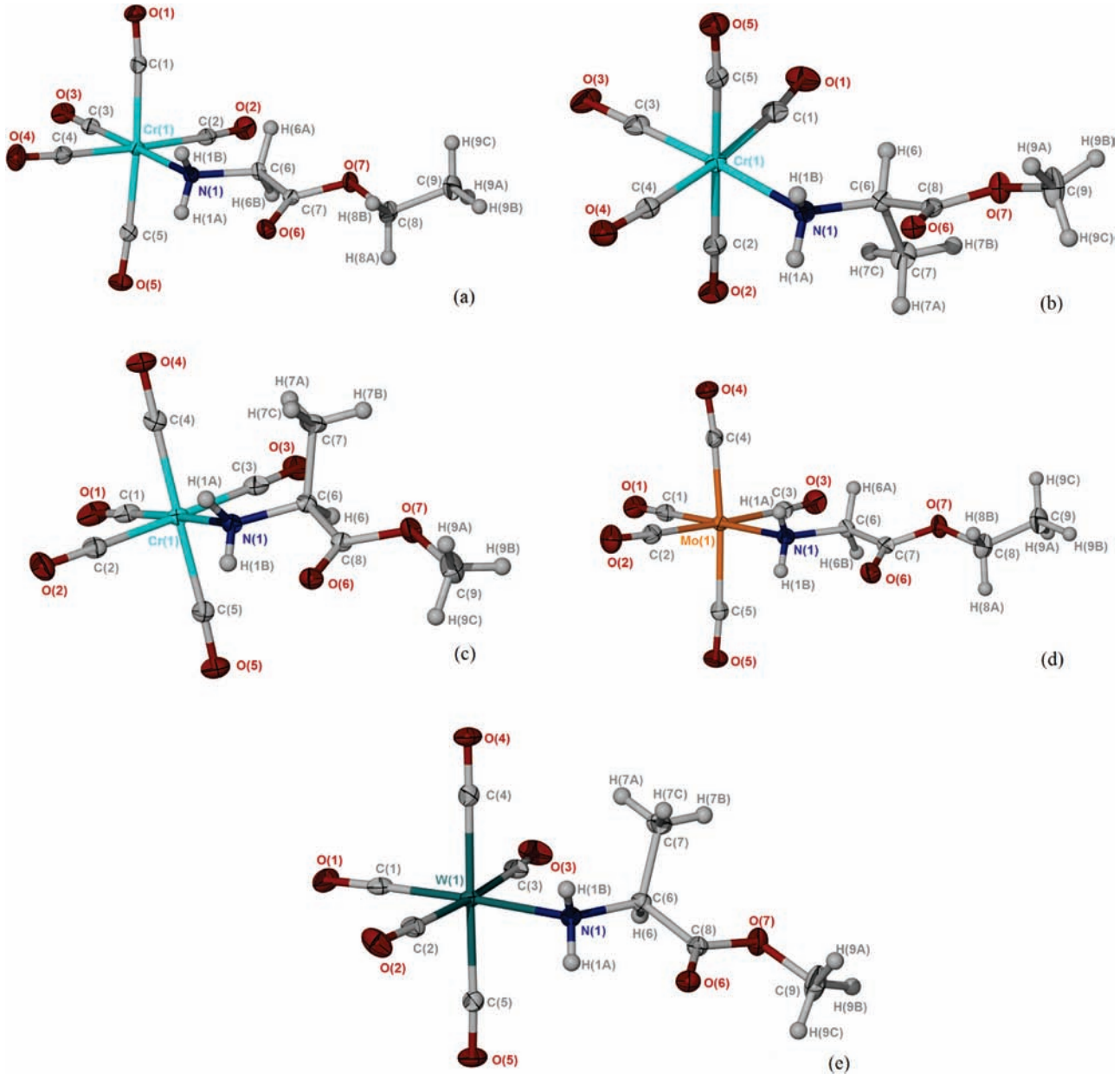


Figure 3. Molecular structures of (a) **1-Cr-a**; (b) **1-Cr-b**; (c) **1-Cr-c**; (d) **1-Mo-a**; (e) **1-W-b**. Thermal ellipsoids in all cases set at the 50% probability level.

agents.[41] However, given that the CO-release from tungsten carbonyl complexes has been sluggish in all cases, it was clear that the corresponding chromium congeners would be of considerable interest.

Reaction of $[Cr(CO)_5(=C\{OMe\}R)]$ (R = Me, Ph, -C≡CPh) with the corresponding amino esters in the presence of base resulted in the formation of amino carbene complexes $[Cr(CO)_5(=C\{NH-CHRCO_2R\}R)]$, **3**, Scheme 1. In addition, it was possible to extend this procedure to the parent glycine with no protection of the carboxylic acid group (complexes **3c-3e**).

For complexes **3b-3h** ^{1}H NMR spectra indicated that a mixture of *E* and *Z* isomers around the C−N bond had been formed: the *E*/*Z* ratios are presented in Scheme 1. In most cases the *Z*-isomer predominates.[41] The NMR spectroscopic data for the complexes are consistent with the presence of Fischer-type carbene ligand with resonances being observed at about δ 280 in the $^{13}C\{^1H\}$ spectra.

Crystals of **3b** suitable for study by X-ray diffraction were obtained by slow diffusion of hexane into a CH_2Cl_2 solution of the complex at −30 °C. The resulting structure determination demonstrated that the complex had selectively crystallized as the *E*-isomer (Figure 5). The structural metrics exhibited by the complex are typical of Fischer-type amino carbene complexes.[42] For example, the Cr−C(1) distance (1.8792(12) Å), which is *trans* to the carbene ligand, is notably shorter than the four Cr−C distances which are *cis* to the carbene (mean 1.9012 Å). The bond between the chromium and the carbene atom is

(41) Salmain, M.; Licandro, E.; Baldoli, C.; Maiorana, S.; Tran-Huy, H.; Jaouen, G. *J. Organomet. Chem.* **2001**, *617*, 376–382.

(42) Wang, C. C.; Wang, Y.; Liu, H. J.; Lin, K. J.; Chou, L. K.; Chan, K. S. *J. Phys. Chem. A* **1997**, *101*, 8887–8901.

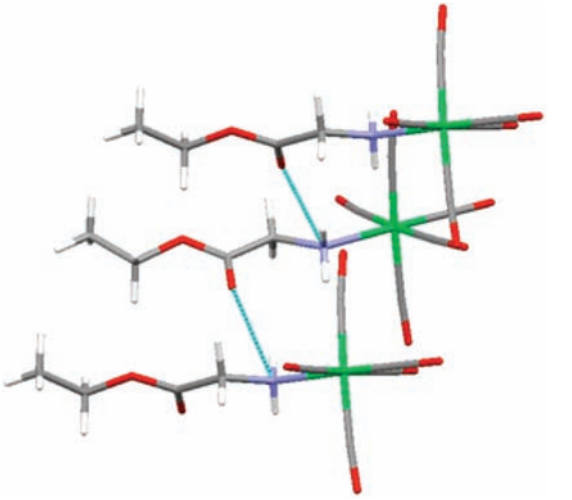


Figure 4. Hydrogen bonding interactions between glycine groups in the structure of **1-Cr-a**.

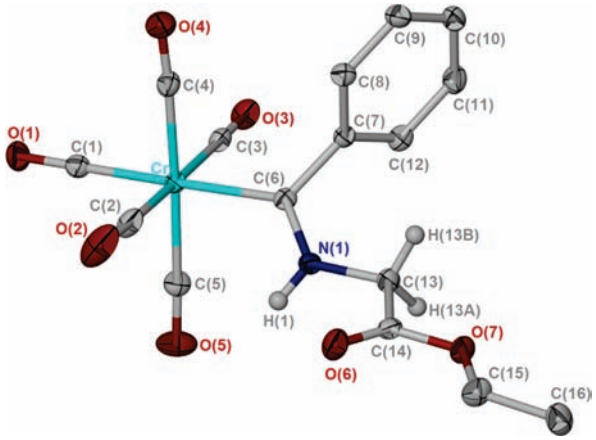
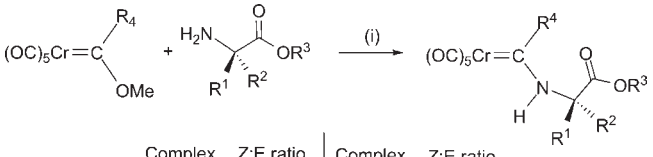


Figure 5. Molecular structure of **3b**. Thermal ellipsoids set at the 50% probability level and selected hydrogen atoms omitted for clarity.

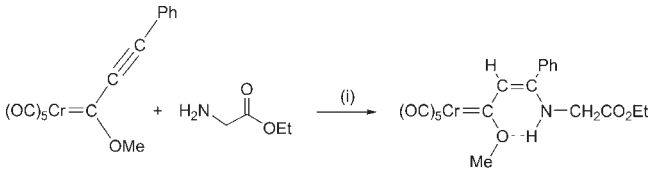
Scheme 1. (i) CH_2Cl_2, 30 Minutes, Ambient Temperature



Complex	Z:E ratio	Complex	Z:E ratio
3a	*E* only	**3e**	*Z* only
3b	1.6:1	**3f**	*E* only
3c	3.5:1	**3g**	3.7:1
3d	3.5:1	**3h**	8.0:1

typical, as is the short C(6)−N(1) distance which highlights the double bond character of this interaction. The carbene ligand sits in a plane essentially bisecting the *cis M-CO* unit (angle between planes containing C(1)−Cr−C(2)−C(3) and Cr−C(6)−N(1)−C(7) = 47.7°). These data indicate that the presence of the ester functionality does not significantly influence the structure of the carbene ligand. The strategy utilized to prepare the amino-substituted carbene complexes was also extended to include novel thio-substituted carbenes. Reaction of **2b** with ester-protected *N*-acetylcysteine, (*R*)-NH(COMe)-$CH(CH_2SH)CO_2Et$, resulted in the formation of the carbene complex **4**. The ^1H and $^{13}C\{^1H\}$ NMR spectra of **4** were consistent with this formulation. In particular, the carbene carbon resonance was observed at δ 362.7, characteristic of sulfur-substituted, as opposed to N- or O- substituted, carbene ligands of this type.[43,44]

Scheme 2. (i) CH_2Cl_2, 30 Minutes, Ambient Temperature



2c **5**

The fact that alkynyl-substituted carbene complexes may undergo facile Michael-type addition[45] at the alkyne triple bond may be also be exploited for the incorporation of pendant amino esters into the periphery of the coordination sphere of chromium carbene complexes. Reaction of **2c** with in situ generated $NH_2CH_2CO_2Et$ resulted in the formation of the alkenyl-substituted carbene complex **5** (Scheme 2). The structure of **5** was confirmed by a single crystal X-ray diffraction study. The bond lengths and angles within this complex are typical.[46] The structure determination demonstrated that the anticipated addition of an N−H unit across the C≡CPh had occurred to produce a *Z*-substituted alkenyl carbene complex (Figure 6). In general, the addition of secondary amines to phenyl-substituted alkynyl carbene complexes affords the corresponding *E*-substituted alkenyl ligands.[45] The difference in the stereochemistry in the case of **5** may be ascribed to the presence of a strong hydrogen bond between the N−H functionality of the alkenyl group and the oxygen of the OMe attached to the carbene (N(1)−H(1)···O(6) 2.6027(17) Å). This effect is also manifested in the ^1H NMR spectrum of **5** with the proton of the N−H group exhibiting a low field resonance at δ 9.34. It is worth noting that the existence of such hydrogen bonds, and the fact that they may favor a *Z*-substitution pattern, has been proposed previously,[46] and the structure of **5** supports this idea.

CO-Release Tests. The ability of the complexes prepared in this study to release CO was evaluated in a myoglobin-based aqueous assay.[47] A solution of deoxymyoglobin (deoxyMb) was prepared and subsequently treated with a solution of the CO-RM 37.8 °C. Any CO released by the CO-RM results in the conversion of deoxyMb to carbonmonoxymyoblobin (MbCO), and this change may be monitored by UV−vis spectroscopy. A typical series of spectra showing the conversion of deoxyMb to MbCO induced by CO release from **1-Cr-a** is shown in Figure 7a. The UV−vis spectra therefore

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(44) Dotz, K. H.; Leue, V. *J. Organomet. Chem.* **1991**, *407*, 337–351.
(45) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964–4002.
(46) Duetsch, M.; Stein, F.; Lackmann, R.; Pohl, E.; Herbstirmer, R.; de Meijere, A. *Chem. Ber.-Rec.* **1992**, *125*, 2051–2065.
(47) Rimmer, R. D.; Richter, H.; Ford, P. C. *Inorg. Chem.* **2009**, *49*, 1180–1185.

allow a quantification of the amount of CO released from the CO-RM with time (Figure 7b). We have defined the half-life, $t_{1/2}$, of CO-released as the time taken for a 60 μM solution of a given CO-RM to produce an MbCO concentration of 30 μM. This has been introduced as a measure to compare the CO-release behavior of a range of CO-RMs which may proceed via a number of different mechanistic pathways. Corresponding half-lives for 40 μM and 20 μM solutions of CO-RM to generate 20 and 10 μM of Mb-CO, respectively, were also determined.

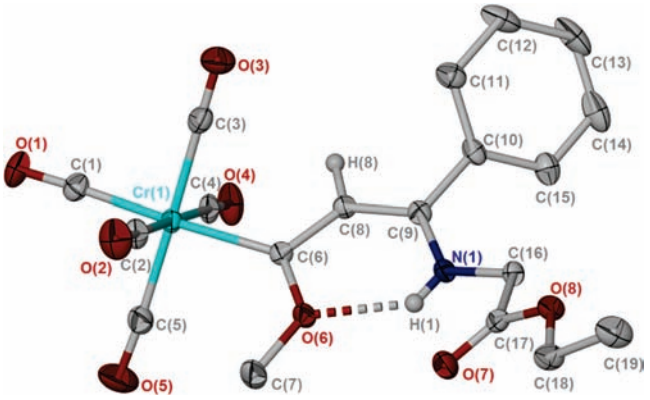

Figure 6. ORTEP representations of the X-ray structures of **5**. Thermal ellipsoids in all cases set at the 50% probability level and selected hydrogen atoms omitted for clarity.

The results of the Mb-based assay for all of the complexes studied are presented in Table 3. The chromium amino acid complexes with general structure **1** all exhibited rapid and well controlled CO-release profiles. For each CO-RM $t_{1/2}$ exhibited little dependence on the concentration of the complex employed presumably indicating a first order process is operative. Within this series of complexes **1-Cr-a** displayed the slowest release; the two enantiomers of the methylester-protected alanine-substituted complexes (**1-Cr-b** and **1-Cr-c**) showed essentially identical release profiles, as did the corresponding ethylester-protected complex **1-Cr-d**. The protected glutamic acid derivative **1-Cr-e** exhibited the fastest release profile of all the chromium amino ester complexes.

In previous studies with complexes based on the $[MX(CO)_5]^-$ (M = Cr, Mo, W) motif, the rate of CO-release has been shown to depend on the metal employed with Cr > Mo≫W. In the case of complexes **1-Cr-a**, **1-Mo-a**, and **1-W-a**, all of which possess an ethyl-ester-protected glycine unit, the tungsten complex was a far slower releaser than the corresponding molybdenum and chromium complexes. However, in this instance, the molybdenum complex exhibited more rapid CO-release than the corresponding chromium species. An important further feature is that both the chromium and molybdenum-based

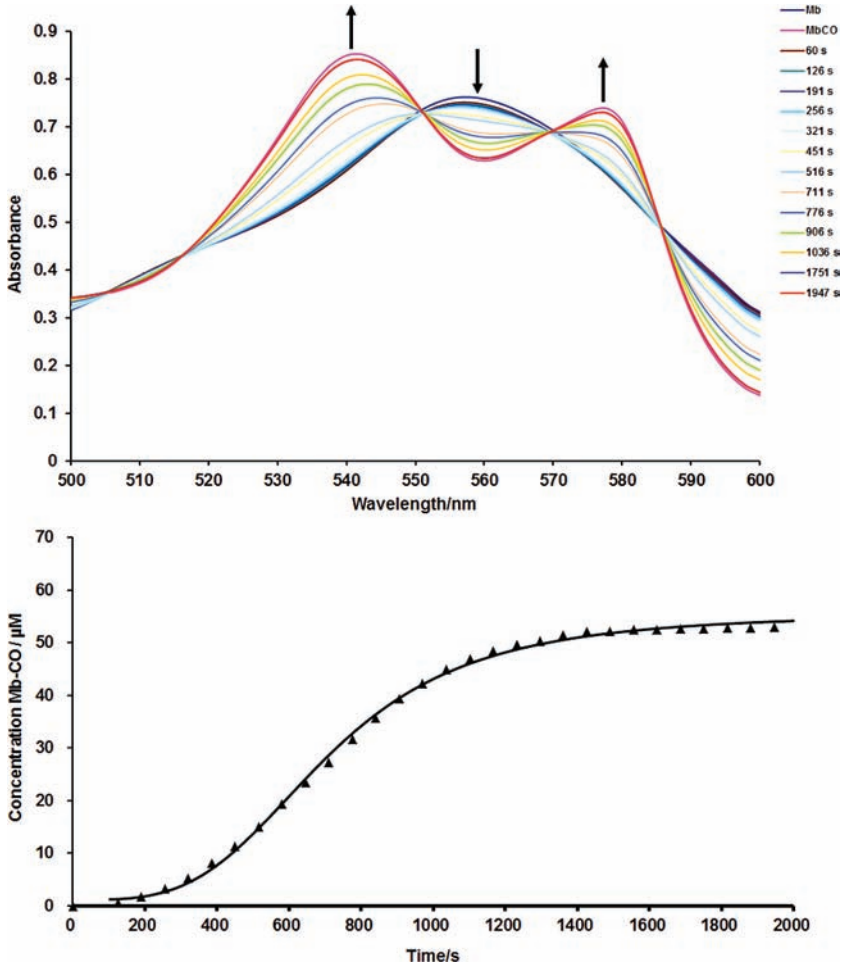

Figure 7. CO release profile for a 40 μM solution of **1-Cr-a** (a) UV−vis spectrum showing the Q-bands during the conversion of deoxy-Mb to MbCO with time. (b) Plot of [Mb-CO] against time.

Table 3. CO-Release Data for Complexes

entry	complex	$t_{1/2}$ 60 μM/s	$t_{1/2}$ 40 μM/s	$t_{1/2}$ 20 μM/s
1	**1-Cr-a**	573	589	565
2	**1-Cr-b**	504	475	447
3	**1-Cr-c**	485	461	425
4	**1-Cr-d**	494	533	521
5	**1-Cr-e**	471	425	441
6	**1-Mo-a**	247	264	317
7	**1-W-a**	3350[a]	*b*	*b*
8	**1-W-b**	7814[a]	*b*	*b*
9	**2a**[c]	306	231	188
10	**2b**[c]	332	297	305
11	**2c**	773	582	646
12	**3a**	*b*	*b*	*b*
13	**3b**	*b*	*b*	*b*
14	**3c**	10366	8230	9530
15	**3d**	7695	5837	3408
16	**3e**	9765	7556	6342
17	**3f**	6905	7913	4880
18	**3g**	1382	1087	821
19	**3h**	6800	4071	5156
20	**4**	378	319	226
21	**5**	*b*	*b*	*b*
22	**7**	313	288	303

[a] Time taken to achieve an Mb-CO concentration of 10 μm. [b] No CO-release detected. [c] Reference 35.

complexes show evidence for the release of multiple CO-ligands. In the case of **1-Mo-a**, it appears that 2.5 mols of CO are released per metal center.

The CO-release exhibited by the amino-acid and amino-ester substituted Fischer-type amino-carbene complexes was far slower. Indeed, no CO-release was detected from the glycine ethylester-substituted complexes **3a** and **3b** nor the alkenyl-substituted methoxy carbene complex **5**. Slow CO-release was observed in the case of the parent glycine complexes **3c**, **3d**, and **3e**, and the most rapid release in the amino-carbene series was observed from the ester-protected cysteine derivative **3g**.

These data contrast sharply with our previously reported investigations into the methoxy-substituted carbene complexes **2a**−**c**: in this instance rapid CO-release was observed, $t_{1/2}$ typically being over an order of magnitude less than the amino-derivatives. Interestingly, the sulfur-substituted carbene complex **4** exhibits rapid CO-release, at a rate similar to complexes **2a**−**c**. It therefore appears that the rate of CO-release from the Fischer carbene complexes is principally dependent on the nature of the heteroatom substituent on the carbene carbon. Consistent with this argument, CO-release from $[Cr(CO)_5(=CPh\{NHMe\})]$, **6**, is extremely slow (requiring over 2 h for a 60 μM solution of **6** to generate an Mb-CO concentration of 10 μM), consistent with the observations obtained in the case of the other amino-substituted carbene complexes.

A theoretical study into the structure of the carbene complexes $[Cr(CO)_5(=CRX)]$ (R = Me, Ph, −C≡CH; X = heteroatom group) has demonstrated that the electrophilicity of the carbene carbon depends on the R and X groups.[48] Better π-donor groups, such as when X = amino or R = −C≡CH, makes the carbene less electrophilic when compared to the case when X = alkoxy and R = Me. As amino-substituted carbene complexes exhibit

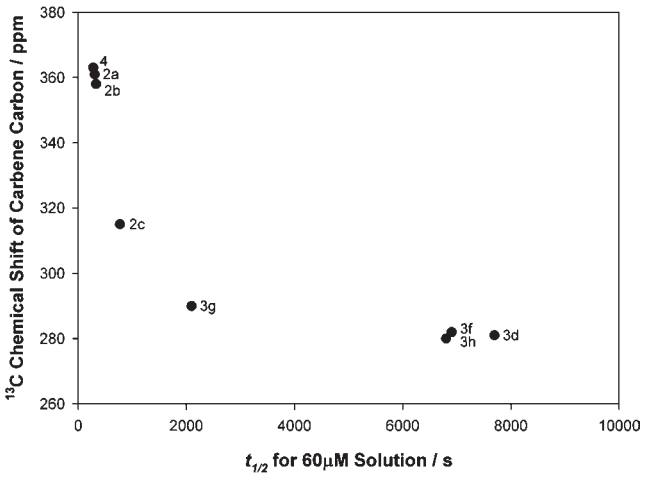

Figure 8. Correlation of chemical shift of the carbene carbon of complexes **2**, **3**, and **4** with $t_{1/2}$ for CO-release.

far slower release than their alkoxy analogues, and complex **2c** (in which the carbene possesses an alkynyl substituent) exhibits slower release than the corresponding methyl and phenyl-substituted compounds, there appears to be a correlation between the electrophilicity of the carbene and the rate of CO-release. This effect is apparent in a comparison of the chemical shift of the carbene carbon in these complexes with their respective $t_{1/2}$ values (Figure 8). The chemical shift of the carbene carbons resonances for the fastest CO-releasing complexes (those with O- or S-substituent) are at significantly lower field that those for the slow-releasing amino analogues.

The hydrolysis of Fischer-type carbene complexes has been extensively studied by Bernasconi and co-workers.[49−52] In the case of carbene complexes without ionizable groups, nucleophilic attack on the carbene carbon is the principal mode of reactivity. Given that the complexes with the most electrophilic carbene atoms release CO at the fastest rate, nucleophilic attack by water onto this group could be crucial in the activation of the CO-RMs.

Mechanistic Investigations. Complexes with the general structure **1** exhibited both rapid and well-controlled CO-release which could be modulated by the choice of metal and amino ester employed; therefore, a study was undertaken into the mechanism by which these species were releasing CO. As previous studies with the $[MX(CO)_5]^-$ series of complexes had suggested that cleavage of the M−X bond was rate controlling in the CO-release process.[35] It was therefore reasoned that loss of the amino-ester may be playing the same role in the case of complexes **1**. Considering that dimethylsulfoxide (DMSO) was the delivery medium into the Mb-based assay; and that we have previously demonstrated that DMSO may activate cobalt-based CO-RMs,[28] $[Cr(CO)_5(DMSO)]$, **7**, was considered as a possible intermediate in the CO-release process. Treatment of a CH_2Cl_2/H_2O solution of $[NEt_4][CrCl(CO)_5]$ with DMSO resulted in the formation

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(49) Bernasconi, C. F.; Sun, W. T. *Organometallics* **1995**, *14*, 5615–5621.
(50) Bernasconi, C. F. *Chem. Soc. Rev.* **1997**, *26*, 299–307.
(51) Bernasconi, C. F.; Flores, F. X.; Kittredge, K. W. *J. Am. Chem. Soc.* **1997**, *119*, 2103–2110.
(52) Zoloff Michoff, M. E.; de Rossi, R. H.; Granados, A. M. *J. Org. Chem.* **2006**, *71*, 2395–401.

of **7** in good yield. Appropriate resonances in the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of the complex were observed: a band in the IR spectrum at 1090 cm^{-1} is consistent with an S-bound DMSO ligand.[53]

Treatment of a $CDCl_3$ solution of **1-Cr-a** with DMSO resulted in the formation of **7** and the uncoordinated glycine ethyl ester, thus demonstrating that the amino ester ligand is labile in these complexes. Similar observations were made when the reaction between **1-Cr-e** and DMSO was monitored by UV−vis spectroscopy in CH_2Cl_2 solution. Complex **1-Cr-e** exhibits a band at 416 nm in the UV−vis spectrum. On addition of DMSO to the solution, this band decreased in intensity, to be replaced by new peak at 376 nm: an isosbestic point was observed at 390 nm (Figure 9a). A similar band was observed from the reaction of complexes **1-Cr-a** and **1-Cr-b** with DMSO in CH_2Cl_2. This is also the band observed in an isolated sample of **7**. These data support the notion that loss of the amino-ester group is the principal mode of reactivity of these species.

To demonstrate if a similar process was occurring under the conditions used to monitor CO-release, a DMSO solution of **1-Cr-e** was added to an aqueous solution containing phosphate-buffered saline (PBS) buffer. This was an attempt to reproduce the conditions of the Mb-based assay, except no protein was added. The resulting solution was monitored by UV−vis spectroscopy (Figure 9b). A band at 402 nm was observed immediately, essentially identical to the persistent band observed for **1-Cr-d** alone in CH_2Cl_2 solution. Over a period of several minutes this band decreased in intensity to be replaced by one at 372 nm which did not significantly increase in intensity over time. Almost identical observations where made when complexes **1-Cr-a** and **1-Cr-b** were employed. In addition, experiments where the delivery solvent was changed from DMSO to either water or EtOH also showed the presence of a similar band at about 372 nm in the UV−vis spectra.

These data appear to indicate that a common intermediate is formed when solutions of the amino ester complexes are dosed into the Mb-based assay. It is proposed that replacement of the amino ester by solvent occurs to give species "$M(CO)_5S$" where S is a solvent molecule. Given that the intensity of the band due to the intermediate does not increase in PBS solution, it is proposed that loss of the amino-ester is the crucial step in the initiation of the CO-releasing process. This is consistent with the observation that the complexes containing more sterically demanding amino esters exhibit faster CO-release. It is important to contrast these data with the elegant mechanistic studies performed by Darensbourg and co-workers on chromium and tungsten glycinate complexes $[M(CO)_4(\kappa^2\{NO\}\text{-}NH_2CH_2CO_2)]^-$ where it was demonstrated that loss of CO is promoted by deprotonation of the amino group.[36,37] In the case of the neutral monodentate complexes, our data indicated that loss of the biologically compatible leaving group is the key step in the reaction mechanism. This difference may be simply rationalized on the basis of the different binding modes of the amino-based ligand.

(53) Price, J. H.; Williamson.A. N.; Schramm, R. F.; Wayland, B. B. *Inorg. Chem.* **1972**, *11*, 1280−1284.

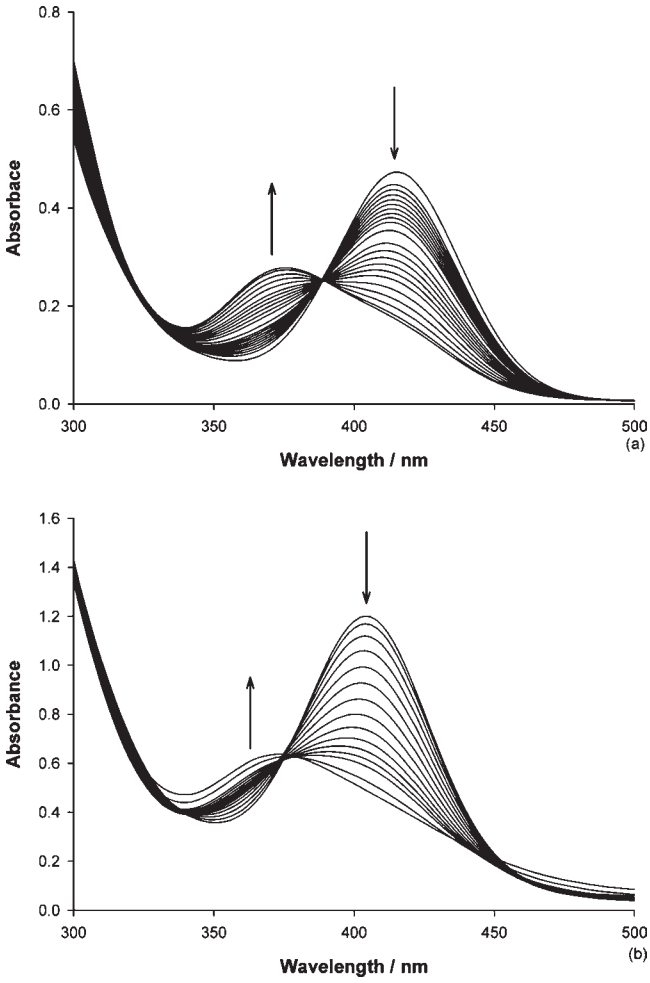

Figure 9. (a) UV−vis spectra showing the decomposition of complex **1-Cr-e**, spectra recorded at regular intervals for a total of 83 min. (b) UV−vis spectra showing the decomposition of complex **1-Cr-e** in PBS solution, spectra recorded at regular intervals for a total of 23 min.

Conclusions

In this paper we have demonstrated that it is possible to incorporate amino acids and amino esters into the coordination sphere of Group 6 metal carbonyl complexes. In the case of complexes **1**, a versatile new route has been developed to prepare complexes which contain an N-bound amino ester coordinated to a $M(CO)_5$ unit. Crucially, loss of the organic group appears to be the principal mode of reaction of these complexes and may play an important role in controlling the rate of CO-release, which appears to occur more readily when sterically demanding amino esters are present. This may be reflected in the Cr−N bond lengths as it appears that the glycine ester in **1-Cr-a** is more tightly bound that the alanine ester in **1-Cr-b** and **1-Cr-c**. However, it is important to note that the precise steps involved in the subsequent dissociation of the carbonyl ligands from putative "$M(CO)_5$" are not yet known.

In the substituted Fischer-type carbene complexes there is a clear correlation between the electrophilicity of the carbene carbon and the rate of CO release. This may indicate that nucleophilic attack by water is the key step in this process.

On a general note, these studies have shown that the incorporation of a biologically compatible amino acid ligand into the coordination sphere of group 6 metal carbonyl complexes

offers considerable potential for tuning and modulating CO-release rates. To date, the vast majority of biological studies have been performed with CO-RM 3, which exhibits a half-life for CO-release of a few minutes. It is therefore evident that related studies employing a library of compounds, which exhibit diverse CO-release profiles, would be an important addition so that the optimum rate of release may be determined. This will almost certainly be application-dependent. Future studies are underway to incorporate peptides into the coordination sphere of this class of CO-RMs.

Experimental Section

All manipulations were accomplished by using standard Schlenk line and glove box apparatus. An Innovative Technologies anhydrous solvent engineering system was used for purification of dichloromethane, pentane, hexane, and toluene. All other solvents were AR grade and used without further purification. Complexes $[NEt_4][MX(CO)_5]$ (M = Cr, Mo, W; X = Cl, Br, I)[54] and $[Cr(=C\{OCH_3\}R)(CO)_5]$ (R = CH_3 **2a**, C_6H_5 **2b**,[55] $C{\equiv}CC_6H_5$ **2c**[56]) were prepared according to literature procedures. Amino acids, amino esters, and $M(CO)_6$ (M = Cr, Mo and W) were purchased from Aldrich; the latter were sublimed prior to use. Myoglobin, light mineral oil, and PBS were purchased from Sigma and sodium dithionite from Alfa Aeasar. Ultraviolet−visible spectra were recorded using a JASCO V-560 instrument. IR spectra were acquired on a Mattson Research Series FTIR spectrometer using CsCl solution cells. NMR spectra were recorded on either a Bruker AMX 300 Spectrometer (Operating frequencies ^{1}H 300.13 MHz; ^{13}C 76.98 MHz) or a Jeol ECX-400 (operating frequencies ^{1}H 400.13 MHz, ^{13}C 100.60 MHz). For ^{13}C NMR data, "*cis*" and "*trans*" carbonyl resonances refer to orientation relative to either amino-ester or carbene substituent as appropriate. Mass spectra were obtained on a Bruker microTOF instrument. Complexes with general structure **1** and **7** only show limited stability in solution and should be stored at low temperature. In some cases this instability has precluded combustion analysis. In addition, no molecular fragments were detected in the ESI-MS of the chromium- and molybdenum-based complexes of type **1**.

Preparation of 1-Cr-a. Method A: $[NEt_4][CrCl(CO)_5]$ (100 mg, 0.28 mmol) dissolved in 5 mL dry methanol. Glycine ethyl ester hydrochloride salt (39 mg, 0.28 mmol) was neutralized by NEt_3 in methanol. The methanol solution of free glycine ethyl ester was added by syringe. The reaction was stirred at 20 °C for 20 min until no more product formed. The methanol was removed under vacuum, and the crude product purified by flash column chromatography on silica gel. $Cr(CO)_5(\eta^1\text{-}NH_2CH_2COOCH_3)$ as a yellow solid (Yield 21 mg, 24%). Diffusion hexane into CH_2Cl_2 solution of the product at −30 °C furnished fine needle crystals suitable for X-ray diffraction structure analysis. IR (CH_2Cl_2, cm^{-1}): 2069w, 1980w, 1933s, 1896; ^{1}H NMR (CD_2Cl_2): δ 1.27 (t, 3H, 6.9 Hz, C***H***$_3$), 2.17 (br, 2H, N***H***$_2$), 3.32 (t, 2H, 7.2 Hz, C***H***$_3$), 4.22(q, 2H, 6.9 Hz, OC***H***$_2$); ^{13}C{^{1}H} NMR (CD_2Cl_2): δ 15.8 (***C***H$_3$), 53.6 (***C***H$_2$NH$_2$) 64.0 (O***C***H$_2$), 172.6 (***C***=O), 215.9 (*cis*-***C***O), 221.6 (*trans*-***C***O); Elemental analysis ($CrC_{10}H_{11}NO_7$) observed (calculated) %: C 36.70 (36.62)%, H 2.97 (3.07)%, N 4.57 (4.75)%. Method B: $[NEt_4][CrCl(CO)_5]$ (100 mg, 0.28 mmol) was dissolved in 5 mL CH_2Cl_2 and cooled to 0 °C. Water (1 mL) was added followed immediately by 1 equiv of $NH_2CH_2COOC_2H_5$ [freshly prepared by the reaction of glycine ethyl ester hydrochloride salt (39 mg, 0.28 mmol) with sodium carbonate (29 mg, 0.28 mmol)]. The reaction was stirred for 5 min and then warmed to 20 °C. The initially light yellow of reaction mixture turned into orange quickly, and the color then faded after 5 min. The course of reaction was followed by IR and TLC. After 20 min, the characteristic carbonyl band of $[NEt_4][Cr(CO)_5Cl]$ at 1923(s) cm^{-1} disappeared to be replaced by a band for the product at 1933(s) cm^{-1}. TLC analysis also identified the yellow spot of the product with R_f = 0.21 (CH_2Cl_2). The CH_2Cl_2 solution was separated and dried over $MgSO_4$. Flash Chromatography on silica-gel afforded pure $[Cr(CO)_5(\eta^1\text{-}NH_2CH_2COOCH_3)]$ as a yellow solid 45 mg (yield 54%).

Method B was employed for the preparation of the following complexes with use of appropriate amino esters as substrates.

Preparation of 1-Cr-b. A 58 mg portion of yellow solid was isolated with yield 70%. Diffusion of hexane into CH_2Cl_2 solution of the product at −30 °C furnished suitable crystals for X-ray diffraction structure analysis. R_f = 0.3 (CH_2Cl_2), IR (CH_2Cl_2, cm^{-1}): 2069w, 1979w, 1933s, 1896; ^{1}H NMR ($CDCl_3$): δ 1.43 (d, 3H, 6.6 Hz, C***H***$_3$), 1.64, 2.61(br, 2H, N***H***$_2$), 3.26 (m, 1H, C***H***NH$_2$), 3.82 (s, 3H, OC***H***$_3$); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 20.6 (***C***H$_3$), 53.1 (O***C***H$_3$) 57.8 (N***C***H), 173.8 (***C***=O), 213.8 (*cis*-***C***O), 219.6 (*trans*-***C***O);

Preparation of 1-Cr-c. A 65 mg portion of a yellow solid was isolated with yield 79%. Diffusion of hexane into a CH_2Cl_2 solution of the product at −30 °C furnished suitable crystals for X-ray diffraction structure analysis. R_f = 0.3 (CH_2Cl_2), IR (CH_2Cl_2, cm^{-1}): 2069w, 1979w, 1933s, 1896; ^{1}H NMR ($CDCl_3$): δ 1.43 (d, 3H, 6.6 Hz, C***H***$_3$), 1.60, 2.61 (br,2H, N***H***$_2$), 3.26 (m, 1H, C***H***NH$_2$), 3.82 (s, 3H, OC***H***$_3$); ^{13}C{^{1}H} NMR($CDCl_3$): δ 20.6 (***C***H$_3$), 53.1(O***C***H$_3$) 57.8 (NCH), 173.8 (C=O), 213.8 (*cis*-CO), 219.6 (*trans*-CO); Elemental Analysis ($CrC_{10}H_{11}NO_7$) observed (calculated) %: C 36.57 (36.62) %, H 2.99 (3.07)%, N 4.57 (4.75)%.

Preparation of 1-Cr-d. A 72 mg portion of a yellow oil was isolated with yield of 83%. TLC R_f = 0.75 (CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}): 2069w, 1980w, 1933s, 1894 m, 1731w; ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, 7.2 Hz, ***C***H$_3$), 1.36 (d, 3H, 6.8 Hz,***C***H$_3$), 2.59 (br, 2H, N***H***$_2$), 3.17 (m, 1H, NH$_2$C***H***), 4.20 (q, 2H, 7.2 Hz, OC***H***$_2$); ^{13}C{^{1}H} NMR($CDCl_3$): δ 14.2 (CO_2***C***H$_3$), 20.9 (***C***H$_3$), 58.1 (NH$_2$***C***H), 62.5 (O***C***H$_2$), 173.5 (***C***=O), 213.9 (*cis*-***C***O), 219.7 (*trans*-***C***O).

Preparation of 1-Cr-e. A 98 mg portion of a yellow oil was isolated with yield of 95%. TLC R_f = 0.66 (CH_2Cl_2/Acetone = 8:1); IR (CH_2Cl_2, cm^{-1}): 2069w, 1980w, 1933s, 1894, 1740w; ^{1}H NMR ($CDCl_3$): δ 2.01 (br, 2H, C***H***$_3$), 2.46 (br, 3H, C***H***$_2$ and N***H***), 2.63 (br, 1H, N***H***), 3.26 (br, 1H, NH$_2$C***H***), 3.74 (s, 3H, OC***H***$_3$), 3.84 (s, 3H, OC***H***$_3$) ; ^{13}C{^{1}H} NMR ($CDCl_3$): δ 30.0 (***C***H$_2$), 30.4 (***C***H$_2$), 52.4 (O***C***H$_3$), 53.2 (O***C***H$_3$), 62.8 (NH$_2$***C***H), 172.6 (***C***=O), 173.4 (***C***=O), 214.0 (*cis*-***C***O), 219.8 (*trans*-CO).

Preparation of 1-Mo-a. A 55 mg portion of yellow crystals was isolated with yield of 30%. Diffusion of hexane into a CH_2Cl_2 solution of the product at −30 °C furnished suitable crystals for X-ray diffraction structure analysis. IR (CH_2Cl_2, cm^{-1}): 2075w, 1981w, 1938s, 1896, 1735w; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, 7.2 Hz, CH_3), 2.58 (br, 2H), 3.47 (t, 2H, 7.35 Hz, CH_2), 4.25(q, 2H, 7.2 Hz, OCH_2); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 14.32 (CH_3), 52.28 ($CHNH_2$), 62.42 (OCH_2), 171.0 (C=O), 203.9 (*cis*-CO), 212.58 (*trans*-CO); Elemental analysis ($MoC_{10}H_{11}NO_7$) observed (calculated) %: C 31.68 (31.88)%, H 2.59 (2.68)%, N 3.98 (4.01) %.

Preparation of 1-W-a. A 57 mg portion of yellow crystals was isolated with yield of 48%. R_f = 0.5 (CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}): 2072w, 1927s, 1883, 1734w; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3H, 7.2 Hz, CH_3), 2.98 (br, 2H, N***H***$_2$), 3.60 (t, 2H, 7.5 Hz, C***H***$_2$NH$_2$), 4.28 (q, 2H, 7.2 Hz, OC***H***$_2$); ^{13}C{^{1}H} NMR($CDCl_3$): δ 14.3 (***C***H$_3$), 54.1 (***C***H$_2$NH$_2$), 62.7 (O***C***H$_2$), 171.3 (***C***=O), 197.9 (*cis*-***C***O), 200.7 (*trans*-***C***O); Elemental analysis ($WC_{10}H_{11}NO_7$) observed (calculated) %: C 25.33 (25.31)%, H 2.00 (2.12)%, N 3.11 (3.28)%.

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Preparation of 1-W-b. An 86 mg portion of yellow crystals was isolated with yield of 50%. R_f = 0.47 (CH_2Cl_2); Diffusion hexane into CH_2Cl_2 solution of the product at −30 °C furnished suitable crystals for X-ray diffraction structure analysis. IR (CH_2Cl_2, cm^{-1}): 2073w, 1927s, 1892, 1740w (C═O); ^1H NMR ($CDCl_3$): δ 1.48 (d, 3H, 6.9 Hz, C***H***$_3$), 2.57 (1H, N***H***$_2$), 3.50 (1H, N***H***$_2$), 3.53 (m, 1H, NH_2C***H***), 3.84 (s, 3H, OC***H***$_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 20.9 (***C***H_3), 53.6 (O***C***H_3) 60.1 (N***C***H), 174.0 (***C***=O), 198.0 (*cis*-***C***O), 200.8 (*trans*-***C***O); HRMS (ESI) *m*/*z* 449.9780 (449.9781 calculated for $C_9H_9N_1NaO_7W[M+Na]^+$).

General Procedure for the Preparation of Complexes 3. A 0.4 mmol quantity of the appropriate Fischer carbene complex **2** (0.4 mmol) and the HCl salt of the amino acid ester (0.4 mmol) were dissolved by 5 mL of solvent (CH_2Cl_2, MeCN or MeOH). The reaction was stirred in the presence of base (NEt_3 or Na_2CO_3). The reaction was monitored by TLC and halted when no further generation of the product was observed, typically 30 min. The solvent was removed under vacuum and the residue purified by column chromatography on silica gel.

Preparation of 3a. Seventy-nine milligrams of yellow oil was isolated (yield 54%). R_f = 0.5 (CH_2Cl_2:hexane 1:1); IR (CH_2Cl_2, cm^{-1}): 2056 m, 1927s, 1742w (C═O); ^1H NMR ($CDCl_3$): δ 1.35 (t, 7.5 Hz, 3H, C***H***$_3$), 2.68 (s, 3H, C***H***$_3$), 4.15 (d, 4.8 Hz, 2H, NC***H***$_2$), 4.35(q, 7.5 Hz, 2H, OC***H***$_2$), 9.34(br, N***H***, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 14.2 (***C***H_3), 37.1 (═C***C***H_3), 48.1 (N***C***H_2), 63.0 (O***C***H_2), 168.0 (***C***=O), 218.0 (*cis*-***C***O), 223.0 (*trans*-***C***O), 286.5 (Cr=***C***); HRMS (ESI) *m*/*z* 343.9831 (343.9833 calculated for $C_{11}H_{11}CrNNaO_7$ $[M+Na]^+$).

Preparation of 3b. Twenty-six milligrams of major product was isolated as a yellow solid (yield 26%). R_f = 0.45 (CH_2Cl_2: hexane 1:1); Diffusion of hexane into a CH_2Cl_2 solution of the product at −30 °C furnished suitable crystals for X-ray diffraction structure analysis. IR (CH_2Cl_2, cm^{-1}): 2056 m, 1936s, 1745w; ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): (*Z*-isomer) δ 1.28 (t, 7.2 Hz, 3H, C***H***$_3$), 3.90 (d, 5.1 Hz, 2H, NC***H***$_2$), 4.27 (q, 7.2 Hz, 2H, OC***H***$_2$), 6.79 (2H, C$_6$***H***$_5$), 7.26 (C$_6$***H***$_5$), 7.42 (2H, C$_6$***H***$_5$), 9.53 (br, N***H***, 1H); ^1H NMR ($CDCl_3$): (*E*-isomer) δ 1.37 (t, 7.2 Hz, 3H, C***H***$_3$), 4.35 (d, 6.9 Hz, 2H, NC***H***$_2$), 4.81 (q, 7.2 Hz, 2H, OC***H***$_2$), 7.02−7.39 (br, m, 5H, C$_6$***H***$_5$), 9.06 (br, N***H***, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) (*Z*-isomer): δ 14.0 (***C***H_3), 50.2 (N***C***H_2), 62.6 (O***C***H_2), 118.6 (***C***$_6H_5$), 127.2 (***C***$_6H_5$), 129.0 (***C***$_6H_5$), 150.0 (***C***$_6H_5$), 167.4 (***C***=O), 216.8 (*cis*-***C***O), 223.3 (*trans*-***C***O), 287.8 (Cr=***C***); HRMS (ESI) *m*/*z* 405.9985 (405.9909 cacld for $C_{16}H_{13}CrNNaO_7$ $[M+Na]^+$); Elemental analysis ($C_{16}H_{13}CrNO_7$) observed (calculated) %: C 49.95 (50.14)%, H 3.38 (3.42)%, N 3.55 (3.65)%

Preparation of 3c. A 94 mg portion of light yellow solid was isolated Yield 78%. R_f = 0.4 (CH_2Cl_2:CH_3OH 3:1); IR (CH_2Cl_2, cm^{-1}): 2056 m, 1974w, 1927s; ^1H NMR ($CDCl_3$): (*Z*-isomer) δ 2.50 (br, 3H, C***H***$_3$), 4.04 (br, 2H, NC***H***$_2$), 9.33 (br, N***H***); ^1H NMR ($CDCl_3$): (*E*-isomer) δ 2.67 (br, 3H, C***H***$_3$), 4.52 (br, 2H, NC***H***$_2$), 9.33 (br, N***H***); $^{13}C\{^1H\}$ NMR ($CDCl_3$): (*Z*-isomer) δ 36.5 (═C***C***H_3), 49.5 (N***C***H_2), 217.7 (*cis*-***C***O), 222.8 (*trans*-***C***O): resonances for the (E)-isomer were not detected. HRMS (ESI) *m*/*z* 291.9562 (291.9555 calculated $[M-H]^-$), $[M-H-CO]^-$ 263.9599, $[M-H-2CO]^-$ 235.9656, $[M-H-3CO]^-$ 207.9707.

Preparation of 3d. Fourteen milligrams of yellow solid was isolated (Yield 10%). TLC R_f = 0.5 (CH_2Cl_2:CH_3OH 2:1); IR(CH_2Cl_2, cm^{-1}): 2056 m, 1977w, 1930s; ^1H NMR ($CDCl_3$/d_6-DMSO): (*Z*-isomer) δ 3.53 (br, 2H, NC***H***$_2$), 6.69−7.30 (br, 5H, C$_6$***H***$_5$); ^1H NMR ($CDCl_3$/d_6-DMSO): (*E*-isomer) δ 4.47 (br, 2H, NC***H***$_2$), 6.92−7.15(br, 5H, C$_6$***H***$_5$); $^{13}C\{^1H\}$ NMR($CDCl_3$/d_6-DMSO): (*Z*-isomer) δ 119.4 (N***C***H_2), 127.7, 129.4, 150.6 (***C***$_6H_5$), 218.0 (*cis*-CO), 223.5(*trans*-CO), 281.3 (Cr=***C***): resonances for the (*E*)-isomer were not detected. HRMS (ESI) *m*/*z* 353.9719 (353.9711 calculated for $C_{14}H_8CrNO_7$ $[M-H]^-$), $[M-H]^-$-CO 325.9765, $[M-H-2CO]^-$ 297.9821, $[M-H-3CO]^-$ 269.9858. Elemental analysis ($C_{14}H_9CrNO_7$) observed (calculated) %: C 47.32 (47.34)%, H 2.58 (2.55)%, N 3.76 (3.94)%.

Preparation of 3e. A 70 mg portion of orange solid was isolated with yield 46%. R_f = 0.5 (CH_2Cl_2:CH_3OH 3:1); IR-(CH_2Cl_2, cm^{-1}): 2056 m, 1979w, 1936s; ^1H NMR ($CDCl_3$): δ 4.30 (br, 2H, NC***H***$_2$), 7.32−7.41 (br, 5H, C$_6$***H***$_5$), 9.55(br, 1H, N***H***), $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 121.14 (C***C***Ph), 130.5 (***C***CPh), 128.4, 131.8(***C***$_6H_5$), 216.9 (*cis*-CO), 223.2 (*trans*-CO); HRMS (ESI) *m*/*z* 378.9779 (378.9784 calculated $[M+H]^+$).

Preparation of 3f. A 116 mg portion of yellow oil was isolated with yield 64%. R_f = 0.4 (petroleum ether/CH_2Cl_2/Acetone 1:1:1); IR (CH_2Cl_2, cm^{-1}): 2056 m, 1938s, 1745w; ^1H NMR ($CDCl_3$): (*E*) δ 3.03 (dd, 15.0 Hz, 4.5 Hz, 1H, C***H***$_2$), 3.17 (dd, 15.0 Hz, 4.5 Hz, 1H, C***H***$_2$), 3.66 (s, 3H, OC***H***$_3$), 4.41(m, 1H, NC***H***), 6.74 (2H, C$_6$***H***$_5$), 6.89 (s, 1H, C_3N_2***H***$_2$), 7.19 (1H, C$_6$***H***$_5$), 7.36 (2H, C$_6$***H***$_5$), 7.66(s, 1H, C_3N_2***H***$_2$), 9.21(br, 1H, N***H***), 11.31 (br, 1H, Imidazole-N***H***); $^{13}C\{^1H\}$ NMR($CDCl_3$):(*E*) δ 29.8 (***C***H_2), 53.0 (O***C***H_3), 61.3 (N***C***H), 113.9 (***C***$_3N_2H_3$), 121.8 (***C***$_3N_2H_3$), 135.7 (***C***$_3N_2H_3$), 119.0 (***C***$_6H_5$), 126.9 (***C***$_6H_5$), 128.8 (***C***$_6H_5$), 149.8 (***C***$_6H_5$), 169.8(***C***=O), 217.2 (*cis*-***C***O), 224.1 (*trans*-***C***O); 283.01(M═C); HRMS (ESI) *m*/*z* 450.0395 (450.0388 calculated $[M]^+$ $C_{19}H_{16}CrN_3O_7$).

Preparation of 3g. A 65 mg portion of red oil was isolated (yield 39%). R_f = 0.52 (CH_2Cl_2/Hexane 2:1); IR (CH_2Cl_2, cm^{-1}): 2058 m, 1940s, 1747w; ^1H NMR ($CDCl_3$): (*Z*-*isomer*) δ 1.47 (t, 8.7, 1H, S***H***), 2.07, 2.94 (m, 2H, SC***H***$_2$), 3.77 (s, 3H, OC***H***$_3$), 4.33 (m, 1H, NC***H***), 6.71−7.36 (m, 5H, C$_6$***H***$_5$), 9.63(br, 1H, N***H***); ^1H NMR ($CDCl_3$): (*E*-*isomer*) δ 1.47(t, 8.7, 1H, S***H***), 3.12 (m, 1H, SC***H***$_2$), 3.39 (m, 1H, SC***H***$_2$), 3.84(s, 3H, OC***H***$_3$), 5.48 (m, 1H, NC***H***), 7.00−7.36(m, 5H, C$_6$***H***$_5$), 9.13 (br, 1H, N***H***); $^{13}C\{^1H\}$ NMR ($CDCl_3$): (*Z*-*isomer*) δ 27.4 (***C***H_2SH), 53.5 (N***C***H), 61.5 (OC***H***$_3$), 118.9 (***C***$_6H_5$), 129.0 (***C***$_6H_5$), 149.4 (***C***$_6H_5$), 168.2 (***C***=O), 216.8 (*cis*-***C***O), 223.4 (*trans*-***C***O), 289.8 (Cr=***C***); $^{13}C\{^1H\}$ NMR ($CDCl_3$): (*E*-*isomer*) δ 27.4 (***C***H_2SH), 53.5 (N***C***H), 61.5 (O***C***H_3), 121.4 (***C***$_6H_5$), 127.4 (***C***$_6H_5$), 155.0 (***C***$_6H_5$), 169.0 (***C***=O), 216.8 (*cis*-***C***O), 223.4 (*trans*-***C***O), 285.0 (Cr=***C***); HRMS (ESI) *m*/*z* 413.9749 (413.9745 calculated $[M]^-$ $C_{13}H_8CrNO_5$) $[M-H-CO]$ 385.9800, $[M-H-2CO]^-$ 357.9849, $[M-H-3CO]^-$ 329.986, $[M-H-4CO]^-$ 301.9938.

Preparation of 3h. A 40 mg portion of yellow oil was isolated (yield 22%). R_f = 0.26 (CH_2Cl_2/Hexane 1:1); IR (CH_2Cl_2, cm^{-1}): 2056 m, 1975w, 1923s, 1740w; ^1H NMR ($CDCl_3$): δ 1.27 (m, 3H, C***H***$_3$), 2.02 (br, 2H, C***H***$_2$), 2.47 (m, 2H, SC***H***$_2$), 4.20 (m, 2H, OC***H***$_2$), 6.70 (2H, C$_6$***H***$_5$), 7.19 (1H, C$_6$***H***$_5$), 7.33 (2H, C$_6$***H***$_5$), 9.13(br, 1H, N***H*** *E*-isomer), 9.63 (br, 1H, N***H*** *Z*-isomer); $^{13}C\{^1H\}$ NMR ($CDCl_3$): (*Z*-isomer) δ 7.53 (***C***H_3), 15.58 (***C***H_2), 31.4 (S***C***H_2), 60.9 (N***C***H), 62.8 (O***C***H_2), 119.0 (***C***$_6H_5$), 128.9 (***C***$_6H_5$), 149.3 (***C***$_6H_5$), 169.3 (***C***=O), 217.1 (*cis*-CO), 223.55 (*trans*-*C*O), 287.2 (Cr=***C***); $^{13}C\{^1H\}$ NMR($CDCl_3$): (*E*-*isomer*) δ 7.5 (***C***H_3), 14.3 (***C***H_2), 29.8 (S***C***H_2), 61.1 (N***C***H), 64.7 (O***C***H_2), 121.1 (***C***$_6H_5$), 127.2 (***C***$_6H_5$), 155.2 (***C***$_6H_5$), 170.3 (***C***=O), 217.1 (*cis*-***C***O), 223.6 (*trans*-***C***O), 282.5 (Cr=***C***); HRMS (ESI) *m*/*z* 456.0232 (456.0215 calculated $[M]^-$ $C_{19}H_{18}CrNO_7S$).

Preparation of 4. A 45 mg portion of red oil was isolated (yield 24%). R_f = 0.65 (CH_2Cl_2/MeCN 4:1); IR (CH_2Cl_2, cm^{-1}): 2060 m, 1947s, 1747w; ^1H NMR ($CDCl_3$): δ 2.04 (s, 3H, SC***H***$_3$), 3.12 (m, 1H, SC***H***$_2$), 3.32(m, 1H, SC***H***$_2$), 3.76 (s, 3H, OC***H***$_3$), 4.65 (m, 1H, NC***H***), 6.08 (br, 1H, N***H***), 6.65, 7.44 (m, 5H, C$_6$***H***$_5$); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 23.2 (S***C***H_2), 45.4 (O═***C***CH_3), 50.8 (N***C***H), 53.2 (O***C***H_3), 117.4 (***C***$_6H_5$), 127.6 (***C***$_6H_5$), 128.7 (***C***$_6H_5$)157.0 (***C***$_6H_5$), 169.9 (***C***=O), 170.1 (***C***=O), 215.3 (*cis*-***C***O), 228.9 (*trans*-***C***O), 362.7 (Cr=***C***); HRMS (ESI) *m*/*z* 458.0000 (457.9996 calculated $[M]^+$ $C_{18}H_{16}CrNO_8S$).

Preparation of 5. An 82 mg portion of orange solid was isolated (yield 58%). R_f = 0.34 (CH_2Cl_2/Hexane 1:1); IR (CH_2Cl_2, cm^{-1}): 2050 m, 1973w, 1925s, 1743w;^1H NMR ($CDCl_3$): δ 1.27 (t, 5.4 Hz, 3H, C***H***$_3$), 3.89 (d, 3.9 Hz, 2H, NC***H***$_2$), 4.24 (q, 5.4 Hz, 2H, OC***H***$_2$), 4.62 (s, 3H, OC***H***$_3$), 6.39 (s, 1H, ═C***H***), 7.36−7.47 (m, 5H, C$_6$***H***$_5$), 9.34 (br, 1H, N***H***); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 14.3 (C***H***$_3$), 47.3 (N***C***H_2), 62.4 (O***C***H_2), 64.7 (O***C***H_3), 120.3 (***C***$_6H_5$), 128.0 (***C***$_6H_5$), 129.2

(C_6H_5), 130.6 (C_6H_5), 134.8 (*C*H=C), 152.7 (CH=*C*), 168.8 (*C*=O), 218.7 (*cis*-*C*O), 224.26 (*trans*-*C*O), 299.5 (Cr=*C*); HRMS (ESI) *m*/*z* 438.0294 (438.0287 calculated for $[M-H]^-$) and 440.429 (440.0432 calculated for $[M+H]^+$).

Preparation of 6. A 62 mg portion of yellow solid was isolated (50% yield). TLC R_f = 0.3 (CH_2Cl_2/Hexane 1:2); IR (CH_2Cl_2, cm^{-1}): 2055 m, 1929s; ^1H NMR ($CDCl_3$): (*Z*-isomer) δ 2.96 (d, 4.4 Hz, 3H, NC*H*$_3$), 6.79,7.26,7.41 (m, 5H, C_6H_5), 9.11 (br, 1H, N*H*); ^1H NMR ($CDCl_3$): (*E*-isomer) δ 3.76 (d, 4.8 3H, NC*H*$_3$), 6.98, 7.26, 7.41 (m, 5H, C_6H_5), 8.73 (br, 1H, N*H*); $^{13}C\{^1H\}$ NMR ($CDCl_3$): (*Z*-*isomer*) δ 37.9 (N*C*H$_3$), 119.0 (C_6H_5), 127.0 (C_6H_5), 128.9 (C_6H_5), 149.5 (C_6H_5), 217.4 (*cis*-*C*O), 223.4 (*trans*-*C*O), 284.0 (Cr=*C*); $^{13}C\{^1H\}$ NMR ($CDCl_3$): (*E*-*isomer*) δ 40.2 (N*C*H$_3$), 121.1 (C_6H_5), 128.0 (C_6H_5), 128.6 (C_6H_5), 155.0 (C_6H_5), 217.9 (*cis*-*C*O), 223.9 (*trans*-*C*O), 281.6 (Cr=*C*); HRMS (ESI) *m*/*z* 309.9821 (309.9813 calculated for $[M]^-$ $C_{13}H_8CrNO_5$).

Preparation of 7. Method B was employed to prepare this species with the exceptions that $[NEt_4][Cr(CO)_5Br]$ was employed as the chromium precursor and DMSO was used in place of the amino ester. IR(CH_2Cl_2, cm^{-1}): 2080w, 2025w, 1953vs; 1090 (w) 1011 (w) ^1H NMR ($CDCl_3$): δ 3.17 (s, C*H*$_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 52.1 (*C*H$_3$), 213.1 (*cis*-*C*O), 219.0 (*trans*-*C*O).

Details of Crystallographic Analysis. Details of the collection and refinement are presented in Table 2. Diffraction data were collected at 110 K on a Bruker Smart Apex diffractometer with Mo−K_α radiation (λ = 0.71073 Å) using a SMART CCD camera. Diffractometer control, data collection, and initial unit cell determination were performed using "SMART".[57] Frame integration and unit-cell refinement were carried out with the "SAINT+" software.[58] Absorption corrections were applied by SADABS (v2.03 or v 2.10 Sheldrick). Structures were solved by direct methods using SHELXS-97[59] and refined by full-matrix least-squares using SHELXL-97.[60] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to the nitrogen of the amino groups were located in the electron difference map, and remaining hydrogen atoms were placed using a "riding model" and included in the refinement at calculated positions. CCDC 766533 (**1-Cr-a**), 766534 (**1-Cr-b**), 766535 (**1-Cr-c**), 766536 (**1-Mo-a**), 766537 (**1-W-b**), 766538 (**3b**) and 766539 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supporting Information Available: Details of CO-release tests, CIF files for complexes **1-Cr-a**, **1-Cr-b**, **1-Cr-c**, **1-Mo-a**, **1-W-b**, **3b**, and **5**, and details of mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

(57) *SMART, diffractometer control software*, v5.625; Bruker AXS GmbH: Karlsruhe, Germany.

(58) *SAINT+*, v6.22; Bruker AXS GmbH: Karlsruhe, Germany.

(59) Sheldrick, G. M. *SHELXS-97, Program for the Solution of Crystal Structures*; Universität Göttingen: Göttingen, Germany, 1997.

(60) Sheldrick, G. M. *SHELXL-97, Program for the Solution of Crystal Structures*; Universität Göttingen: Göttingen, Germany, 1997.